New insights in the surgical treatment of chronic ischemic mitral regurgitation

Citation for published version (APA):

Gelsomino, S. (2009). *New insights in the surgical treatment of chronic ischemic mitral regurgitation*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht.
<https://doi.org/10.26481/dis.20090424sg>

Document status and date:

Published: 01/01/2009

DOI:

[10.26481/dis.20090424sg](https://doi.org/10.26481/dis.20090424sg)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

New Insights in the *Surgical Treatment* of
Chronic Ischemic Mitral Regurgitation

ISBN 978 90 5278 825 8
© Sandro Gelsomino, Florence, Italy 2009

Printed by Datawyse | Universitaire Pers Maastricht

Financial Support by Bio-Si International SRL, Florence, Italy and the University of Florence for the publication of this thesis is gratefully acknowledged.

Additional support was granted by St Jude Medical and Terumo.

New Insights in the *Surgical Treatment* of Chronic Ischemic Mitral Regurgitation

DISSERTATION

to obtain the degree of Doctor at
the Maastricht University,
on the authority of the Rector Magnificus
Prof. dr. G.P.M.F. Mols,
in accordance with the decision of the Board of Deans,
to be defended in public
on Friday 24 April 2009, at 12.00 hours

by

Sandro Gelsomino

Supervisor

Prof. dr. JG Maessen

Co-supervisors

Dr. R Lorusso, Civic Hospital, Brescia, Italy

Dr. ir. FH van der Veen

Assessment Committee

Prof. dr. JH Zwaveling (chairman)

Prof. dr. AM Calafiore, Ospedale Ferrarotto, Catania, Italy

Prof. dr. L Hofstra

Prof. dr. M Klautz, UMC Leiden

*"Two things awe me most, the starry sky above me and the moral law within me."
Immanuel Kant, The Critique of Practical Reason*

*"Considerate la vostra semenza: fatti non foste a viver come bruti, ma per seguir
virtute e canoscenza"
Dante Alighieri, Divina Commedia, Inferno canto XXVI, 116-120*

*"Consider ye the seed from which ye sprang; Ye were not made to live like unto
brutes, But for pursuit of virtue and of knowledge."
Dante Alighieri, The Divine Comedy, Evil XXVI, 116-120,
Translation by Henry Wadsworth Longfellow*

To Cecilia
*"Shall I compare thee to a summer's day?
Thou art more lovely and more temperate:
Rough winds do shake the darling buds of May,
And summer's lease hath all too short a date:
Sometime too hot the eye of heaven shines,
And often is his gold complexion dimmed,
And every fair from fair sometime declines,
By chance, or nature's changing course untrimmed:
But thy eternal summer shall not fade,
Nor lose possession of that fair thou ow'st,
Nor shall death brag thou wander'st in his shade,
When in eternal lines to time thou grow'st,
So long as men can breathe, or eyes can see,
So long lives this, and this gives life to thee".
William Shakespeare. Sonnet XVIII*

*To my mother, my father, my grandmother Carmela
my sister Gabriella, my aunt Maria,
my nephew Gianmarco, my nieces Federica and Valentina,
my brother-in-law Orlando and my devoted friend Francesco.
"When you turn the look to your life,
the greatest joys are those of the family."
J. Brothers*

TABLE OF CONTENTS

Preface	9
Acknowledgements	11
Abbreviations and acronyms	12
 CHAPTER 1	
Introduction	13
 CHAPTER 2	
Five-year echocardiographic results of combined undersized mitral ring annuloplasty and coronary artery bypass grafting for chronic ischemic mitral regurgitation	43
 CHAPTER 3	
Left ventricular reverse remodeling after undersized mitral ring annuloplasty in patients with ischemic regurgitation	65
 CHAPTER 4	
Insights on left ventricular and valvular mechanisms of recurrent ischemic mitral regurgitation after restrictive annuloplasty and coronary artery bypass grafting	91
 CHAPTER 5	
Impact of anterior leaflet tethering on recurrence of ischemic mitral regurgitation after restrictive annuloplasty	115
 CHAPTER 6	
Left ventricular diastolic function after restrictive mitral ring annuloplasty in chronic ischemic mitral regurgitation and its predictive value on outcome and recurrence of regurgitation	137
 CHAPTER 7	
Prognostic value of doppler-derived mitral deceleration time on left ventricular reverse remodeling after undersized mitral annuloplasty	159
 CHAPTER 8	
Conclusions	181
 CHAPTER 9	
Summary	195
Riassunto	199
Samenvatting	205
Publications	211
Curriculum vitae	219

Music was probably born of the natural rhythms of life. Since ancient the time of Greece, music has been able to excite people, or calm people. Orpheus, the son of Calliope, on a voyage with Jason and the Argonauts, played lively melodies on his lyre to energize fatigued oarsmen, and shooting tunes them when they quarreled.

It should not come as a surprise when people who dedicate themselves to life science release their creative energy in music. Music has always been an interesting domain for the application of new scientific discoveries inviting composers to combine artistic creativity with scientific methods.

Indeed both music and medicine are strict disciplines, even though one is considered an art and one a science. Both demand practitioners who learn complex skills, practice them exhaustively, then impose a set of rules on what is naturally messy—a disease, an injury, a series of unrelated sounds. And both require enormous dedication, so much that it would seem impossible for one person to do both. But some scientists manage. They realize medicine and music are not mutually exclusive.

Not only can the two disciplines coexist; given the right conditions, they can coalesce.

I was raised in a family where Mozart was never played.

My family was unusual in the respect that both my parents enjoyed classical music, but neither were Mozart fans. In fact, my dad never played Mozart because he said his music was “too happy”.

I first heard “Don Giovanni K 527” as a 10-year-old boy and I was struck immediately by the power of Mozart’s music. Then I heard “Madamina il catalogo è questo”, “La ci darem la mano”, “Dalla sua pace”, “Il mio tesoro intanto” again, and then again, and I heard more and more in it, until it became the soundtrack of my life. Since then Mozart’s Fantasia in D Minor K.397, his clarinet concerto in A major K. 622, the piano Concerto No 20 in D Minor K466, have inspired and

encouraged me in every day life. His music reminded me of possibility, hope and belief. I turned to his melodies when I felt down, in need of courage or to express my feelings. The magnificence of his music helped me turn sadness into hope or fear into courage. His eternal melodies helped me to believe in love, to know I was not alone, to laugh, to cry...

There is something magical in his music because, after more than 35 years, in re-listening to *The Marriage of Figaro* K492, *Die Zauberflöte* K620, *Die Entführung aus dem Serail* K.384, "I am affected again and again and the more I listen to Mozart's music, the more I love it. His music still touches me profoundly, because it is so luminous and yet at the same time so deep." His music is by no means just entertainment; it contains the whole tragedy of human existence", the Holy Father Benedict XVI recently said.

In a normal day at the hospital, the Mozart's music fill the operating theatre: it relaxes me, and focuses my attention. I think that any music could be good for routine operation but only Mozart for trickier ones. All my research was deeply inspired by Mozart's music and I couldn't spend many, many hours in the Experimental Surgery laboratory without listening to "un'aura amorosa", "la ci darem la mano", "che soave zeffiretto". His music carries an important component of human thought, namely formal abstraction, which can be very inspiring for medical research.

Mozart's music is universal. He speaks to almost everybody and he never pushes us. If all you want from one of his compositions are some good tunes and seraphic harmonies, he will surely provide them. If you want much, much more, Mozart, in virtually all of his mature pieces, will provide that, too. Bach and Beethoven tell us exactly what they want to tell us, while Mozart lets us find what we want in him, on our own levels of need and understanding.

In 1906, the pianist and composer Ferruccio Busoni was asked to write a series of aphorisms to celebrate the 150th anniversary of Mozart's birth and 100 years later most of us would echo what he had to say. "... Up to now he is the most complete manifestation of musical gifts... He disposes of light and shadow, but his light does not pain and his darkness still shows clear outlines... He is young as a boy and wise as an old man, never old-fashioned and never modern, carried to the grave and always alive.

... His smile, which was so human, still shines on us transfigured."

ACKNOWLEDGEMENTS

11

I would like to express my endless gratitude to Roberto Lorusso who brought me out of the darkness.

I would like to extend my heartfelt thanks to Professor Gian Franco Gensini for his invaluable support to my research.

Special appreciation should be devoted to Erik van der Veen and Jos Maessen who strongly supported me for the Doctorate. Without them and Roberto I would never have been here.

A special thank has to be addressed to my friends Giuseppe De Cicco who made most of the illustrations of this thesis, and Mario Romano for his friendly help.

Thank you to my brother-in-law Orlando for your help in statistical analysis.

Finally, I would like to reserve a special thank to all colleagues cooperating in my research.

ABBREVIATIONS AND ACRONYMS

IMR	Ischemic Mitral Regurgitation
CIMR	Chronic Ischemic Mitral Regurgitation
UMRA	Undersized Mitral Ring Annuloplasty
MI	Myocardial Infarction
MV	Mitral Valve
MR	Mitral Regurgitation
IMLC	Incomplete Mitral Leaflet Closure
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Grafting
PM(s)	Papillary Muscle(s)
PPM	Posterior Papillary Muscle
APM	Anterior Papillary Muscle
LV	Left Ventricle
LVR	Left Ventricular Reverse Remodeling
ERO(A)	Effective Regurgitant Orifice (Area)
RF	Regurgitant Fraction
RV	Regurgitant Volume
PISA	Proximal Isovelocity Surface Area
NYHA	New York Heart Association
CCS	Canadian Cardiovascular Society
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography
EDD	(Left ventricular) End Diastolic diameter
ESD	(Left ventricular) End Systolic diameter
LA	Left Atrium (mm)
ESVI	(Left ventricular) End Systolic Volume Index
EDVI	(Left ventricular) End Diastolic Volume Index
LVEF	Left Ventricular Ejection Fraction
MPI	Myocardial Performance Index
SPI	Sphericity Index
WMSI	Wall Motion Score Index;
AML	Anterior Mitral Leaflet
PML	Posterior Mitral Leaflet
TA	Tenting Area
CH	Coaptation Height
CL	Coaptation Length
MAs	(Systolic) Mitral Annular Area
Mad	(Diastolic) Mitral Annular Area
MΔp	Trans Mitral Diastolic Gradient
α'	Anterior Mitral Leaflet Tethering Angle
β'	Posterior Mitral Leaflet Tethering Angle
α_{EX}	Anterior Mitral Leaflet Excursion Angle
β_{EX}	Posterior Mitral Leaflet Excursion Angle
γ	Bending Angle
IQR	Interquartile Range

1

Introduction

INTRODUCTION

15

Ischemic mitral regurgitation is a relatively common manifestation of coronary artery disease and occurs after acute myocardial infarction (MI) or as a chronic condition, and less commonly as regional episodic ischemia. Chronic Ischemic mitral regurgitation (CIMR) is a functional mitral regurgitation (MR), as opposed to organic MR, because of the normal appearance of the mitral valve (MV) leaflets. CIMR is associated with a markedly worse prognosis after myocardial infarction (MI) and coronary revascularization¹⁻⁵, and is a common cause of post-MI congestive heart failure^{6,7}. CIMR is present in 10% to 20% of patients with coronary artery disease (CAD)⁸⁻¹⁰.

DEFINITION

Ischemic mitral regurgitation should be distinguished from mitral regurgitation due to structural leaflet disease (such as rheumatic or mitral valve prolapse) and fortuitously associated with coronary artery disease. Conversely, mitral regurgitation of ischemic etiology can be the consequence of papillary muscle rupture, which represents a severe, albeit rare, complication of acute MI that requires emergency intervention¹¹⁻¹³.

Chronic IMR should be defined as mitral regurgitation occurring more than 1 week after MI with (1) one or more left ventricular segmental wall motion abnormalities; (2) significant coronary disease in the territory supplying the wall motion abnormality; and (3) structurally normal MV leaflets and chordae tendineae. The third criterion is particularly important as it excludes patients with organic MR and associated CAD.

HISTORICAL NOTES

Burch, De Pasquale, and Phillips^{13,14} initially ascribed ischemic MR to papillary muscle (PM) dysfunction. Normally, as the left ventricle (LV) shortens, PM contraction maintains the distance between the PM tips and mitral annulus to prevent prolapse. PM damage could then produce prolapse, consistent with its frequently late-systolic murmur. Experimental damage to the PMs themselves, however, fails to produce MR acutely without damage to the underlying myocardial wall as well¹⁵. Burch et al^{13,14} alternatively postulated restricted leaflet motion. The PMs, normally parallel to the LV long axis and perpendicular to the leaflets, efficiently balance forces generated by ventricular pressure on the leaflet surface. Ischemia or heart failure causes the myocardial segments underlying the PMs to bulge posterior and outward, displacing the PMs, so that they pull the leaflets non perpendicularly, away from their normal coaptation. The distance between the PM tips and the annulus

also increases, drawing the leaflets into the ventricle and restricting their motion toward closure, as proposed by Paul Dudley White, Levy and Edwards, Silverman and Hurst¹⁶, and Perloff and Roberts¹⁷. Two-dimensional echocardiography first directly demonstrated apical restricted leaflet motion, termed “incomplete mitral leaflet closure” (IMLC)^{18,19}. Godley, Weyman, et al¹⁹ associated IMLC with inferior dyskinesis, postulating increased leaflet tethering. Based on myocardial injection studies, Alain Carpentier has succinctly renamed PM dysfunction “PM wall dysfunction”, namely, tethering caused by displacement of the leaflet attachments. Kaul et al²⁰ elegantly confirmed that reducing PM perfusion produced neither prolapse nor MR. In contrast, global hypoperfusion with LV dilatation, despite continued PM perfusion and thickening, caused MR with IMLC in direct correlation with LV dysfunction²⁰. In those studies, however, akinesia of the PMs and their underlying wall also failed to produce MR acutely. This led to the postulate that MR results from global LV dysfunction, decreasing the leaflet closing force,²¹ as opposed to PM wall tethering. Conceivably, however, the acute PM wall displacement in that study was insufficient to produce MR, and as the authors acknowledged, LV dilatation paralleled global dysfunction, precluding separation of dysfunction from dilatation as primary cause of MR. This distinction has practical implications: LV contractile dysfunction would demand inotropic therapy, revascularization, or transplantation, whereas tethering might respond to modifying LV wall or PM geometry. New models were therefore required to dissect the effects of dysfunction and dilatation. He et al²² reproduced MR in excised mitral valves by displacing the PMs apically, posteriorly, and outward, as in patients. In vivo, Otsuji et al²³ created global LV dysfunction pharmacologically but limited LV expansion through pericardial restraint and decreased preload. Contractile dysfunction (ejection fraction <20%) without dilatation produced only trace MR; LV dilatation was a prerequisite for IMLC and MR²³. To quantify tethering geometry, these authors used 3D echocardiographic data to standardize the tethering length from the PM tips to the anterior mitral annulus. In global dysfunction, Otsuji et al²³ found that tethering length was the only independent predictor of MR, not LV ejection fraction or dP/dt. MR also correlated with LV sphericity, consistent with the key observation of Kono, Sabbah et al²⁴⁻²⁶ increased sphericity that could potentially displace the PMs posterolaterally, as verified by 3D echocardiography²³. The centrality of geometric change was confirmed in acute segmental inferior ischemia, studied with and without external constraint²⁷, and in the chronic sheep model of Gorman and Edmunds, in which MR, initially absent, evolves in parallel with LV remodeling and PM displacement²⁸⁻³⁰. In patients, Yiu, Enriquez-Sarano et al³¹ strongly related PM tethering, leaflet tenting, and MR, which is frequently due to localized remodeling of the posterior PM-bearing walls, without the global remodeling required for MR with anterior infarctions¹⁰. By 3D echocardiography, the medial mitral valve is most tented in ischemic cardiomyopathy, because the inferomedial PM is most displaced³²; this asymmetry might

augment MR through asymmetrical coaptation between posterior leaflet scallops³³. Although the annulus is dilated in global dysfunction³⁴, isolated annular dilatation without increased tethering length in atrial fibrillation is not associated with important MR³⁵. Finally, Otsuji and colleagues³⁶ recognized restricted diastolic as well as systolic leaflet excursion, an echocardiographic clue that tethering is increased. The simple story, however, is often incomplete. First, although PM damage does not produce MR acutely, MR does occur in the chronic phase of ethanol injection, with PM scarring and retraction¹⁵. Second, occasional patients with MI actually do have prolapse with PM elongation³⁷. These observations, rather than disproving tethering, actually confirm that tethering distance is the final common pathway determining the level of leaflet coaptation. The change in tethering distance is the resultant of two vectors: Displacement of the PM-bearing wall is modulated by changes in PM length. As Frater et al³⁸ have shown, MR increases biphasically with too long or too short a tethering length. We can therefore understand how PM contractile dysfunction can paradoxically diminish MR. Messas et al³⁹ created a limited inferobasal MI with wall bulging and MR; making the adjacent PM acutely ischemic caused it to elongate in response to ventricular forces and reduced tethering distance and MR. Preserved PM shortening increases tethering and MR⁴⁰, which confirms the central role of tethering length and the concept of PM-ventricular wall complex expressed by Komeda, Miller et al⁴¹. Tethering is one facet of a unifying principle of mitral valve function: that leaflet motion is determined by the 3D geometry of the leaflets and their attachments, relative to the surrounding flow field. Another example is the relation between systolic anterior mitral valve motion and anterior PM displacement combined with leaflet elongation, the converse of posterior PM displacement and leaflet restriction in ischemic MR.

The dichotomy between tethering versus closing forces is also a simplification: both are involved. The equilibrium position of the mitral leaflets is determined by the balance of forces acting on them, including annular and PM tethering forces and LV-generated closing forces. Normally, little force is required to close the thin leaflets, so MR is not produced by global dysfunction without tethering²³. However, once tethering is increased, leaflet closure is further. This balance of competing forces creates a unique dynamic pattern, recognized by Schwammenthal et al⁴², with flow and orifice area greatest in early and late systole and often paradoxically decreased in mid systole, when peak LV pressure maximizes leaflet closure. Tethering sets the stage for MR; transmitral pressure modulates its variation throughout the cardiac cycle^{22,43}. We therefore understand the early systolic leaflet “loitering” described by Glasson, Miller et al⁴⁴ and late systolic MR and murmurs in patients with inferior MIs, in whom tethering increases as the inferior wall is “left behind” the contracting ventricle⁴⁵.

PATHOPHYSIOLOGY

The mitral valve has a complex anatomy contributing actively to the process of systolic valvular closing. This mechanism consists of a combination of interactions of the ventricle, annulus, and papillary muscles. Therefore, any alterations in one or more of these structures may contribute to the regurgitation. Normal MV function requires coordinated operation of all components including the annulus, leaflets, chordae tendineae, and papillary muscles (PMs). The annulus is a saddle like structure whose main function is to act as a fulcrum for the mitral leaflets and to decrease the size of the mitral orifice (by 10% to 20%) during late diastole and systole⁴⁶⁻⁴⁸. A dilated mitral annulus is often reported as an important etiologic factor in CIMR⁴⁹, but isolated annular dilation does not cause significant MR⁵⁰. The second component of the MV apparatus are the leaflets. The leaflets are morphologically normal in CIMR, but there is tethering and retraction of the leaflet bodies. As stated before, it is important to exclude patients with organic MV leaflet pathology and associated CAD from CIMR studies, as these patients have a much better prognosis. Chordae tendineae are the third component of the MV apparatus, connecting the PMs to the leaflets. Primary chordae attach to the free edge of the leaflets and prevent prolapse during systole. Secondary chords attach to the belly of the leaflet and are thicker than primary chords.

Apical displacement of the PMs leads to tethering of the secondary chords and decreased leaflet coaptation. The final component of the MV apparatus is the PMs, named according to their relationship with the commissural area. The anterolateral PM has a dual blood supply from branches of the circumflex and left anterior descending arteries. The posteromedial PM, in contrast, is supplied by a single artery arising from either the right coronary or from the terminal circumflex artery and is therefore more prone to infarction. Clinical studies have confirmed that CIMR is more likely to occur after posteroinferior than anterolateral MI^{51,52}. However, the previously held notion that CIMR is due to isolated PM dysfunction is incorrect. Large animal studies have revealed that isolated PM infarction does not cause significant MR⁵³, and may in fact paradoxically improve ischemic regurgitation⁵⁴.

Left ventricular distortion and remodeling after MI displace PMs away from the mitral annulus^{24,51,55}. The displacement puts excessive tension on the chordae, resulting in apical mitral leaflet tethering, restricting their coaptation during systole^{23,24,31,52-56}. Leaflet tethering is compounded by LV contractile dysfunction, which decreases the closing force on the leaflets (Figure 1)²³. Once IMR is initiated, end-diastolic LV volume and wall stress increase in tandem with preload^{10,32,52}. Left ventricular mass also increases progressively without a concomitant increase in end-diastolic wall thickness⁵⁷ resulting in generalized loss of myocardial contractile function^{10,58}. Increased wall stress causes more LV dysfunction⁵⁹, which in turn results in further PM displacement and leaflet tenting. If LV dilation occurs, it leads to

annular enlargement and dysfunction thereby increasing valvular incompetence⁶⁰. Chronic IMR therefore begets MR in a self-perpetuating manner (Figure 2).

Figure 1. In the Infarcted heart the displacement of papillary muscle results in tension on the chordae and tethering which lead to leaflet malcoaptation.

Figure 2. Self-maintaining mechanism leading to heart failure and death.

CLINICAL EXAMINATION AND DIAGNOSIS

Clinical Examination

The severity of symptoms (dyspnea, fatigue, pulmonary congestion) in patients with CIMR is mainly related to the underlying ventricular dysfunction. Therefore, ischemic MR is often unrecognized clinically. A murmur is heard only in a small percentage of patients, with estimates ranging from 4% to 50%^{1,5,10,61-62}. In contrast to structural mitral regurgitation, in ischemic mitral regurgitation the intensity of murmur is less and correlates poorly with the degree of regurgitation due to the decreased left ventricular systolic function and atrial compliance⁶³. Indeed, in the non-compliant left atrium, the energy of the regurgitation created by a large effective regurgitant orifice cannot be transformed into kinetic energy which, in turn, produces a large regurgitant volume and a loud murmur. It is rather transformed into potential energy resulting in an increase of pressure as demonstrated by the high left atrial pressure and V wave^{7,64}. Therefore, in ischemic mitral regurgitation, the regurgitant volume tends to be smaller and is associated with less intense murmur. However, this apparently “milder” regurgitation portends poor hemodynamics and worse outcomes^{7,64}. As a result, the clinician cannot rely on cardiac auscultation to diagnose it or assess its severity.

Invasive investigations

Left ventricular angiography is frequently associated with coronary angiography and some consider it as the reference method for the assessment of the volume of mitral regurgitation. This is mainly related to historical reasons, but grading using ventricular angiography is also subject to limitations, in particular due to the influence of loading conditions. Quantitative Doppler echocardiography provides more objective data regarding the prognostic role of the regurgitation than ventricular angiography.

Echocardiography

The limitations of the clinical exam in the detection of ischemic mitral regurgitation underscore the necessity of a test that is more sensitive than the mere bedside examination.

Historically, mitral regurgitation was assessed by left ventriculography^{1,10,65}, relying on retrograde opacification of the left atrium but this technique does not provide adequate information on the anatomy of the valve and the etiology of the regurgitation. Echocardiography is the preferred method to assess valvular heart disease. The two-dimensional examination yields information on the geometry of the ventricles and valve anatomy, such as left ventricular dilatation, regional wall motion abnormalities, annulus dilatation, and especially valvular tenting. This provides information on the potential mechanisms of regurgitation which enables

distinguishing ischemic mitral regurgitation from mitral regurgitation fortuitously associated with coronary artery disease. Standard color Doppler imaging is a highly sensitive method to detect even mild degrees of ischemic mitral regurgitation, and the measurement of the area of the regurgitant jet has been widely used to evaluate semi-quantitatively the amount of the regurgitation⁶⁶. One unique advantage of echocardiography is that it accurately quantifies the severity of mitral regurgitation by measuring the effective regurgitant orifice area and the regurgitant volume using Doppler methodology (continuity equation or proximal isovelocity surface area [PISA], which is the preferred method). The effective regurgitant orifice area (EROA) is a measure of the severity of the lesion while the regurgitant volume (RV) is a measure of volume overload; therefore, the former is not dependent on hemodynamic conditions.

Current guidelines recommend thresholds to define severe mitral regurgitation as a regurgitant volume ≥ 60 ml and an effective regurgitant orifice ≥ 40 mm^{67,68}. For ischemic mitral regurgitation, however, adverse outcomes are associated with lower values for these parameters⁷ suggesting that 30 ml for regurgitant volume and 20 mm² for effective regurgitant orifice should be the preferred thresholds of severity.

The dynamic nature of ischemic mitral regurgitation was recently underscored. The exercise-induced increase in mitral regurgitation (effective regurgitant orifice change >13 mm²) caused by changes in local remodeling was associated with increases in pulmonary pressure, pulmonary edema⁶⁹, and cardiac death⁷⁰. This may explain why small amounts of regurgitation at rest are associated with adverse outcomes. There are currently no data that suggest the optimal timing for imaging after myocardial infarction. This matter will require further studies.

PREVALENCE OF CHRONIC ISCHEMIC MITRAL REGURGITATION

The prevalence of CIMR has been difficult to calculate as a result of the heterogeneity of MR patients presented in previous studies^{49,51,71}. Studies have reported a high incidence of IMR (11% to 19%) in patients undergoing cardiac catheterization for symptomatic CAD^{9,8,10}. Hickey and colleagues¹⁰ projected the incidence of moderate-to-severe IMR to be 7% within this patient cohort. Approximately 14.6 million Americans have angina pectoris (chest pain) or a history of MI⁸⁴. Combining the above statistics, it can be estimated that the prevalence of IMR in the United States is 1.6 million to 2.8 million patients^{9,10,72}, a one-third increase from 1995⁴⁹. These statistics show that CIMR continues to be a widespread problem and may increase as survival rates for acute MI improve.

NATURAL HISTORY OF CHRONIC ISCHEMIC MITRAL REGURGITATION

Patients with CIMR have a worse natural history than patients with CAD and no MR. A study of 11,748 cardiac catheterization patients revealed that severe ischemic MR was associated with a 1-year mortality of 40%, moderate IMR 17%, and mild IMR 10%⁹. If no IMR was present at catheterization, the 1-year mortality rate was 6%. Data from trials on thrombolysis for acute MI showed similarly poor prognosis for IMR⁹. Post-myocardial infarction patients have a 1-year mortality rate of 52% if they have severe IMR, 22% if they have mild-moderate IMR, and 11% if they have no ischemic MR.

The Survival and Ventricular Enlargement (SAVE) study¹ demonstrated that mild chronic IMR increases the risk of cardiovascular mortality, even in patients without congestive heart failure. Patients with CIMR had a higher incidence of cardiovascular mortality (29% versus 12%) and heart failure (24% versus 16%) than patients without ischemic regurgitation at a mean of 3.5 years after MI. Adjustment for differences in baseline characteristics revealed that mild-to-moderate (1+ or 2+) CIMR strongly predicted mid-term mortality¹.

MEDICAL THERAPY AND CARDIAC RESYNCHRONIZATION

The literature regarding medical therapy is comparatively sparse. Surprisingly, post-MI and heart failure patients commonly present with moderate MR despite the use of diuretics, ACE inhibitors, and β -adrenergic antagonists. Two questions arise: (1) Can medical therapy reduce regurgitation of a tethered valve? And (2) can it attenuate or reverse the underlying ventricular remodeling? First, recall the dynamic balance of tethering and closing forces that determines ischemic MR^{23,73,74}. Transmitral pressure, which drives regurgitant flow, also promotes valve closure⁷⁵. Therefore, it would appear that increased systemic blood pressure could reduce MR by increasing closing force. However, noninotropic vasopressors will increase afterload and LV volume, and therefore tethering and MR. Inotropic agents, in contrast, can raise LV pressure without increasing tethering, so MR will decrease, as with dobutamine infusion^{74,76}; however, this is not a viable outpatient option. Transmitral pressure can also be increased by decreasing atrial pressure, so diuretics and nitrates can reduce regurgitant orifice area and flow⁷⁷⁻⁸⁰. Preload reduction and the initial decrease in MR can decrease ventricular size and further reduce tethering, creating a beneficial cycle. In severe heart failure, Stevenson and colleagues⁷⁸ have shown that vasodilators and diuretics can partially reduce MR (from moderate to mild-to-moderate); Levine et al⁸¹ have uptitrated ACE inhibitors and nitrates to reduce MR partially. However, if afterload reduction is not accompanied by decreased PM tethering (for example, with fixed inferior wall scarring or a dilated, hypokinetic ventricle), regur-

gitant orifice area may paradoxically increase as closing force decreases, as illustrated by Kizilbash, Grayburn, et al⁸² with nitroprusside.

Regarding the second question, acute LV decompression by vasodilators and diuretics is not the same as true reversal of the complex molecular, cellular, and interstitial remodeling process. Unfortunately, there are no strong data about ACE inhibitors and ischemic MR. In the SAVE (Survival And Ventricular Enlargement) study, Lamas et al¹ found comparable cardiovascular mortality in patients with MR receiving captopril versus placebo; post-MI LV remodeling could only be partially attenuated by early ACE inhibition, but not reversed or completely prevented⁸³⁻⁸⁵. Ventricular dilatation and distortion may continue to progress beyond 1 year of therapy, and even those who do not initially dilate may “escape” later.

In SOLVD (Studies Of Left Ventricular Dysfunction), ACE inhibitors could arrest progressive LV dilatation⁸⁶, and might even reverse it⁸⁷, but there are no published data from large trials regarding whether attenuation of remodeling by ACE inhibitors or receptor blockers decreases the post-MI incidence of ischemic MR. MR appears to remain common despite use of these drugs and significantly increases morbidity and mortality.

Carabello and colleagues^{88,89} have firmly established that β -adrenergic receptor blockade can reverse the contractile and structural abnormalities caused by chronic nonischemic MR. Accordingly, in patients with chronic heart failure, β -blockade with carvedilol, when added to ACE inhibitors, can significantly decrease functional MR by reducing LV dilatation^{89,91}.

The CARMEN study (Carvedilol and ACE Inhibitor Remodeling Mild Heart Failure Evaluation Trial)⁹², with mainly ischemic cardiomyopathy, demonstrated synergistic reverse remodeling by carvedilol and enalapril in mild heart failure, and CAPRICORN (Carvedilol Post-Infarct Survival Controlled Evaluation)⁹³ has recently shown incremental benefit of carvedilol over ACE inhibitors on ventricular remodeling after MI the effects on MR, however, are unreported.

Tei et al⁹⁴ have demonstrated a reduction in LV volume and MR in congestive heart failure with vasodilatation after warm bath and sauna, but chronic benefits require study. Limiting ventricular remodeling will ultimately be most effective early in its evolution. It remains to be seen whether vigorous combinations of vasodilator, β -blocking, and diuretic therapy, including spironolactone and other inhibitors of fibrosis and extracellular matrix degradation⁹⁵, can limit the development of ischemic MR. Presently, such agents are not routinely administered to patients with inferior MI, whose localized remodeling may generate considerable MR. Practically, we must deal with the many patients with existing MR and the incomplete effectiveness of current medical therapy.

A more favorable balance of forces on the valve can also be restored by electrical therapy in patients with heart failure. St. John Sutton, and colleagues⁹⁶ have reported significantly decreased MR in the Multicenter InSync Randomized Clinical Evalu-

ation. Biventricular pacing, with more effective LV contraction, can reduce end-systolic volume and therefore tethering. In heart failure, delayed lateral wall activation produces discoordinated PM contraction, malalignment of leaflet scallops, and MR; Kanzaki, Goresan, et al⁹⁷ have shown that eliminating such delays by LV pacing reduces MR. Resynchronization also increases the leaflet closing force throughout systole, as shown by Breithardt, Sinha, Schwammenthal et al⁹⁸ in patients with left bundle branch block; pacing can increase the rate of rise of LV pressure, thereby prolonging the time during systole when high LV and transmitral pressures oppose tethering to reduce regurgitant orifice area⁹⁸, in direct correlation with dP/dt . Electrical therapy will therefore be most useful in those patients with cardiomyopathy whose dP/dt rises and lateral wall conduction delay falls with pacing; its benefit extends to exercise, but with no evidence of benefit with preserved LV synchronicity or inferior MI.

SURGICAL TREATMENT

Isolated CABG Versus MV Surgery and CABG

The indications for surgery in chronic IMR are not well defined. It is generally agreed that patients who have indications for coronary artery bypass grafting (CABG) with moderate-to-severe CIMR (3+ or 4+) should also undergo concomitant MV surgery^{99,100}. Rarely, patients present with episodic IMR that occurs only during episodes of acute ischemia. Such patients can be treated with revascularization alone with good results. It is controversial whether CABG patients with mild-to-moderate MR (1+ or 2+) should undergo concomitant MV surgery. Mallidi and coworkers¹⁰³ compared patients undergoing isolated CABG with mild-to-moderate MR to patients without MR. They found a higher prevalence of heart failure symptoms and decreased cardiac event-free survival in MR patients during follow-up. In addition, 30% of patients progressed to 3+ or 4+ MR during a mean follow-up of 16 months.

Worsening of ischemic regurgitation after isolated CABG surgery has been demonstrated by other investigators and is associated with decreased long-term survival^{102,103}. Aklog and coworkers¹⁰² found persistent moderate or severe MR in 77% of patients treated with revascularization alone and were unable to identify predictors of postoperative improvement. Wong and coworkers¹⁰⁴ described more long-term MR, but no difference in survival, among patients with 3+ IMR who underwent isolated CABG versus patients who underwent CABG plus MV repair. Such findings would suggest that MV surgery should be performed at the time of CABG in patients with mild-to-moderate IMR. However, the risk of long-term MR and heart failure progression must be balanced against the increased perioperative risk of the additional MV procedure. Data from the STS database suggests that concomitant MV surgery increases the perioperative risk of CABG by roughly

twofold¹⁰¹. We therefore recommend that patients with mild-to-moderate CIMR and multiple comorbidities, or a life expectancy of less than 5 years, should be treated conservatively and undergo CABG only. Low-risk patients with mild-to-moderate CIMR should undergo concomitant MV surgery provided the procedure can be performed with low mortality rates, namely, 5% or lower.

Mitral Valve Replacement

The preferred surgical approach to severe CIMR in early studies was MV replacement with a mechanical or tissue prosthesis. Mitral valve replacement involved complete excision of the subvalvular apparatus, but subsequent studies revealed a detrimental effect on LV function with this technique¹⁰⁵. The negative effect on LV function may explain the high mortality rates in early CIMR surgical series. Preservation of the entire subvalvular apparatus can usually be performed in these patients because the MV leaflets and chordae are thin and pliable. Subvalvular preservation results in maintenance of annulo-ventricular continuity and improved preservation of LV function¹⁰⁶. Mitral valve replacement is still a reasonable surgical option in many patients with CIMR, predominantly because of its reliability and reproducibility. Mitral valve replacement should be considered for patients with CIMR and multiple comorbidities, complex regurgitant jets (noncentral jet or more than one jet), or severe tethering of both MV leaflets^{71,107,108}. Calafiore and coworkers¹⁰⁷ recommend MV replacement when the distance between the coaptation point of the leaflets and the plane of the mitral annulus exceeds 10 mm.

Mitral Valve Repair

The suboptimal early results for MV replacement led surgeons to start performing MV repair for CIMR. There have been no randomized trials to date comparing MV repair to replacement for chronic ischemic MR, but there have been a number of retrospective studies. The two largest and most methodologically sound studies are those performed by Gillinov and associates¹⁰⁸ and Grossi and colleagues¹⁰⁹. These investigators demonstrated that both MV repair and replacement are effective at eliminating MR immediately postoperatively, but MV repair was associated with lower perioperative mortality. However, patients at the highest risk with the most severe MR did just as well, and possibly better, with MV replacement^{71,108}. Regardless of which surgical technique was employed, 5-year survival rates were uniformly disappointing at approximately 50%^{108,109}.

Currently, there is general consensus in the cardiac surgery community that MV repair results in lower perioperative mortality than MV replacement and should therefore be performed whenever possible¹⁰⁷. A recent study by Al-Radi and coworkers¹¹⁰ confirmed a lower perioperative mortality from MV repair in patients with CIMR. The survival advantage decreased over time, however, and was no longer apparent by 5 years after surgery.

The most common surgical procedure currently performed for CIMR is undersized mitral ring annuloplasty (UMRA). Bolling and colleagues¹¹ popularized this approach, using very small (size 24 to 26) mitral annuloplasty rings. The rationale is that undersizing the mitral annulus will result in increased leaflet coaptation and decreased regurgitation. Although this procedure does not fully address the ventricular causes of CIMR, it is simple to perform and reproducible, and therefore has been widely adopted by the cardiac surgery community. The type of ring that should be used for UMRA is unclear, with several authors arguing the merits of rigid versus flexible and complete versus incomplete rings¹¹². A close examination of the literature does not reveal any definite advantages for any specific type of annuloplasty ring, however, with the exception of poor long-term results for pericardial bands¹¹³. The initial results for undersized mitral annuloplasty seemed encouraging, with low perioperative mortality rates¹¹⁴. However, subsequent studies at various centers revealed a significant proportion of patients develop recurrent MR during follow-up. A recent article from the Cleveland Clinic examined 585 patients undergoing undersized annuloplasty surgery over a 17-year period¹¹⁵. In 28% of patients, moderate or more MR developed 6 months postoperatively, an incidence that is similar to that described by other investigators^{116,117}. Mitral regurgitation recurrence tends to occur early postoperatively with relatively low recurrence rates thereafter¹¹³. The relatively high MR recurrence rate associated with UMRA has led a number of investigators to examine alternative surgical therapies.

Recently, the issue of annulus re-shaping during annuloplasty has been addressed by some authors¹¹⁸. In contrast with rigid/semi-flexible plane annuloplasty rings which may flatten the natural saddle shape causing greater tension on chordae and leaflets, innovative annular rings mimic the shape of healthy mitral annulus^{119,120}.

Alternative Surgical Procedures

Messas and coworkers³ proposed to reduce leaflet tethering by cutting a limited number of critically positioned second-order chordae tendineae. Secondary chords are the most responsible chordae for leaflet restriction in CIMR, but are not required to prevent leaflet prolapse (Figure 3). Dividing secondary chordae in a sheep model of CIMR resulted in improved leaflet coaptation and reduced MR, without leaflet prolapse or decline in LV ejection fraction³. Other investigators have demonstrated, however, that second-order chordae cutting may adversely affect LV function¹²¹. A recent case report described no MR and improved LV function in a patient undergoing chordal cutting surgery¹²². The Group of Tirone David¹²³ has recently adopted the technique of chordal cutting for patients with CIMR. They divide all second-order chords arising from the affected PM (usually the posteromedial muscle) at their insertion on the anterior and posterior leaflets, and insert a slightly undersized (size 28 to 30) flexible posterior annuloplasty ring. They have performed this operation in more than 30 patients, with a perioperative mortality rate of 6%. Follow-up

Figure 3. Secondary chordae cut may improve leaflet coaptation.

Figure 4. Alfieri's edge-to-edge correction: creation of a double orifice.

echocardiography revealed trivial or mild MR in 97% of patients for as long as 24 months postoperatively. In addition, there has been no decrease in LV function in the early postoperative period. Although we are enthusiastic about this procedure at this time, the long-term results and durability of the repair remain to be seen.

Alfieri and colleagues^{124,125} have described an edge-to-edge MV leaflet repair technique for many different causes of MR (Figure 4). The technique is quick and relatively simple to perform. A suture is used to join the center of the anterior and posterior leaflets, creating a double orifice MV. A mitral annuloplasty ring is inserted because long-term results without an annuloplasty ring are suboptimal¹²⁵. Although many studies have indicated good results for the Alfieri repair technique, most had small numbers of patients with CIMR. An exception is the recent study by Bhudia and colleagues¹²⁶ that included 143 patients with ischemic cardiomyopathy. These investigators found a progressive increase in MR recurrence in CIMR patients, with more than 30% of patients having moderate-to-severe MR 1 year postoperatively.

They concluded that other MV repair techniques are required for this patient population.

Liel-Cohen and associates³⁰ devised an infarct placcation procedure to reverse LV remodeling in sheep. The infarcted region of the LV is plicated with mattressed sutures to reduce myocardial bulging and to bring the displaced PM tips back toward the anterior mitral annulus (Figure 5).

The plication process also reduces the proportion of LV circumference occupied by infarcted myocardium. Infarct plication for CIMR was recently described in humans. Ramadan and colleagues¹²⁷ performed plication of posterolateral myocardial scar without mitral annuloplasty in 3 patients. Two patients had no MR and 1 had trivial MR 7 months postoperatively. Although this technique appears promising, more data are required before it can be recommended for CIMR patients.

Menicanti and associates¹²⁸ devised a LV restoration procedure for the treatment of CIMR and dilated ischemic cardiomyopathy. The procedure consists of coronary revascularization, LV restoration with a Dor procedure, and imbrication of the PMs without a prosthetic ring (Figure 6 A, B). The Dor procedure may reduce MR in dilated ischemic cardiomyopathy by reducing LV size and improving PM orientation¹²⁹. These Authors have used this approach in 46 patients with previous anterior transmural MI and MR. Postoperative MR was mild or less in 84% of the patients.

Another complex surgical approach to CIMR, the papillary muscle sling, has been recently described by Hvass and colleagues¹³⁰. This technique consists of correcting abnormal PM displacement with an intraventricular Gore-Tex sling. The device is implanted through the left atrium and across the mitral orifice, encircling the trabecular base of both PMs (Figure 7). Tightening the sling with sutures decreases the distance between the PMs, and a moderately undersized mitral annuloplasty ring is inserted. A double ring is thereby produced: one inside the ventricle and one on the mitral annulus. These Authors have applied this technique in 10 patients, with reduced mitral tenting and decreased MR in all patients immediately postoperatively. However, the long-term effects of this technique are unknown.

Kron and associates⁶⁰ have described another technique, the surgical re-location of the posterior papillary muscle, for the treatment of CIMR, particularly in patients with severe restriction of the P3 segment of the mitral valve. A suture is used to connect the posterior PM to the mitral annulus, adjacent to the right fibrous trigone, and a mitral annuloplasty ring is inserted (Figure 8). The suture between the PM and the mitral annulus is shortened to alleviate tethering of the P3 segment and to increase leaflet coaptation. These authors have performed this procedure in 18 patients, with all patients having no or trace MR eight weeks postoperatively.

Finally, Fundaro and associates¹³¹ devised a relatively simple technique to ameliorate posterior leaflet tethering and restore normal distance between the annulus and PM (posterior mitral valve restoration). An incision is made at the base of the posterior leaflet and the basal chordae are transected to increase posterior leaflet

Figure 5. Left Ventricular plication reduces left ventricular bulging and papillary muscle displacement.

Ventricular Apex Wiew

Figure 6. Papillary muscle imbrication: a 2-0 polyester double-armed suture with a pledged is applied from the ventricular side to atrial side. The two arms of this stitch with a running suture were conducted toward the left trigone. The stitch runs a few millimeters from the mitral annulus biting atrial and ventricular muscle. The posterior annulus is completely bounded by this suture. The left trigone is reached, and the two arms of the suture are conducted from the atrial side to the ventricular side through the trigone just below the aortic valve. A 23-mm sizer is introduced into the mitral valve to create an undersized orifice but leave a surface area bigger than 3 cm², and the suture is tied over a second pledged. Then the ventricular restoration is performed.

mobility. The detached portion of the mitral annulus is then plicated and the resulting defect in the posterior leaflet is closed with a running suture. The plicated annulus is reinforced with a short Gore-Tex strip or posterior annuloplasty band (Figure 9). The data on this procedure are poor.

Experimental Procedures

The Alfieri MV repair technique has recently been applied percutaneously¹³². A double-armed clip device, deployed through the femoral vessels, was developed in a large animal model and is now undergoing trials in patients. The results for

Figure 7. Papillary muscle sling: a Gore-Tex sling is placed around the trabecular base of both papillary muscles.

Figure 8. Surgical Relocation of the posterior papillary muscle: the posterior papillary muscle is connected by a pledged suture to the mitral annulus.

this device are pending, but MR recurrence rates may be higher compared with the conventional Alfieri operation because a mitral annuloplasty ring is not inserted¹²⁴.

Percutaneous mitral annuloplasty has been recently described in large animal models of CIMR by two separate groups. Devices were inserted percutaneously into the coronary sinus in sheep¹³³ and dogs¹³⁴. Both studies revealed acute reductions in MR, but long-term animal studies are pending. Percutaneous annuloplasty offers the advantage of avoiding an operation, but has the potential disadvantage of coro-

Figure 9. Transection of basal chordae through an incision of the posterior mitral leaflet (A-B). This is followed by a plication of the annulus (C) and posterior annuloplasty with a Gore-Tex strip (D).

nary sinus perforation or thrombosis, or injury to the adjacent circumflex artery¹³⁵. In addition, the durability of this approach may be compromised by the coronary sinus having no fibrous connections to the mitral annulus.

Septolateral annular cinching was recently used by Tibayan and colleagues¹³⁶ in an ovine model of CIMR. Septolateral annular cinching is performed by anchoring a single suture to the midseptal annulus, then exteriorizing the suture through the posterior lateral annulus. The suture is tightened under echocardiographic guidance to reduce lateral displacement of the posterior PM. As opposed to undersized ring annuloplasty, septolateral annular cinching is not associated with impaired mobility of either the anterior or posterior leaflets¹³⁷. Septolateral annular cinching decreased ischemic MR and reduced the septolateral diameter in sheep¹³⁶, but clinical studies are pending.

The Coapsys device (Myocor, Maple Grove, Minnesota) is designed to restore septolateral annular geometry in patients with IMR¹³⁸. It is inserted through a sternotomy but without cardiopulmonary bypass. The device consists of two epicardial pads and an expanded polytetrafluoroethylene-coated subvalvular chord. The posterior pad has two heads that change the shape of the LV at the mitral annulus and PM level. The anterior pad is adjustable and is fixed after echocardiographically confirmed positioning of the posterior pad. The Coapsys device has been successfully used in a dog model¹⁴⁰, and is currently undergoing clinical assessment.

The CorCap Cardiac Support Device (CSD) (Acorn Cardiovascular, Inc., St. Paul, Minnesota)^{139,140} is a mesh-like device that is surgically implanted around the heart. The device is designed to provide circumferential myocardial wall support, and reduce wall stress and myocyte stretch.

In a recent study¹⁴⁰ it has been implanted in 24 patients with dilated cardiomyopathy, severe LV dysfunction, and advanced heart failure (NYHA class II-IV) at four centers in Italy and Sweden.

Investigators demonstrated improvements in cardiac structure and function as well as in patient functional status after CorCap CSD implantation. Nonetheless its efficacy in CIMR is still uncertain. Finally, Hung and associates² devised a Dacron patch inflatable balloon to reverse LV remodeling and reduce IMR. The balloon device is secured externally onto the infarcted myocardium and is inflated under echocardiographic guidance. The infarcted myocardium and PM is displaced inward toward the anterior mitral annulus, thereby decreasing leaflet tethering. The inflatable balloon has the benefit of not requiring cardiopulmonary bypass, but is yet to be tested in humans.

REFERENCES

1. Lamas GA, Mitchell GF, Flaker GC, et al. for the Survival and Ventricular Enlargement Investigators. Clinical significance of mitral regurgitation after acute myocardial infarction. *Circulation* 1997;96 (3):827–33.
2. Hung J, Guerrero JL, Handschumacher BS, Supple G, Sullivan S, Levine RA. Reverse ventricular remodeling reduces ischemic mitral regurgitation: echo-guided device application in the beating heart. *Circulation* 2002;106:2594–600.
3. Messas E, Pouzet B, Touchot B, et al. Efficacy of chordal cutting to relieve chronic persistent ischemic mitral regurgitation. *Circulation* 2003;108(Suppl 2):111–5.
4. Barzilai B, Gessler C, Perez JE, et al. Significance of Doppler detected mitral regurgitation in acute myocardial infarction. *Am J Cardiol* 1988;61:220–3.
5. Lehmann KG, Francis CK, Dodge HT, and the TIMI Study Group. Mitral regurgitation in early myocardial infarction: incidence, clinical detection, and prognostic implications. *Ann Intern Med* 1992;117:10–7.
6. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001;103 (13):1759–64.
7. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003;91:538–43.
8. Hickey MS, Smith LR, Muhlbaier LH, et al. Current prognosis of ischemic mitral regurgitation: implications for future management. *Circulation* 1988;78(Suppl 1):I-51–9.
9. Tcheng JE, Jackman JD Jr, Nelson CL, et al. Outcome of patients sustaining acute ischemic mitral regurgitation during myocardial infarction. *Ann Intern Med* 1992;117:18–24.
10. Frantz E, Weininger F, Oswald H, Fleck E. Predictors for mitral regurgitation in coronary artery disease. In: Vetter HO, Hetzer R, Schmutzler H, eds. *Ischemic mitral incompetence*. New York: Springer-Verlag, 1991:57.
11. Kishon Y, Oh JK, Schaff HV, Mullany CJ, Tajik AJ, Gersh BJ. Mitral valve operation in postinfarction rupture of a papillary muscle: immediate results and long-term follow-up of 22 patients. *Mayo Clinic Proceedings* 1992; 67(11): 1023–30.
12. Birnbaum Y, Chamoun AJ, Conti VR, Uretsky BF. Mitral regurgitation following acute myocardial infarction. *Coron Artery Dis* 2002;13(6): 337–44.
13. Burch GE, DePasquale NP, Phillips JH. Clinical manifestations of papillary muscle dysfunction. *Arch Intern Med*. 1963;112:112–117.
14. Burch GE, DePasquale NP, Phillips JH. The syndrome of papillary muscle dysfunction. *Am Heart J*. 1968;75:399–415.
15. Mittal AK, Langston M Jr, Cohn KE, Selzer A, Kerth WJ. Combined papillary muscle and left ventricular wall dysfunction as a cause of mitral regurgitation: an experimental study. *Circulation*. 1971;44:174–180.

16. Silverman ME, Hurst JW. The mitral complex: interaction of the anatomy, physiology, and pathology of the mitral annulus, mitral valve leaflets, chordae tendineae, and papillary muscles. *Am Heart J*. 1968;76:399–418.
17. Perloff JK, Roberts WC. The mitral apparatus: functional anatomy of mitral regurgitation. *Circulation*. 1972;46:227–239.
18. Ogawa S, Hubbard FE, Mardelli TJ, Dreifus LS. Cross-sectional echocardiographic spectrum of papillary muscle dysfunction. *Am Heart J*. 1979;97:312–321.
19. Godley RW, Wann LS, Rogers EW, Feigenbaum H, Weyman AE. Incomplete mitral leaflet closure in patients with papillary muscle dysfunction. *Circulation*. 1981;63:565–571.
20. Kaul S, Spotnitz WD, Glasheen WP, Touchstone DA. Mechanism of ischemic mitral regurgitation: an experimental evaluation. *Circulation*. 1991;84:2167–2180.
21. Dent JM, Spotnitz WD, Nolan SP, Jayaweera AR, Glasheen WP, Kaul S. Mechanism of mitral leaflet excursion. *Am J Physiol*. 1995;269:H2100–H2108.
22. He S, Fontaine AA, Schwammenthal E, Yoganathan AP, Levine RA. Integrated mechanism for functional mitral regurgitation: leaflet restriction versus coapting force: in vitro studies. *Circulation*. 1997;96:1826–1834.
23. Otsuji Y, Handschumacher MD, Schwammenthal E, Jiang L, Song JK, Guerrero JL, Vlahakes GJ, Levine RA. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. *Circulation*. 1997;96:1999–2008.
24. Kono T, Sabbah HN, Rosman H, Alam M, Jafri S, Goldstein S. Left ventricular shape is the primary determinant of functional mitral regurgitation in heart failure. *J Am Coll Cardiol*. 1992;20:1594–1598.
25. Sabbah HN, Rosman H, Kono T, Alam M, Khaja F, Goldstein S. On the mechanism of functional mitral regurgitation. *Am J Cardiol*. 1993;72:1074–1076.
26. Sabbah HN, Kono T, Stein PD, Mancini GB, Goldstein S. Left ventricular shape changes during the course of evolving heart failure. *Am J Physiol*. 1992;263:H266–H270.
27. Otsuji Y, Handschumacher MD, Liel-Cohen N, Tanabe H, Jiang L, Schwammenthal E, Guerrero JL, Nicholls LA, Vlahakes GJ, Levine RA. Mechanism of ischemic mitral regurgitation with segmental left ventricular dysfunction: three-dimensional echocardiographic studies in models of acute and chronic progressive regurgitation. *J Am Coll Cardiol*. 2001;37:641–648.
28. Llaneras MR, Nance ML, Streicher JT, Lima JA, Savino JS, Bogen DK, Deac RF, Ratcliffe MB, Edmunds LH Jr. Large animal model of ischemic mitral regurgitation. *Ann Thorac Surg*. 1994;57:432–439.
29. Gorman RC, McCaughan JS, Ratcliffe MB, Gupta KB, Streicher JT, Ferrari VA, St John-Sutton MG, Bogen DK, Edmunds LH Jr. Pathogenesis of acute ischemic mitral regurgitation in three dimensions. *J Thorac Cardiovasc Surg*. 1995;109:684–693.
30. Liel-Cohen N, Guerrero JL, Otsuji Y, Handschumacher MD, Rudski LG, Hunziker PR, Tanabe H, Scherrer-Crosbie M, Sullivan S, Levine RA. Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: insights from 3-dimensional echocardiography. *Circulation*. 2000;101:2756–2763.

31. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation*. 2000;102:1400–1406.
32. Kwan J, Shiota T, Agler DA, Popovic ZB, Qin JX, Gillinov MA, Stewart WJ, Cosgrove DM, McCarthy PM, Thomas JD. Geometric differences of the mitral apparatus between ischemic and dilated cardiomyopathy with significant mitral regurgitation: real-time three-dimensional echocardiography study. *Circulation*. 2003;107:1135–1140.
33. Lai DT, Tibayan FA, Myrmel T, Timek TA, Dagum P, Daughters GT, Liang D, Ingels NB Jr, Miller DC. Mechanistic insights into posterior mitral leaflet inter-scallop malcoaptation during acute ischemic mitral regurgitation. *Circulation*. 2002;106(suppl I):I40–I45.
34. Boltwood CM, Tei C, Wong M, Shah PM. Quantitative echocardiography of the mitral complex in dilated cardiomyopathy: the mechanism of functional mitral regurgitation. *Circulation*. 1983;68:498–508.
35. Kisanuki A, Minagoe S, Levine RA, Tei C. Isolated annular dilation does not usually cause important functional mitral regurgitation: comparison between patients with lone atrial fibrillation and those with idiopathic or ischemic cardiomyopathy. *J Am Coll Cardiol*. 2002;39:1651–1656.
36. Otsuji Y, Gilon D, Jiang L, He S, Leavitt M, Roy MJ, Birmingham MJ, Levine RA. Restricted diastolic opening of the mitral leaflets in patients with left ventricular dysfunction: evidence for increased valve tethering. *J Am Coll Cardiol*. 1998;32:398–404.
37. Jouan J, Tapia M, Cook RC, Lansac E, Acar C. Ischemic mitral valve prolapse: mechanisms and implications for valve repair. *Eur J Cardiothorac Surg*. 2004;26:1112–1117.
38. Frater RWM, Cornellissen P, Sisto D. Mechanisms of ischemic mitral insufficiency and their surgical correction. In: Vetter HO, Hetzer R, Schmutzler H, eds. *Ischemic Mitral Incompetence*. New York, NY: Springer-Verlag; 1991:117–130.
39. Messas E, Guerrero JL, Handschumacher MD, Chow CM, Sullivan S, Schwammenthal E, Levine RA. Paradoxical decrease in ischemic mitral regurgitation with papillary muscle dysfunction: insights from three dimensional and contrast echocardiography with strain rate measurement. *Circulation*. 2001;104:1952–1957.
40. Khankirawatana B, Khankirawatana S, Mahrous H, Porter TR. Assessment of papillary muscle function using myocardial velocity gradient derived from tissue Doppler echocardiography. *Am J Cardiol*. 2004;94:45–49.
41. Komeda M, Glasson JR, Bolger AF, Daughters GT II, Ingels NB Jr, Miller DC. Papillary muscle-left ventricular wall “complex.” *J Thorac Cardiovasc Surg*. 1997;113:292–301.
42. Schwammenthal E, Chen C, Benning F, Block M, Breithardt G, Levine RA. Dynamics of mitral regurgitant flow and orifice area; physiologic application of the proximal flow convergence method: clinical data and experimental testing. *Circulation*. 1994;90:307–322.
43. Hung J, Otsuji Y, Handschumacher MD, Schwammenthal E, Levine RA. Mechanism of dynamic regurgitant orifice area variation in functional mitral regurgitation: physiologic insights from the proximal flow convergence technique. *J Am Coll Cardiol*. 1999;33:538–545.

44. Glasson JR, Komeda M, Daughters GT, Bolger AF, Karlsson MO, Foppiano LE, Hayase M, Oesterle SN, Ingels NB Jr, Miller DC. Early systolic mitral leaflet "loitering" during acute ischemic mitral regurgitation. *J Thorac Cardiovasc Surg.* 1998;116:193–205.
45. Schwammenthal E, Popescu AC, Popescu BA, Freimark D, Hod H, Eldar M, Feinberg MS. Mechanism of mitral regurgitation in inferior wall acute myocardial infarction. *Am J Cardiol.* 2002;90:306–309.
46. Miller DC. The three-dimensional geometry of the mitral valve: implications for surgical therapy. Proceedings of the 84th Annual Meeting of the American Association for Thoracic Surgery, Toronto, Ontario, 2004.
47. Condado JA, Vélez-Gimón. Catheter-based approach to mitral regurgitation. *J Intervent Cardiol* 2003;16:523–34.
48. Kodavatiganti R. Intraoperative assessment of the mitral valve by transoesophageal echocardiography: an overview. *Ann Card Anaest* 2002;5:27–34.
49. Gorman RC, Gorman JH III, Edmunds LH Jr. Ischemic mitral regurgitation. In: Cohn LH, Edmunds LH Jr, eds. *Cardiac surgery in the adult*. New York: McGraw-Hill, 2003:751–69.
50. Otsuji Y, Kumanohoso T, Yoshifuku S, et al. Isolated annular dilation does not usually cause important functional mitral regurgitation: comparison between patients with lone atrial fibrillation and those with idiopathic or ischemic cardiomyopathy. *J Am Coll Cardiol* 2002;39:1651–6.
51. Iung B. Management of ischaemic mitral regurgitation. *Heart* 2003;89:459–64.
52. Kumanohoso T, Otsuji Y, Yoshifuku S, et al. Mechanism of higher incidence of ischemic mitral regurgitation in patients with inferior myocardial infarction: quantitative analysis of left ventricular and mitral valve geometry in 103 patients with prior myocardial infarction. *J Thorac Cardiovasc Surg* 2003;125:135–43.
53. Miller GE, Kerth WJ, Gerbode F. Experimental papillary muscle infarction. *J Thorac Cardiovasc Surg* 1968;56:611–6.
54. Messas E, Guerrero JL, Handschumacher MD, et al. Paradoxical decrease in ischemic mitral regurgitation with papillary muscle dysfunction: insights from three-dimensional and contrast echocardiography with strain rate measurement. *Circulation* 2001;104:1952–7.
55. Carabello B. The pathophysiology of mitral regurgitation. *J Heart Valve Dis* 2000;9:600–8.
56. Messas E, Guerrero JL, Handschumacher MD, et al. Chordal cutting. A new therapeutic approach for ischemic mitral regurgitation. *Circulation* 2001;104:1958–63.
57. Corin WJ, Monrad ES, Murakami T, et al. The relationship of afterload to ejection performance in chronic mitral regurgitation. *Circulation* 1987;76:59–67.
58. Jackson BM, Gorman JH III, Moainie SL, et al. Extension of borderzone myocardium in postinfarction dilated cardiomyopathy. *J Am Coll Cardiol* 2002;40:1160–7.
59. Rumberger JA. Ventricular dilatation and remodeling after myocardial infarction. *Mayo Clin Proc* 1994;64:664–74.
60. Kron IL, Green GR, Cope JT. Surgical relocation of the posterior papillary muscle in chronic ischemic mitral regurgitation. *Ann Thorac Surg* 2002;74:600–1.

61. Lehmann KG, Francis CK, Dodge HT. Mitral regurgitation in early myocardial infarction. Incidence, clinical detection, and prognostic implications. TIMI Study Group. *Annals of Internal Medicine* 1992;117(1):10-7.
62. Bursi F, Enriquez-Sarano M, Nkomo VT, et al. Heart Failure and Death after Myocardial Infarction in the Community: the Emerging Role of Mitral Regurgitation. *Circulation* 2005; 11 (3): 254-6.
63. Desjardins VA, Enriquez-Sarano M, Tajik AJ, Bailey KR, Seward JB. Intensity of murmurs correlates with severity of valvular regurgitation. *American Journal of Medicine* 1996; 100(2):149-56.
64. Enriquez-Sarano M, Rossi A, Seward JB, Bailey KR, Tajik AJ. Determinants of pulmonary hypertension in left ventricular dysfunction. *Journal of the American College of Cardiology* 1997; 29(1):153-9.
65. Hickey MS, Smith LR, Muhlbaier LH, et al. Current prognosis of ischemic mitral regurgitation. Implications for future management. *Circulation* 1988;78(3 Pt 2):I51-9.
66. Spain MG, Smith MD, Grayburn PA, Harlamert EA, DeMaria AN. Quantitative assessment of mitral regurgitation by Doppler color flow imaging: angiographic and hemodynamic correlations. *Journal of the American College of Cardiology* 1989;13(3):585-90.
67. Roger VL, Jacobsen SJ, Weston SA, et al. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. *Annals of Internal Medicine* 2002;136(5): 341-8.
68. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *Journal of the American Society of Echocardiography* 2003; 16(7): 777-802.
69. Pierard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. *N Engl J Med* 2004; 351(16): 1627-34.
70. Lancellotti P, Troisfontaines P, Toussaint AC, Pierard LA. Prognostic importance of exercise-induced changes in mitral regurgitation in patients with chronic ischemic left ventricular dysfunction. *Circulation* 2003; 108(14): 1713-7.
71. Miller DC. Ischemic mitral regurgitation redux-to repair or to replace? *J Thorac Cardiovasc Surg* 2000;122:159-62.
72. 2004 Heart and stroke statistical update. available at: www.americanheart.org (accessed July 15, 2008).
73. Schwammenthal E, Chen C, Benning F, Block M, Breithardt G, Levine RA. Dynamics of mitral regurgitant flow and orifice area; physiologic application of the proximal flow convergence method: clinical data and experimental testing. *Circulation*. 1994;90:307-322.
74. Keren G, Katz S, Strom J, Sonnenblick EH, LeJemtel TH. Dynamic mitral regurgitation: an important determinant of the hemodynamic response to load alterations and inotropic therapy in severe heart failure. *Circulation*. 1989;80:306-313.
75. Rodbard S, Williams F. The dynamics of mitral insufficiency. *Am Heart J*. 1954;48:521-539.
76. Heinle SK, Tice FD, Kisslo J. Effect of dobutamine stress echocardiography on mitral regurgitation. *J Am Coll Cardiol*. 1995;25:122-127.

77. Keren G, Bier A, Strom JA, Laniado S, Sonnenblick EH, LeJemtel TH. Dynamics of mitral regurgitation during nitroglycerin therapy: a Doppler echocardiographic study. *Am Heart J*. 1986;112:517–525.
78. Stevenson LW, Bellil D, Grover-McKay M, Brunken RC, Schwaiger M, Tillisch JH, Schelbert HR. Effects of afterload reduction (diuretics and vasodilators) on left ventricular volume and mitral regurgitation in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1987;60:654–658.
79. Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Walden J, Woo M. Sustained reduction in valvular regurgitation and atrial volumes with tailored vasodilator therapy in advanced congestive heart failure secondary to dilated (ischemic or idiopathic) cardiomyopathy. *Am J Cardiol*. 1991;67:259–263.
80. Rosario LB, Stevenson LW, Solomon SD, Lee RT, Reimold SC. The mechanism of decrease in dynamic mitral regurgitation during heart failure treatment: importance of reduction in the regurgitant orifice size. *J Am Coll Cardiol*. 1998;32:819–824.
81. Levine AB, Muller C, Levine TB. Effects of high-dose lisinoprilisobutide dinitrate on severe mitral regurgitation and heart failure remodeling. *Am J Cardiol*. 1998;82:1299–1301.
82. Kizilbash AM, Willett DL, Brickner ME, Heinle SK, Grayburn PA. Effects of afterload reduction on vena contracta width in mitral regurgitation. *J Am Coll Cardiol*. 1998;32:427–431.
83. Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *N Engl J Med*. 1988;319:80–86.
84. Levine and Schwammenthal Ischemic Mitral Regurgitation Downloaded from circ.ahajournals.org by on July 24, 2008
85. Sr John Sutton M, Pfeffer MA, Moye L, Plappert T, Rouleau JL, Lamas G, Rouleau J, Parker JO, Arnold MO, Sussex B, Braunwald E. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation*. 1997;96:3294–3299.
86. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, Shelton B. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of the SOLVD echocardiography substudy. *Circulation*. 1995;91:2573–2581.
87. Konstam MA, Kronenberg MW, Rousseau MF, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinan D; SOLVD (Studies of Left Ventricular Dysfunction) Investigators. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. *Circulation*. 1993;88:2277–2283.
88. Carabello BA, Nakano K, Corin W, Biederman R, Spann JF Jr. Left ventricular function in experimental volume overload hypertrophy. *Am J Physiol*. 1989;256:H974–H981.
89. Tsutsui H, Spinale FG, Nagatsu M, Schmid PG, Ishihara K, DeFreyte G, Cooper G IV, Carabello BA. Effects of chronic beta-adrenergic blockade on the left ventricular and cardiocyte abnormalities of chronic canine mitral regurgitation. *J Clin Invest*. 1994 93:2639–2648.

90. Lowes BD, Gill EA, Abraham WT, Larrain JR, Robertson AD, Bristow MR, Gilbert EM. Effects of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure. *Am J Cardiol*. 1999;83:1201–1205.
91. Capomolla S, Febo O, Gnemmi M, Riccardi G, Opasich C, Caporotondi A, Mortara A, Pinna GD, Cobelli F. Beta-blockade therapy in chronic heart failure: diastolic function and mitral regurgitation improvement by carvedilol. *Am Heart J*. 2000;139:596–608.
92. Remme WJ, Riegger G, Hildebrandt P, Komajda M, Jaarsma W, Bobbio M, Soler-Soler J, Scherhag A, Lutiger B, Ryden L. The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction: the carvedilol and ACE inhibitor remodeling mild heart failure evaluation trial (CARMEN). *Cardiovasc Drugs Ther*. 2004;18:57–66.
93. Dougherty RN, Whalley GA, Walsh HA, Gamble GD, Lopez-Sendon J, Sharpe N; CAPRICORN Echo Substudy Investigators. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. *Circulation*. 2004;109:201–206.
94. Tei C, Horikiri Y, Park JC, Jeong JW, Chang KS, Toyama Y, Tanaka N. Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. *Circulation*. 1995;91:2582–2590.
95. Mukherjee R, Brinsa TA, Dowdy KB, Scott AA, Baskin JM, Deschamps AM, Lowry AS, Escobar GP, Lucas DG, Yarbrough WM, Zile MR, Spinale FG. Myocardial infarct expansion and matrix metalloproteinase inhibition. *Circulation*. 2003;107:618–625.
96. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, Loh E, Kocovic DZ, Fisher WG, Ellestad M, Messenger J, Kruger K, Hilpisch KE, Hill MR; Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation*. 2003;107:1985–1990.
97. Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorcsan J III. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: insights from mechanical activation strain mapping. *J Am Coll Cardiol*. 2004;44:1619–1625.
98. Breithardt OA, Sinha AM, Schwammenthal E, Bidaoui N, Markus KU, Franke A, Stellbrink C. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. *J Am Coll Cardiol*. 2003;41:765–770.
99. Condado JA, Vélez-Gimón. Catheter-based approach to mitral regurgitation. *J Intervent Cardiol*. 2003;16:523–34.
100. Canadian Cardiovascular Consensus 2004: surgical management of valvular heart disease. *Can J Cardiol*. 2004;20:33E–49E.
101. Mallidi HR, Pelletier MP, Lamb J, et al. Late outcomes in patients with uncorrected mild to moderate mitral regurgitation at the time of isolated coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2004;127:636–44.
102. Aklog L, Filsoufi F, Flores KQ, et al. Does coronary artery bypass grafting alone correct moderate ischemic mitral regurgitation? *Circulation*. 2001;12(Suppl 1):68–75.

103. Lam BK, Gillinov AM, Blackstone EH, et al. Importance of moderate ischemic mitral regurgitation. *Ann Thorac Surg* 2005;79:462–70.
104. Wong DR, Agnihotri AK, Hung JW, et al. Long-term survival after surgical revascularization for moderate ischemic mitral regurgitation. *Ann Thorac Surg* 2005;80:570–8.
105. David TE, Uden DE, Strauss H. The importance of the mitral apparatus in left ventricular function after correction of mitral regurgitation. *Circulation* 1983;68(Suppl 2):76–82.
106. David TE, Armstrong S, Sun Z. Left ventricular function after mitral valve surgery. *J Heart Valve Dis* 1995;4(Suppl):175–80.
107. Calafiore AM, Di Mauro M, Gallina S, et al. Mitral valve surgery for chronic ischemic mitral regurgitation. *Ann Thorac Surg* 2004;77:1989–97.
108. Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg* 2001;122:1125–41.
109. Grossi EA, Goldberg JD, LaPietra A, et al. Ischemic mitral valve reconstruction and replacement: comparison of longterm survival and complications. *J Thorac Cardiovasc Surg* 2001;122:1107–24.
110. Al-Radi OO, Austin PC, Tu JV, David TE, Yau TM. Mitral repair versus replacement for ischemic mitral regurgitation. *Ann Thorac Surg* 2005;79:1260–7.
111. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;115:381–6.
112. McCarthy PM. Does the intertrigonal distance dilate? Never say never. *J Thorac Cardiovasc Surg* 2002;124:1078–9.
113. McGee EC, Gillinov AM, Blackstone EH, et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 2004;128:916–24.
114. Bolling SF, Deeb GM, Bach DS. Mitral valve reconstruction in elderly, ischemic patients. *Chest* 1996;109:35–40.
115. Tahta SA, Oury JH, Maxwell JM, Hiro SP, Duran CM. Outcome after mitral valve repair for functional ischemic mitral regurgitation. *J Heart Valve Dis* 2002;11:11–8.
116. von Oppell UO, Stemmet F, Brink J, Commerford PJ, Heijke SA. Ischemic mitral valve repair surgery. *J Heart Valve Dis* 2000;9:64–74.
117. Hung J, Papakostas L, Tahta SA, et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. *Circulation* 2004; 110(Suppl 2):85–90.
118. Votta E, Maisano F, Bolling SF, Alfieri O, Montecvecchi FM, Redaelli A. The Geoform disease-specific annuloplasty system: a finite element study. *Ann Thorac Surg*. 2007;84(1):92–101.
119. Salgo IS, Gorman JH, Gorman RC, et al. Effect of Annular Shape on Leaflet Curvature in Reducing Mitral Leaflet Stress. *Circulation*. 2002; 106:711–717.
120. Jimenez JH, Yoganathan AP, et al. Effects of a saddle shaped annulus on mitral valve function and chordal force distribution: An in vitro Study. *Annals of Biomedical Engineering*. Vol. 31, pp. 1171–1181, 2003.

121. Rodriguez F, Langer F, Harrington KB, et al. Importance of mitral valve second-order chordae for left ventricular geometry, wall thickening mechanics, and global systolic function. *Circulation* 2004;110(Suppl 2):115–22.
122. Yamamoto H, Iguro Y, Sakata R, Arata K, Yotsumoto G. Effectively treating ischemic mitral regurgitation with chordal cutting in combination with ring annuloplasty and left ventricular reshaping approach. *J Thorac Cardiovasc Surg* 2005;130:589–90.
123. Borger MA, Alam A, Murphy PM, Doenst T, David TE. Chronic Ischemic Mitral Regurgitation: Repair, Replace or Rethink?. *Ann Thorac Surg* 2006; 81: 1153-61.
124. Alfieri O, Maisano F, De Bonis M, et al. The double orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg* 2001;122:674–81.
125. Maisano F, Caldarola A, Blasio A, De Bonis M, La Canna G, Alfieri O. Midterm results of edge-to-edge mitral valve repair without annuloplasty. *J Thorac Cardiovasc Surg* 2003; 126:1987–97.
126. Bhudia SK, McCarthy MM, Smedira NG, et al. Edge-to-edge (Alfieri) mitral repair. *Ann Thorac Surg* 2004;77:1598–606.
127. Ramadan R, Al-Attar N, Mohammadi S, et al. Left ventricular infarct plication restores mitral function in chronic ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 2005;129:440-2.
128. Menicanti L, Di Donato M, Frigoiola A, et al. Ischemic mitral regurgitation: intraventricular papillary muscle imbrication without mitral ring during left ventricular restoration. *J Thorac Cardiovasc Surg* 2002;123:1041–50.
129. Sabatier M, Di Donato M, Montiglio F, Toso A, Maioli M. Efficacy of endoventricular patch plasty in large postinfarction akinetic scar and severe left ventricular dysfunction: comparison with a series of large dyskinetic scars. *J Thorac Cardiovasc Surg* 1998;116:50-9.
130. Hvass U, Tapia M, Baron F, Pouzet B, Shafy A. Papillary muscle sling: a new functional approach to mitral repair in patients with ischemic left ventricular dysfunction and functional mitral regurgitation. *Ann Thorac Surg* 2003;75: 809-11.
131. Fundaro P, Pocar M, Moneta A, et al. Posterior mitral valve restoration for ischemic regurgitation. *Ann Thorac Surg* 2004;77:729-30.
132. Fann JI, St Goar FG, Komtebedde J, et al. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. *Circulation* 2004;110:988-9.
133. Daimon M, Shiotani T, Gillinov AM, et al. Percutaneous mitral valve repair for chronic ischemic mitral regurgitation: a real-time three-dimensional echocardiographic study in an ovine model. *Circulation* 2005;111:2183–9.
134. Maniu CV, Patel DG, Reuter DG, et al. Acute and chronic reduction of functional mitral regurgitation in experimental heart failure by percutaneous mitral annuloplasty. *J Am Coll Cardiol* 2004;44:1652– 61.
135. Singh SK, Borger MA. Percutaneous valve replacement: fact or fiction? *Can J Cardiol* 2005;21:829-32.
136. Tibayan F, Rodriguez F, Langer F, et al. Does septal-lateral annular cinching work for chronic ischemic mitral regurgitation? *J Thorac Cardiovasc Surg* 2004;127:654–63.
137. Timek TA, Dagum P, Glasson JR, et al. Restricted posterior leaflet motion after mitral ring annuloplasty. *Ann Thorac Surg* 1999;68:2100–6.

138. Fukamachi K, Inoue M, Popovic' ZB, et al. Off-pump mitral valve repair using the Coapsys device: a pilot study in a pacing-induced mitral regurgitation model. *Ann Thorac Surg* 2004;77:688-93.
139. Konertz W, Rombeck B, Horz H. Short-term safety of the Acorn cardiac support device in patients with advanced heart failure. *J Am Coll Cardiol* 2000; 35:182A.
140. Livi U, Alfieri O, Vitali E, et al. One-year clinical experience with the Acorn CorCap cardiac support device: results of a limited market release safety study in Italy and Sweden. *Ital Heart J.* 2005 Jan;6(1):59-65

2

Five-Year Echocardiographic Results of Combined Undersized Mitral Ring Annuloplasty and Coronary Artery Bypass Grafting for Chronic Ischemic Mitral Regurgitation

Sandro Gelsomino, MD, Roberto Lorusso, MD, PhD, Giuseppe De Cicco, MD,
Irene Capecchi, MD, Carlo Rostagno, MD, Sabina Caciolli, MD, Stefano Romagnoli, MD,
Ugo Dabrot, MD, Pierluigi Stefano, MD, Gian Franco Gensini, MD.

Published in: Eur Heart J. 2008; 29(2):231-40

ABSTRACT

Aims. We present 5-year echocardiographic results of combined undersizing mitral ring annuloplasty (UMRA) and coronary artery bypass grafting (CABG) in ischemic mitral regurgitation (CIMR).

Methods and Results. Two-hundred-fifty-one patients (age 68.4 ± 8.1 , 62.5% male) undergoing combined CABG and UMRA in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and March 2007, were prospectively enrolled in the study. Median follow up was 32.9 months (interquartile range [IQR] 17.5-51.6). Fourteen patients with significant residual mitral regurgitation (MR) needing immediate intraoperative revision (n=3) or at discharge (n=11) were excluded from the study. Serial echocardiograms were performed in 220 survivors at baseline, discharge and annually thereafter. Additionally, 17 patients died (2 early and 15 late deaths) and were also excluded from the study. MR remained stable at 1 year and re-increased at 3 years ($p<0.001$) and 5 years ($p<0.001$). Five-year actuarial survival was 83.2 ± 4.4 . Five-year freedom from reoperation for failed repair was $78.2 \pm 4.9\%$. Mean systolic and diastolic diameters decreased significantly at discharge ($p=0.001$ and $p=0.01$, respectively) and at early follow up ($p=0.004$ and $p=0.02$) but was raised at 3 years ($p<0.001$) and 5 years ($p<0.001$). Systolic and diastolic sphericity indexes improved at discharge ($p<0.001$), remained stable at 1-year but they re-increased at 3-year control ($p=0.006$ and $p=0.03$, respectively) with a late raise exceeding the preoperative value ($p<0.001$). Left ventricular reverse remodeling was observed in 44.2% of the study population with 10.3% of patients showing further left ventricular dilatation. At multivariable model, end-systolic volume ≥ 145 ml, systolic sphericity Index ≥ 0.7 , Myocardial performance Index ≥ 0.9 and wall motion score Index ≥ 1.5 were predictors of recurrent MR.

Conclusions Our findings emphasize the need for improved repair technique and better patient selection to identify patients with anticipated repair failure who could benefit more from valve replacement or other procedure directly addressing ventricular tethering.

INTRODUCTION

Despite of improvements in mitral reparative techniques in the recent years¹, chronic ischemic mitral regurgitation (CIMR) still remains a challenging surgical problem. Combined coronary artery bypass grafting (CABG) and annular reduction with an annuloplasty ring (undersized mitral ring annuloplasty, UMRA) is the most common surgical technique employed to relieve ischemic regurgitation². Nonetheless, conflicting data are reported in the literature about long-term effectiveness of this approach³⁻⁷.

In the present study, we present 5-year echocardiographic results after combined UMRA and CABG in terms of recurrence of mitral regurgitation (MR), global and local LV remodeling and left ventricular reverse remodeling (LVRR). We also explore potential useful predictors of recurrence of MR following combined undersized annuloplasty and coronary artery bypass.

METHODS

PATIENTS POPULATION

Chronic ischemic mitral regurgitation was defined as the combination of mild-to-severe MR with 1) Prior myocardial infarction (MI) >16 days; 2) seventy-five percent or greater stenosis of at least one coronary vessel; 3) a corresponding regional wall motion abnormality; 4) type IIIb leaflet dysfunction following Carpentier's classification⁸ with or without annular dilatation.

Exclusion criteria were: 1) degenerative or other non-ischemic etiology; 2) ischemic isolated type I or type II dysfunction⁸; 3) additional mitral valve repair procedures; 4) other valvular or congenital heart diseases.; 5) previous cardiac surgery/percutaneous transluminal coronary angioplasty; 6) atrial fibrillation or sinus rhythm with heart rate at rest >100 bts/min.

Two-hundred-fifty-one patients undergoing combined CABG and UMRA in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and March 2007, were prospectively enrolled in the study (Table 1). Clinical follow up information was obtained from all survivors through outpatient visits and phone calls and was 100% complete. Median follow up was 32.9 months (interquartile range [IQR] 17.5-51.6).

Following the World Medical Association guidelines concerning ethical principles for medical research involving human subjects⁹, the study was approved by Institutional Ethics Board. Furthermore, all patients gave their informed consent.

Table 1. Perioperative data (n=251).

Age (years)	68.4 ± 8.1
Gender M/F	155/93 (62.5/37.5)
NYHA class	3.2 ± 0.6
CCS angina class	3.09 ± 0.4
Euroscore	
Additive	8.0 ± 4.3
Logistic	13.6 ± 6.1
Hypertension	92 (36.6)
Diabetes	71 (28.6)
COPD	32 (12.7)
Chronic renal disease	26 (10.3)
Cerebral vascular disease	15 (6.0)
Peripheral vascular disease	11 (4.3)
Familiar history	101 (40.2)
Myocardial infarction	
>3 months	197 (78.4)
≤3 months	54 (21.6)
Inferior/Posterior	122 (48.6)
Anterior/Septal	22 (8.8)
Lateral	49 (19.5)
Combined	58 (23.1)
Diseased coronary vessels	2.4 ± 0.5
1	15 (6.0)
2	107 (42.6)
≥3	129 (51.4)
Left Main	38 (15.1)
Medications	
Angiotensin-converting enzyme inhibitors	197 (78.4)
B-adrenergic blockers	132 (52.6)
Long-acting nitrates	109 (43.4)
Diuretics	185 (73.7)
Digitalis	50 (19.9)
Calcium antagonists	33 (13.1)
Preoperative IABP	11 (4.3)
Surgery	
Cardioplegia	
Antegrade	218 (86.8)
Antegrade and Retrograde	33 (13.2)
CPB time (min)	123 ± 31
CCL time (min)	92 ± 18

Surgical Approach	
Left atriotomy	207 (82.4)
Transseptal	25 (10.0)
Transseptal extended to LA roof	19 (7.6)
Ring	
*Carpentier Classic	133 (52.9)
*Physio	118 (47.1)
Ring size (mm)	27.4 ± 1.5
24 mm	10 (4.1)
26 mm	92 (36.6)
28 mm	112 (44.6)
30 mm	37 (14.7)
CABG	
Anastomoses/patient	2.2 ± 1.1
Arterial graft/patient	1.07 ± 0.1

Continuous variables are presented as mean±standard deviation; Discrete variables are presented as percentage. Abbreviations: M/F=Male/Female; NYHA=New York Heart Association; CCS=Canadian Cardiovascular Society; COPD=Chronic obstructive pulmonary disease; IABP=Intaaortic balloon pump; CPB=Cardiopulmonary bypass; CCL=(Aortic) Cross-clamp; MR=Mitral regurgitation; CABG=Coronary artery bypass grafting. *Edwards LifeSciences, Irvine, CA.

SURGERY

All patients underwent associated coronary artery bypass grafting. For the purpose of this study, complete revascularization was accomplished when, at least one graft was placed distal to an approximately 50% diameter narrowing in each of the three major vascular system in which arterial narrowing of this severity was noted in a vessel ≥ 1.5 mm of diameter. It was not considered necessary to bypass all obstructed diagonal branches of the anterior descending or marginal branches of the circumflex coronary arteries for a classification of complete revascularization. Following this definition 100% patients underwent complete revascularization.

The ring size was determined by standard measurements of the inter-trigonal distance and anterior leaflet height. A downsizing by two ring sizes was performed in all patients. After cardiopulmonary bypass (CPB), a transesophageal echocardiography (TEE) was performed to assess residual MR: leaflet coaptation ≥ 0.5 cm, MR ≤ 1 and systolic MV area $> 2\text{cm}^2$ was assessed as successful repair. Three patients needed immediate intraoperative revision for failed repair: all underwent mitral valve replacement and were excluded from the study.

ECHOCARDIOGRAPHIC MEASUREMENTS AND CALCULATIONS

The clinical echocardiographic evaluation was as follows. A transthoracic echocardiogram (TTE) and a TEE were performed within 5 days before surgery and serial TTE were performed at discharge and annually thereafter. Eleven patients (4.4%) with residual MR defined as the insufficiency $\geq 2+$ following valve repair documented at discharge, were excluded from the study. Five-year echocardiograms were available from 61 patients (27.7%). This patient dropout was independent of the disease status and totally due to the different number of patients reaching different study intervals (1-year, 187 patients [85%]; 3-year 122 [55.4%]). Echocardiographic studies were carried out on Acuson Sequoia imaging device equipped with a 3.5-MHz ultrasound transducer (Acuson Corporation, Mountain View, CA). Standard parasternal and apical views (long axis, short-axis, 2-4-5-chamber views) were employed. The reliability of echocardiographic measurements was assessed by calculating between-observer (IC and CR) interval of agreements of main direct measures used in this study in a different group of 20 subjects (10 MR)¹¹.

MITRAL REGURGITATION

The following quantitative measurements were simultaneously employed to grade the severity of MR and final results were averages of measured values¹²⁻¹⁴: (1) Quantitative Doppler. (2) Proximal Isovelocity Surface Area (PISA). For each measurement a minimum of three cardiac cycles was averaged. The respective thresholds for mild, moderate and severe MR were <30 , 30-59 and ≥ 60 ml/beat for regurgitant volume (RV), <30 , 30-49 and $\geq 50\%$ for regurgitant fraction (RF), <20 , 20-39 and $\geq 40\text{mm}^2$ for effective regurgitant orifice (ERO), respectively. In patients with no or trivial MR by color Doppler, RV and RF were used as calculated, and ERO was assumed as null.

The tenting area (TA) was measured by the area enclosed between the annular plane and mitral leaflets from the parasternal long-axis view at mid-systole. The distance between leaflet coaptation and the mitral annulus plane at early and end systole measured displacement of mitral coaptation toward the LV apex^{15,16}. Mitral annular areas were obtained from mitral annular dimensions in apical long-axis, 4-chamber, and 2-chamber views, using an ellipsoid assumption¹⁷.

Recurrent MR was the insufficiency $\geq 2+$ at follow up appointments in patients with no/trivial MR at discharge.

GLOBAL LV REMODELING

LV volumes and left ventricular ejection fraction (LVEF) were assessed by the bi-apical Simpson disk method¹⁸. According to Stellbrink et coworkers¹⁹ a decrease

in LV end systolic volume >15% from baseline value was considered LVRR. The myocardial performance index (MPI) was measured using the method described by Tei et al.²⁰. Sphericity indexes were obtained at end diastole and end systole (SI_D and SI_S, respectively) as the volume of the left ventricle divided by the volume of a sphere with a diameter equal to the longest axis of the left ventricle measured in the apical view²¹. The wall motion score index (WMSI) was calculated according to a 17-segment model²²

LOCAL LV REMODELING

The displacement of papillary muscles (PMs) was quantified as distances from well-defined anatomic landmarks at early and end systole¹⁵. Lateral and posterior displacements of anterior papillary muscles (APM) and posterior papillary muscles (PPM) were measured as distances from these fixed references. Separation between papillary muscles was directly measured (from body to body of PMs). In the long-axis view the apical displacement of the PPM was measured as the distance between the papillary muscle head and the fixed inter-valvular fibrosa (annular-papillary distance). The WMSI of the basal and mid-posterior and inferior segments for the PPM and of basal and mid-lateral and anterior segments for the APM were calculated²³.

STATISTICAL ANALYSIS

The sample size was determined by GraphPad StatMate release 2.00 (GraphPad Prism Software, Inc, San Diego, CA), on the basis of preliminary data obtained by echocardiography and was determined on the basis of the following assumptions: Type I error of 0.05 (two-sided), power of 80%, difference in end systolic volume between patients with or without recurrent mitral regurgitation of 0.78, standard deviation of 2.4. The calculated study population was 300. However 256 patients were recruited to allow for possible analytic problems while processing the or other eventualities potentially leading to patient attrition. Continuous variables are presented as mean and standard deviation (SD), categorical variables as n/N (%), odds ratios as OR, and pertinent 95% confidence intervals as CI. The bivariate association between the independent variables and recurrent mitral regurgitation was assessed by the Student's t-test, Mann Whitney U test, χ^2 test and Fisher exact test where appropriate. Echocardiographic variables over time were analyzed by means of ANOVA repeated measures followed by Tukey post-hoc test and Friedman test, where appropriate to detect differences at different study points (discharge vs. baseline; 1-year vs. discharge; 3-year vs. 1-year and 5-year vs. 3-year).

Multivariable logistic regression analysis by means of a backward stepwise algorithm (cut-off for entry 0.05, for removal 0.10) was performed to select independent

predictors of recurrent regurgitation. Model assumptions (linearity and additivity assumptions) were checked by piecewise cubic polynomials (spilne functions) and pooled interaction test²⁴, respectively, and found to be satisfied. Goodness of fit of the final logistic regression models was assessed with the Hosmer–Lemeshow statistic²⁵ and predictive accuracy was assessed by the concordance (c) index²⁴. Internal validation of predictors generated by multivariable logistic regression was performed by means of bootstrapping techniques, with 1000 cycles and generation of OR and bias corrected 95% CI²⁴.

Optimal cutoff values were determined as the rounding cut-off that gives the maximum sum of sensitivity and specificity. This value should be the shoulder at the top left of the ROC (receiver operating characteristic curve). Bootstrapping techniques were employed to validate the results. Cumulative probability for death and reoperation were estimated by use of the Kaplan-Meier method.

SPSS 12.0 (SPSS, Chicago, IL, USA) and Stats Direct 2.5.7 (StatsDirect, Sale, UK) were used for these calculations. Significance for hypothesis testing was set at the 0.05 two-tailed level.

RESULTS

OVERALL SURVIVAL

Early (30-day) mortality was 0.8% (n= 2, respiratory failure and low-output syndrome). During the follow-up 15 patients died: six of cardiac causes (heart failure [n=3; 36, 45, and 54 months], myocardial infarction [n=2; 31 and 42 months] and arrhythmia [n=1; 59 months]), eight of non-cardiac causes (multiorgan failure [n=1; 6 months], respiratory failure [n=1; 14 months], infection [n=2; 3, 8 months], stroke [n=2; 12, 43 months] and malignancy [n=2; 55, 59 months]) and 1 of sudden, unexplained death (22 months). Five-year actuarial survival was 83.2 ± 4.4 (Figure 1).

RESIDUAL AND RECURRENT MR

Among 220 patients surviving CABG and reductive annuloplasty (Figure 2) mean MR remained stable at 1 year and re-increased at 3-year ($p<0.001$) and 5-year studies ($p<0.001$, Table 2). At 5-year echocardiography 17 patients (27.8%) had no/trivial recurrent MR, 17 (27.8%) had MR 2+, 19 (31.1%) 3+ and 8 (13.1%) 4+ (Figure 3). Seventeen patients underwent reoperation for failed repair due to recurrent MR: four (3.7%) had a re-MV repair and 13 (12.1%) underwent mitral valve replacement. Freedom from reoperation for failed repair was $78.2 \pm 4.9\%$ (Figure 4).

Figure 1. Five-year survival and 95% Confidence interval (dotted lines) following undersized mitral ring annuloplasty and coronary artery bypass grafting in patients with ischemic mitral regurgitation.

GLOBAL LV REMODELING AND LV REVERSE REMODELING

Figure 2. Patient selection. Abbreviations: UMRA=Undersized mitral ring annuloplasty; CABG=Coronary artery bypass grafting; MR=Mitral regurgitation. See text for definitions.

Ventricular diameters and left atrial dimensions reduced significantly at discharge ($p < 0.001$, $p = 0.005$, $p = 0.002$, respectively), showing no further significant change at subsequent controls (Table 3). Mean ESV and EDV decreased significantly at discharge ($p = 0.001$ and $p = 0.01$, respectively) and at early follow up ($p = 0.004$ and $p = 0.02$) but re-increased at 3-year ($p < 0.001$) and 5-year ($p < 0.001$) studies. Furthermore, ejection fraction and MPI did not show significant changes over time. Systolic and diastolic sphericity indexes improved at discharge ($p < 0.001$), remained stable at 1-year ($p = \text{ns}$) but they were raised at 3-year control ($p = 0.006$ and $p = 0.03$ for SI_s and SI_d , respectively) with a late increase exceeding the preoperative value ($p < 0.001$). Finally, WMSI reduced significantly at discharge, remained constant at 1 year, but re-increased at 3-year ($p = 0.02$) and 5-year ($p < 0.001$) echocardiograms. Sixty percent of patients ($n = 132$) showed reverse remodeling at discharge and percent of patients showing LVRR increased significantly at

Table 2. Mitral regurgitation

	Baseline n=220	Discharge n=220	1 Year n=187	3 Years n=122	5 Years n=61	*p
MR	3.1 ± 0.6	0.3 ± 0.5*	0.3 ± 0.6	1.2 ± 0.7 [‡]	2.1 ± 1.2 [§]	0.001
Direction of regurgitant jet						
Central	70 (31.8)	-	-	-	-	
Anterior	28 (12.7)	-	-	-	-	
Posterior	54 (24.6)	-	-	-	-	
Complex	68 (30.9)	-	-	-	-	
Carpentier's classification						
Type IIIb	134 (60.9)	-	-	-	-	
Type IIIb + annular dilatation	86 (39.1)	-	-	-	-	
Quantitative data						
TA	3.4 ± 1.1	1.9 ± 0.5*	1.9 ± 0.5	2.1 ± 0.6 [‡]	2.4 ± 0.7 [§]	<0.001
ERO	36 ± 11	-	-	-	19 ± 11 [§]	-
RF	45 ± 10	-	-	-	26 ± 14 [§]	-
RV	56 ± 13	-	-	-	29 ± 16 [§]	-
CH	1.2 ± 0.3	0.8 ± 0.2 [§]	0.8 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	0.02
MA _s	4.1 ± 1.2	2.6 ± 0.7*	2.6 ± 0.4	2.6 ± 0.7	2.6 ± 0.7	0.001
MA _d	5.0 ± 1.1	3.3 ± 0.5*	3.4 ± 0.6	3.4 ± 0.9	3.4 ± 0.9	<0.001
MΔp	-	2.3 ± 0.5	2.4 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	0.2

Continuous variables are presented as mean ± standard deviation. Discrete data are presented as n (%). p=ANOVA over time significance. *^{†‡§} Significance vs. preoperative, discharge, 1 year, 3 years, respectively (see text). Abbreviations: MR=Mitral Regurgitation; TA=Tenting area (cm²); ERO=effective regurgitant orifice (mm²); RF=Regurgitant fraction (%); RV=Regurgitant volume (ml); CH=Coaptation height (cm); MAs=(Systolic) Mitral annular area (cm²); MA_d=(Diastolic) Mitral annular area (cm²); MΔp=Trans mitral diastolic gradient (mmHg);

1-year (p<0.001), but LVRR was reduced at 3-year (p<0.001) and at 5-year (p=0.01) studies (Figure 3).

LOCAL LV REMODELING

For local remodeling (Table 4), indexes of posterior and lateral displacement of both papillary muscles, PM separation, PPM fibrosis and WMSI_s were reduced significantly at discharge and remained constant at 1 year; nevertheless, PPM posterior (3 years, p=0.01; 5 years, p=0.02), PPM lateral (3 years, p=0.008; 5 years, p=0.02), PM_s separation (3 years, p<0.001; 5 years, p=0.02) and PPM fibrosis (p<0.001)

Figure 3. Mitral Regurgitation (%) at different echocardiographic controls ($p < .001$).

Figure 4. Five-year freedom from reoperation for recurrent ischemic mitral regurgitation (Dotted lines, 95% Confidence interval).

Table 3. Global LV remodeling.

	Baseline	Discharge	1 Year	3 Years	5 Years	p
EDD	62 ± 7	54 ± 7*	55 ± 7	53 ± 7	54 ± 7	0.03
ESD	52 ± 8	44 ± 6*	43 ± 6	42 ± 6	43 ± 6	0.04
LA	50 ± 7	45 ± 3*	46 ± 3	46 ± 3	46 ± 4	0.053
ESV	150 ± 24	114 ± 15*	108 ± 16†	121 ± 11†	136 ± 11§	<0.001
EDV	195 ± 35	164 ± 26*	156 ± 19†	171 ± 23‡	191 ± 23§	0.02
LVEF	30 ± 12	31 ± 10	30 ± 10	30 ± 11	29 ± 12	0.38
MPI	0.79 ± 0.2	0.76 ± 0.1	0.75 ± 0.1	0.75 ± 0.1	0.76 ± 0.1	0.2
SI _s	0.65 ± 0.2	0.50 ± 0.1*	0.50 ± 0.1	0.58 ± 0.1‡	0.66 ± 0.2§	0.03
SI _d	0.72 ± 0.1	0.62 ± 0.1*	0.60 ± 0.1	0.66 ± 0.1‡	0.74 ± 0.1§	0.01
WMSI	1.4 ± 0.7	1.2 ± 0.3*	1.1 ± 0.2	1.3 ± 0.4‡	1.5 ± 0.5§	0.006

Continuous variables are presented as mean ± standard deviation. p=ANOVA over time significance. *†‡§ Significance vs. preoperative, discharge, 1 year, 3 years, respectively (see text).

Abbreviations: EDD=(Left ventricular) End diastolic diameter(mm); ESD=(Left ventricular) End systolic diameter (mm); LA=Left atrium (mm); ESV=(Left ventricular) End systolic volume(ml); EDV=(Left ventricular) End diastolic volume (ml); LVEF=Left ventricular ejection fraction (%); MPI=Myocardial performance Index; SI_s=Systolic sphericity Index; SI_d=Diastolic sphericity Index; WMSI=Wall motion score Index.

Table 4. Local LV remodeling

	Baseline	Discharge	1Year	3 Years	5 Years	p
PPM posterior D	2.6 ± 0.6	2.2 ± 0.5*	2.1 ± 0.3	2.3 ± 0.3‡	2.5 ± 0.6§	0.02
APM posterior D	2.9 ± 0.5	2.5 ± 0.2*	2.4 ± 0.3	2.4 ± 0.3	2.4 ± 0.3	<0.001
PPM lateral D	2.0 ± 0.4	1.6 ± 0.3*	1.6 ± 0.3	1.8 ± 0.3‡	2.1 ± 0.3§	0.01
APM lateral D	1.3 ± 0.3	1.0 ± 0.2*	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.008
PM _s separation	3.6 ± 0.5	3.2 ± 0.2*	3.0 ± 0.2	3.3 ± 0.2‡	3.5 ± 0.4§	<0.001
PPM-fibrosa D	6.7 ± 0.6	6.0 ± 0.4*	6.0 ± 0.4	6.4 ± 0.4‡	6.6 ± 0.5§	0.02
PPM WMSI	2.2 ± 0.2	2.0 ± 0.2*	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	0.03
APM WMSI	1.3 ± 0.4	1.0 ± 0.1*	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.003

Continuous variables are presented as mean ± standard deviation. p=ANOVA over time significance. *†‡§ Significance vs. preoperative, discharge, 1 year, 3 years, respectively. (see text).

Abbreviations: D=Distance (cm); PPM=Posterior papillary muscle; APM=Anterior papillary muscle; PM_s Papillary muscles; WMSI=Wall motion Score Index.

Figure 5. Left ventricular reverse remodeling ($p=0.02$).

re-increased significantly at subsequent controls. Contrastingly, lateral and posterior displacements of the anterior papillary muscle as well as wall motion score indexes did not show further significant changes.

PREDICTORS OF RECURRENT MR

The unadjusted relationship between recurrent mitral regurgitation and independent variables are shown in Table 5. Multivariable logistic regression analysis identified systolic sphericity Index (OR= 4.97, 95% CI =2.11-6.40, $p<0.001$), myocardial performance Index (OR= 4.66, 95% CI= 2.01-5.43, $p<0.001$), end systolic volume (OR= 2.59, 95% CI = 1.19-3.77, $p=0.003$) and wall motion score Index (OR= 1.99, 95% CI =0.88-2.37, $p=0.04$) as independent predictors of the occurrence of recurrent MR.

Internal validation of such multivariable analysis by means of bootstrapping, including the same variables of standard logistic regression model, further confirmed the significant predictive of recurrent MR (bootstrap OR=2.3, 95% bias-corrected 95% CI=1.1-5.2). Finally, logistic regression model was reliable (Hosmer–Lemeshow test, $p=0.7$) and accurate (c-index=0.81).

ROC analysis showed that SI_s had 100% of sensitivity and specificity with an optimal cutoff ≥ 0.7 (95% CI by bootstrapping 0.58-0.81) [area under curve 1; 95% CI 0.70-1; $p<0.001$]. MPI with a cutoff ≥ 0.9 (95% CI by bootstrapping 0.75-0.96) had 85% of sensitivity and 84% of specificity (area under curve 0.94; 95% CI 0.67-1; $p<0.001$). In addition, $ESV \geq 145$ ml (95% CI by bootstrapping 134-155) had 90% of sensitivity and specificity (area under curve 0.87; 95% CI 0.80-0.94; $p<0.001$).

Table 5. Bivariate relationship of Independent variables with recurrent MR

	MR+	MR-	P
Age (years)	69.2 ± 6.4	67.8 ± 8.3	0.25
Male gender	98 (62.1)	38 (65.5)	0.9
NYHA class	3.2 ± 0.5	3.2 ± 0.5	0.74
CCS angina class	3.0 ± 0.3	3.1 ± 0.3	0.32
Euroscore			
Additive	7.9 ± 3.5	8.1 ± 4.6	0.66
Logistic	12.9 ± 6.3	12.8 ± 5.5	0.88
Hypertension	63 (39.9)	25 (40.3)	>0.9
Diabetes	51 (32.2)	17 (21.4)	0.49
COPD	21 (13.2)	7 (11.2)	0.71
Chronic renal disease	20 (12.6)	4 (6.5)	0.18
Cerebral vascular disease	10 (6.4)	4 (6.5)	0.9
Peripheral vascular disease	8 (5.1)	2 (3.3)	0.6
Familiar history	67 (42.4)	31 (50.0)	0.31
MI posterior/inferior	79 (50.0)	28 (45.1)	0.6
Grade of MR	3.0 ± 0.4	3.1 ± 0.4	0.1
Central direction of regurgitant jet	49 (31.0)	21 (33.8)	0.8
Annular dilatation	66 (41.7)	20 (32.2)	0.19
TA	3.3 ± 1.1	3.6 ± 1.2	0.06
ERO	38.3 ± 13	36.1 ± 11	0.09
RF	45.6 ± 11	44.7 ± 12	0.61
RV	57.4 ± 13	55.0 ± 10	0.25
CH	1.3 ± 0.2	1.1 ± 0.1	0.004
MA _s	4.1 ± 1.2	4.3 ± 1.2	0.3
MA _d	4.9 ± 1.2	5.2 ± 1.2	0.11
Number of diseased coronary vessels	2.5 ± 0.4	2.4 ± 0.4	0.11
Left main coronary artery	28 (17.7)	8 (12.9)	0.3
Preoperative IABP	6 (3.7)	2 (3.2)	0.88
Ring size	27.6 ± 0.5	27.3 ± 0.9	0.21
Anastomoses/patient	2.2 ± 1.2	2.1 ± 1.0	0.51
Arterial Graft/patient	1.09 ± 0.1	1.06 ± 0.1	0.43
CCL time	124.4 ± 30	123.28	0.8
CPB time	92.7 ± 16	90.7 ± 18	0.61
EDD	65.1 ± 4	60.6 ± 5	0.003
ESD	53.9 ± 4	51.3 ± 3	0.01
LA dimensions	49.2 ± 7	50.3 ± 7	0.66
ESV	164.7 ± 23.9	131.2 ± 19.8	<0.001
EDV	215.3 ± 38.1	194.1 ± 39.2	0.09
LVEF	24.4 ± 7	34.1 ± 6	<0.001
MPI	0.90 ± 0.15	0.69 ± 0.17	<0.001
SI _s	0.74 ± 0.1	0.54 ± 0.1	<0.001
SI _d	0.80 ± 0.1	0.64 ± 0.09	0.002

	MR+	MR-	p
WMSI	1.6 ± 0.2	1.1 ± 0.1	<0.001
PPM posterior D	2.4 ± 0.4	2.6 ± 0.5	0.2
APM posterior D	2.7 ± 0.4	2.9 ± 0.5	0.08
PPM lateral D	1.9 ± 0.4	2.0 ± 0.4	0.59
APM lateral D	1.3 ± 0.3	1.1 ± 0.2	0.008
PM _s separation	3.6 ± 0.5	3.6 ± 0.4	0.74
PPM fibrosa D	6.7 ± 0.6	6.6 ± 0.5	0.25
PPM WMSI	2.0 ± 0.1	2.2 ± 0.2	0.069
APM WMSI	1.3 ± 0.4	1.1 ± 0.3	0.04

Abbreviations: MR+(-)=Presence (absence) of recurrent mitral regurgitation; NYHA=New York Heart Association; CCS=Canadian Cardiovascular Society; COPD=Chronic obstructive pulmonary disease; MI=Myocardial infarction; MR=Mitral regurgitation; MR=Mitral regurgitation; CABG=Coronary artery bypass grafting; TA=Tenting area (cm²); ERO=effective regurgitant orifice (mm²); RF=Regurgitant fraction (%); RV=Regurgitant volume (ml/beat); CH=Coaptation height (mm); MAs=Systolic mitral annular area (cm²); MAd=Diastolic mitral annular area (cm²); IABP=Intraaortic balloon pump; CPB=Cardiopulmonary bypass; CCL=(Aortic).

Cross-clamp; EDD=End diastolic diameter (mm); ESD=End systolic diameter (mm); LA=Left atrium (mm); ESV=End systolic volume (ml); EDV=End diastolic volume (ml); LVEF=Left ventricular ejection fraction (%); MPI=Myocardial performance Index; SIS=Systolic sphericity Index; SID=Diastolic sphericity Index; WMSI=Wall motion score Index; D=Distance (mm); PPM=Posterior papillary muscle; APM=Anterior papillary muscle; PMs=Papillary muscles.

Finally, WMSI ≥ 1.5 (95% CI by bootstrapping 1.35-1.62) had 80% of sensitivity and 82% of specificity (area under curve 0.81; 95% CI 0.77-0.91; $p=0.002$).

DISCUSSION

An established therapeutic approach to relieve CIMR, in association with coronary artery bypass grafting (CABG), is and undersized mitral ring annuloplasty (UMRA)² which, by reducing the septal-lateral dimensions and the valve area, brings both mitral leaflets into apposition. Nonetheless, after encouraging initial results²⁶, different studies have revealed a significant proportion of patients developing recurrent MR during follow-up^{4,7,27} which has been mainly related to continued LV remodeling and persistent leaflet tethering^{5,28}. We reported our experience with this technique. Patients were followed-up by serial TTE over a 5-year period and recurrence of MR, local and global LV remodeling and LV reverse remodeling were explored. We also identified potential useful predictors of MR-recurrence following combined UMRA and CABG.

Because of unavailable complete echocardiographic data, 15 patients who died late after surgery were excluded from the study.

RECURRENCE OF MITRAL REGURGITATION

In our report, recurrent MR significantly increased at 3 year and 5-year controls with and 27.8% of patients showing mild, 31.1% moderate and 13.1% severe MR at latest follow-up. Five-year freedom from reoperation for failed repair was $78.2 \pm 4.9\%$. Hung and coworkers⁵ showed 72% of patients with moderate/severe MR at late control (47 ± 27 months) after ring annuloplasty and CABG. Accordingly, Tahta et al²⁷ in a large single-center surgical series, reported a 29% incidence of MR ≥ 2 over a 3-year follow-up period. However, in these studies annuloplasty had not been routinely performed in a restrictive fashion. In contrast with these results, Braun and coworkers⁴ reported, in 87 patients undergoing restrictive ring annuloplasty (2 ring sizes, median ring size 26), no patient showing MR ≥ 3 and 2 with MR graded 2+ at 18-month follow-up. In addition, Geidel²⁹ and co-workers reported 15 of 29 patients having no MR (52%), nine patients with MR1+ (31%) and five patients MR2+ (17%) 13 ± 7 months after mitral annuloplasty and CABG. Of interest, they performed mitral downsizing in a “dynamic fashion” dependent on LV function (2, 3 or 4 ring sizes for LVEF >30, 20-30%, <20%, respectively).

LV REMODELING

In our experience, we observed a significant global remodeling late after restrictive annuloplasty: LV volumes increased significantly and WMSI exceeded its preoperative value. Furthermore, LV became more spherical with sphericity indexes exceeding their baseline values at 5-year echocardiography. Regarding local remodeling, we observed a late “asymmetric” lateral and posterior displacement of PPM with APM displacement which remained constant over time. Of interest, WMSI of the segments underlying both papillary muscles, after a transient reduction, were relatively stable and these data suggest that the late PPM displacement seems to be due to the continued global remodeling, rather than local remodeling in this area.

LVRR

According to Stellbrink and coworkers¹⁹, we considered a decrease in LV end systolic volume >15% from baseline value as LVRR. In this fashion LVRR was observed, at late control, in 44.2% of patients with 10.3% showing further increment in ESV. Braun and coworkers⁶ reported 60.5% of patients with significant reverse LV remodeling 18 months after restrictive mitral annuloplasty. We had comparable results at 12-month follow-up (77.5%) but LVRR dramatically worsened at late controls. However, our data are not comparable because this Group considered a 10% reduction in EDD as significant LVRR; However, measurements of LV

volumes have been demonstrated to be more reliable than LV diameters in assessing LV remodeling, especially in enlarged ventricles³⁰.

PREDICTORS OF RECURRENT MR

At multivariable model, $ESV \geq 145$ ml, $SI_s \geq 0.7$, $MPI \geq 0.9$ and $WMSI \geq 1.5$ were predictors of recurrent MR. These results emphasize the importance of the extent of preoperative LV global remodeling as having a central role in predicting inadequate results after UMRA. A new finding in this study is that MPI predicts the likelihood of MR, whereas LVEF was not significant. The MPI is a combined systolic and diastolic Doppler-derived index for the assessment of global LV performance which, differently from LVEF, is independent of LV loading conditions and heart rate.

STUDY LIMITATION

Our study findings should be viewed in light of some inherent limitations.

- Evaluation of LVRR was based on volumes obtained by echocardiography; Volumetry by 2D echocardiography depends on geometric assumptions and is subject to image-plane positioning errors. Hence it is not accurate in left ventricles that are distorted in shape such as after myocardial infarction. However, this limitation belongs to most of published paper regarding this pathology.
- Viability testing was not performed in these patients. Therefore lack of LVRR in non responders might be also due to irreversible ischemic myocardial damage (not-viable myocardium). This issue deserves further investigation.
- Postoperative evaluation of the coronary status was not assessed. It would have been helpful to differentiate between surgical failure (valve repair and CABG) and the progress of the coronary disease.
- Fifteen patients with late deaths were not included in the study. They could have benefited from serial echocardiograms possibly with different results.
- Estimated cutoffs are known to be very susceptible to changes in the study population. We employed bootstrapping techniques to validate the results, nonetheless, it has also been documented that the sensitivity/specificity associated with these cutoffs are overly optimistic.

STRENGTH OF THE STUDY

As far as we know, this is the largest cohort reported with UMRA in CIMR patients with detailed echocardiographic follow-up. Furthermore our patient cohort was more homogeneous than in other study³¹: all patients underwent associated CABG, they had no concomitant MV procedures, and the entire cohort was uniform regarding the MV ischemic leaflet dysfunction. Moreover, to assess results

for MV repair, we studied true “recurrent” MR excluding those patients with “residual” MR in whom the insufficiency was presumably never eliminated at surgery. Additionally, we undertook valve sizing in a standardized fashion and the degree of undersizing was homogeneous over the 5-year period of the study. Finally, we used only two rings (Carpentier’s rigid or semi-flexible rings).

CLINICAL IMPLICATIONS

In our experience UMRA does not ensure successful and durable elimination of MR in all patients. Those who can benefit from combined UMRA and CABG should be preoperatively identified utilizing echo predictors of recurrent MR. However, restrictive annuloplasty resulted to be ineffective in a large percentage of patients and results of this study suggest the need for different approaches directly addressing ventricular tethering in most of CIMR patients³²⁻³⁵. Such procedures may include LV plasty with volume reduction, chordal elongation or cutting, PM displacement and leaflet elongation techniques as well as cardiac the employment of support devices introduced in recent years in clinical practice^{36,37}. Mitral valve replacement, largely employed in the past in ischemic regurgitation, although eliminates the short-term risk of recurrent MR, it is associated with poor long-term survival³⁸. Thus, in our actual policy, we do not consider MV replacement as a reasonable alternative to repair.

CONCLUSIONS

Combined UMRA and CABG provided poor mid-term results with significant recurrent MR. Our findings emphasize the need for improved repair technique and better patient selection to identify patients with anticipated repair failure who could benefit more from valve replacement or other procedure directly addressing ventricular tethering. Long term prospective studies on this controversial issue are encouraged.

REFERENCES

1. Miller DC. Ischemic mitral regurgitation redux-to repair or to replace? *J Thorac Cardiovasc Surg* 2001;122 (6):1059-62.
2. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998; 115(2):381– 6.

3. Bax JJ, Braun J, Somer ST, Klautz R, Holman ER, Versteegh MI, Boersma E, Schalij MJ, van der Wall EE, Dion RA. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation*. 2004; 110[suppl II]:II103-8.
4. McGee EC, Gillinov AM, Blackstone EH, Rajeswaran J, Cohen G, Najam F, Shiota T, Sabik JF, Lytle BW, McCarthy PM, Cosgrove DM. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 2004; 128(6):916-24.
5. Hung J, Papakostas L, Tahta SA, Hardy BG, Bollen BA, Duran CM, Levine RA. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. *Circulation* 2004; 110[suppl.II]:II85- 90.
6. Braun J, Bax JJ, Versteegh MI, Voigt PG, Holman ER, Klautz RJ, Boersma E, Dion RA. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. *Eur J Cardiothorac Surg* 2005; 27(5):847-53.
7. Serri K, Bouchard D, Demers P, Coutu M, Pellerin M, Carrier M, Perrault LP, Cartier R, Page P, Cossette M, Basmadjian AJ. Is a good perioperative echocardiographic result predictive of durability in ischemic mitral valve repair? *J Thorac Cardiovasc Surg*. 2006; 131(3):523-9.
8. Carpentier A. Cardiac valve surgery-The "French correction". *J Thorac Cardiovasc. Surg.* 1983; 86(3): 326-37.
9. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. Edinburgh, Scotland: World Medical Association, October 2000. Available at http://www.wma.net/e/policy/17-c_3.html. Accessed June 22, 2001.
10. Jones E, Weintraub WS. The importance of completeness of revascularization during long-term follow-up after coronary artery operations. *J Thorac Cardiovasc Surg* 1996; 112:222-37.
11. Bland MJ, Altman DJ. Statistical method for assessing agreement between two methods of clinical measurements. *Lancet* 1986; 1:307-310.
12. Gardin JM, Adams DB, Douglas PS, Feigenbaum H, Forst DH, Fraser AG, Grayburn PA, Katz AS, Keller AM, Kerber RE, Khandheria BK, Klein AL, Lang RM, Pierard LA, Quinones MA, Schnittger I; American Society of Echocardiography. Recommendations for a standardized report for adult transthoracic echocardiography: a report from the American Society of Echocardiography's Nomenclature and Standards Committee and Task Force for a Standardized Echocardiography Report. *J Am Soc Echocardiogr* 2002; 15 (3):275-90.
13. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; 16 (7):777-802.
14. Enriquez-Sarano M, Tribouilloy C. Quantitation of mitral regurgitation: rationale approach and interpretation in clinical practice. *Heart* 2002, 88 (suppl IV):1-4.
15. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation* 2000, 102(12):1400-6.

16. Boltwood CM, Tei C, Wong M, Shah PM. Quantitative echocardiography of the mitral complex in dilated cardiomyopathy: the mechanism of functional mitral regurgitation. *Circulation* 1983; 68(3):498-508.
17. Vijayaraghavan G, Boltwood CM, Tei C, Wong M, Shah PM. Simplified echocardiographic measurement of the mitral annulus. *Am Heart J* 1986; 112(5): 985-91.
18. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2(5):358
19. Stellbrink C, Breithardt OA, Franke A, Sack S, Bakker P, Auricchio A, Pochet T, Salo R, Kramer A, Spinelli J; PATH-CHF (Pacing Therapies in Congestive Heart Failure) Investigators; CPI Guidant Congestive Heart Failure Research Group. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol.* 2001; 38(7):1957-65.
20. Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, Tajik AJ, Seward JB. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function a study in normals and dilated cardiomyopathy. *J Cardiol* 1995; 26(6):357-66.
21. Kono T, Sabbah HN, Rosman H, Alam M, Jafri S, Goldstein S. Left ventricular shape is the primary determinant of functional mitral regurgitation in heart failure. *J Am Coll Cardiol.* 1992; 20(7):1594-8.
22. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation.* 2002; 105(4):539-42.
23. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KL, Tajik AJ. Ischemic Mitral Regurgitation. Long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001; 103(13):1759-64.
24. Harrel FE Jr, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stats Med* 1996:361-87.
25. Hosmer DW, Lemeshow S. *Applied Logistic regression*. 2nd ed. New York: Wiley-Interscience; 2000:143-202.
26. Bolling SF, Deeb GM, Bach DS. Mitral valve reconstruction in elderly, ischemic patients. *Chest* 1996;109(1):35- 40.
27. Tahta SA, Oury JH, Maxwell JM, Hiro SP, Duran CM. Outcome after mitral valve repair for functional ischemic mitral regurgitation. *J Heart Valve Dis.* 2002;11(1):11-8;

28. Kuwahara E, Otsuji Y, Iguro Y, Ueno T, Zhu F, Mizukami N, Kubota K, Nakashiki K, Yuasa T, Yu B, Uemura T, Takasaki K, Miyata M, Hamasaki S, Kisanuki A, Levine RA, Sakata R, Tei C. Mechanism of recurrent/persistent ischemic/functional mitral regurgitation in the chronic phase after surgical annuloplasty: importance of augmented posterior leaflet tethering. *Circulation*. 2006 Jul 4; 114(Suppl):I529-34.
29. Geidel S, Lass M, Schneider C, Groth G, Boczor S, Kuck KH, Ostermeyer J.. Downsizing of mitral valve and coronary revascularization in severe ischemic mitral regurgitation results in reverse left ventricular and left atrial remodeling. *Eur J Cardiothorac Surg* 2005;27:1011-16
30. Dujardin KS, Enriquez-Sarano M, Rossi A, Bailey KR, Seward JB. Echocardiographic assessment of left ventricular remodeling: are left ventricular diameters suitable tools? *J Am Coll Cardiol*. 1997 Nov 15; 30(6):1534-41.
31. Adams DH, Anyanwu A. Pitfalls and limitations in measuring and interpreting the outcomes of mitral valve repair. *J Thorac Cardiovasc Surg*. 2006; 131(3):523-9.
32. Batista RJ, Verde J, Nery P, Bocchino L, Takeshita N, Bhayana JN, Bergsland J, Graham S, Houck JP, Salerno TA. Partial left ventriculectomy to treat end-stage heart disease. *Ann Thorac Surg*. 1997; 64(3):634-8.
33. Dor V, Sabatier M, Di Donato M, Montiglio F, Toso A, Maioli M. Efficacy of endoventricular patch plasty in large postinfarction akinetic scar and severe left ventricular dysfunction: comparison with a series of large dyskinetic scars. *J Thorac Cardiovasc Surg*. 1998;116(1):50-9
34. Messas E, Guerrero JL, Handschumacher MD, Conrad C, Chow CM, Sullivan S, Yoganathan AP, Levine RA. Chordal cutting: a new therapeutic approach for ischemic mitral regurgitation. *Circulation*. 2001; 104(16):1958-63.
35. Tibayan FA, Rodriguez F, Langer F, Zasio MK, Bailey L, Liang D, Daughters GT, Ingels NB Jr, Miller DC. Does septal-lateral annular cinching work for chronic ischemic mitral regurgitation? *J Thorac Cardiovasc Surg*. 2004;127(3):654-63
36. Konertz W, Rombeck B, Hotz H. Short-term safety of the Acorn cardiac support device in patients with advanced heart failure. *J Am Coll Cardiol* 2000; 35:182A.
37. Fukamachi K, McCarthy PM. Initial safety and feasibility clinical trial of the myosplint device. *J Card Surg*. 2005 Nov-Dec;20(6):S43-7
38. Gillinov AM, Wierup PN, Blackstone EH, Bishay ES, Cosgrove DM, White J, Lytle BW, McCarthy PM. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg*. 2001;122(6):1125-41

3

Left Ventricular Reverse Remodeling After Undersized Mitral Ring Annuloplasty In Patients With Ischemic Regurgitation

Sandro Gelsomino, MD, Roberto Lorusso, Ph.D, Irene Capecchi, MD, Carlo Rostagno, MD,
Stefano Romagnoli, MD, Giuseppe Billè, MD, Giuseppe De Cicco, MD, Cecilia Tetta, MD,
Pierluigi Stefàno, MD and Gian Franco Gensini, MD.

Published in: Ann Thorac Surg. 2008 Apr;85(4):1319-30

ABSTRACT

Background. Long-term durability of combined coronary artery bypass grafting and of under-sized mitral ring annuloplasty (UMRA) is uncertain with a considerable number of patients showing recurrent regurgitation. This study examines the difference in the benefit of UMRA on clinical end points and recurrence of mitral regurgitation between responders and non-responders of left ventricular reverse remodeling. *Methods.* Study eligibility criteria were fulfilled by 204 patients with chronic ischemic mitral regurgitation (CIMR) who survived combined coronary artery bypass and reductive annuloplasty between September 2001 and September 2006. Patients underwent echocardiography preoperatively, at discharge and at follow-up appointments (100% complete; early, median 6 months [interquartile range 3-8 months]; late, 35 months [21-50 months]). Reverse remodeling was defined as a reduction in left ventricular end systolic volume Index >15%.

Results There were 84 (41.2%) responders of reverse remodeling (age 68 ± 7.4 ; 51 males) and 120 (58.8%) non-responders (age 67 ± 7.6 ; 78 males). Non-responders had a higher recurrence of mitral regurgitation ($p < 0.001$), higher reoperation rate for failed repair ($p < 0.001$) significantly larger left ventricular volumes and dimension at any study point ($p < 0.001$) with significant late increase of sphericity indexes exceeding preoperative values ($p < 0.001$). At multivariable analysis baseline myocardial performance Index < 0.90 ($p < 0.001$), systolic sphericity Index < 0.72 ($p < 0.001$) and wall motion score Index < 1.59 ($p = 0.003$) resulted as independent predictors of reverse remodeling.

Conclusions. Our experience suggests that more information on possible echo predictors of an inadequate result may improve preoperative decision-making of CIMR patients for UMRA.

INTRODUCTION

Despite better understanding of mechanisms leading to chronic ischemic mitral valve regurgitation (CIMR) and notwithstanding improvement of mitral repair results^{1,2}, ongoing dissatisfaction with outcomes has yielded different techniques³⁻⁶.

An established therapeutic approach to relieve CIMR, in association with coronary artery bypass grafting (CABG), is undersized mitral ring annuloplasty (UMRA)^{7,8} which, by reducing the anterior-posterior dimensions (or septal-lateral in anatomic terms) and the valve area, brings both mitral leaflets into apposition. However, the long-term efficacy of UMRA is still unclear and recurrence of mitral regurgitation (MR) has been predominantly related to progressive left ventricular remodeling⁹⁻¹¹. Cardiac remodeling is a well known important aspect of myocardial disease progression making left ventricular reverse remodeling (LVRR) a critical postoperative factor¹².

This study examines the difference in the benefit of UMRA on clinical end points and recurrence of MR between responders and non-responders of LVRR. It also explores potential useful predictors of successful reverse remodeling including clinical and surgical data, volumetric and geometric parameters and indexes of left ventricular function assessed by echocardiography.

MATERIAL AND METHODS

ETHICAL ISSUE

Following the World Medical Association guidelines concerning ethical principles for medical research involving human subjects¹³, the study was approved by Institutional Ethics Board. Furthermore, all patients gave their informed consent.

PATIENTS POPULATION

Chronic ischemic mitral regurgitation was defined as the combination of mild-to-severe MR with 1) Prior myocardial infarction (MI)>16 days¹⁴; 2) seventy-five percent or greater stenosis of at least one coronary vessel; 3) a corresponding regional wall motion abnormality; 4) type IIIb leaflet dysfunction following Carpentier's classification¹⁵ with or without annular dilatation. Exclusion criteria were: 1) degenerative or other non-ischemic etiology; 2) ischemic isolated type I or type II dysfunction¹⁵; 3) additional mitral valve repair procedures; 4) other valvular or congenital heart diseases; 5) previous cardiac surgery/percutaneous transluminal coronary angioplasty; 6) atrial fibrillation or sinus rhythm with heart rate at rest >100 bts/min.

Among 239 Subjects with chronic ischemic mitral regurgitation undergoing combined CABG and UMRA in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and September 2006 and prospectively enrolled in the study, 35 were excluded: 4 had intraoperative annuloplasty failure, 12 showed residual MR, defined as the insufficiency $\geq 2+$ following valve repair documented at discharge, 4 died within 30 days and 15 had incomplete data available.

PATIENTS CLASSIFICATION

Following Stellbrink and coworkers¹⁶ patients were classified as responders in terms of LVRR if the end systolic volume Index (ESVI) was reduced $>15\%$ at late follow-up compared with baseline volumes, and as non-responders if ESVI was reduced $\leq 15\%$.

Among the 204 patients there were 84 (41.2%) responders to LVRR and 120 (58.8%) non-responders.

FOLLOW UP

Clinical follow up information was obtained from all survivors through outpatient visits and phone calls and was 100% complete. Median follow up were: early, median 6 months, interquartile range [IQR] 3-8 months; late, 35 months, IQR 21-50 months).

SURGERY

All patients underwent associated CABG. For the purpose of this study, complete revascularization was accomplished when, at least one graft was placed distal to an approximately 50% diameter narrowing in each of the three major vascular system in which arterial narrowing of this severity was noted in a vessel ≥ 1.5 mm of diameter. It was not considered necessary to bypass all obstructed diagonal branches of the anterior descending or marginal branches of the circumflex coronary arteries for a classification of complete revascularization. Following this definition 100% patients underwent complete revascularization.

The ring size was determined by standard measurements of the inter-trigonal distance and anterior leaflet height. A downsizing by two ring sizes was performed in all patients. Two types of ring were employed in all patients: Carpentier's classic ring (Edwards Life Sciences, Irvine, CA) in 112 patients (54.9%) and Physio ring (Edwards Life Sciences, Irvine, CA) in 92 (45.1%). Median ring size was 28 mm (Interquartile range [IQR] 26-28 mm. No difference was detected in ring size between two types of ring employed (both, 28 mm (IQR 26-28 mm, $p>0.9$)).

After cardiopulmonary bypass (CPB), a transesophageal echocardiography (TEE) was performed to assess residual MR: leaflet coaptation ≥ 0.5 cm, MR ≤ 1 and systolic MV area > 2 cm² was assessed as successful repair.

ECHOCARDIOGRAPHIC MEASUREMENTS AND CALCULATIONS

The clinical echocardiographic evaluation was as follows: transthoracic (TTE) and transesophageal (TEE) echocardiograms were performed within five days before surgery. Then a transthoracic echocardiography was performed at discharge and at follow-up appointments. Echocardiographic studies were carried out on an Acuson Sequoia imaging device equipped with a 3.5-MHz ultrasound transducer (Acuson Corporation, Mountain View, CA) preoperatively, at discharge and at follow-up appointments. The reliability of echocardiographic measurements was assessed by calculating between-observer (IC and CR) interval of agreements of main direct measures used in this study in a different group of 20 subjects (10 MR)¹⁷.

GLOBAL LV REMODELING

LV volumes and left ventricular ejection fraction (LVEF) were assessed by the bi-apical Simpson disk method¹⁸. The myocardial performance index (MPI) was measured using the method described by Tei et al.¹⁹. The sphericity index (SI) was obtained at end diastole and end systole (SI_D and SI_S, respectively) as the volume of the left ventricle divided by the volume of a sphere with a diameter equal to the longest axis of the left ventricle measured in the apical view²⁰. The wall motion score index (WMSI) was calculated according to a 17-segment model²¹.

QUANTIFICATION OF MR AND DEFINITIONS

The following quantitative measurements were simultaneously employed to grade the severity of MR and final results were averages of measured values^{1,22,23}: (1) Quantitative Doppler. (2) Proximal Isovelocity Surface Area (PISA). For each measurement a minimum of three cardiac cycles was averaged. The tenting area (TA) was measured by the area enclosed between the annular plane and mitral leaflets from the parasternal long-axis view at mid-systole. Apical displacement of the coaptation was measured as coaptation height (CH) and coaptation length (CL) was directly measured^{2,24}. Mitral annular areas were obtained from mitral annular dimensions in apical long-axis, 4-chamber, and 2-chamber views, using an ellipsoid assumption²⁵.

Recurrent MR was an insufficiency $\geq 2+$ at follow up appointments in patients with no/trivial MR at discharge.

LOCAL LV REMODELING

Lateral and posterior displacements of anterior papillary muscles (APM) and posterior papillary muscles (PPM) were measured as distances from well-defined anatomic landmarks at early and end systole². Separation between papillary muscles was directly measured from body to body of PM_s. In the long-axis view the apical displacement of the PPM was measured as the distance between the papillary muscle head and the fixed inter-valvular fibrosis (annular papillary distance). The WMSI of the basal and mid-posterior and inferior segments for the PPM and of basal and mid-lateral and anterior segments for the APM were calculated¹.

STATISTICAL ANALYSIS

The sample size was determined by GraphPad StatMate release 2.00 (GraphPad Prism Software, Inc, San Diego, CA), on the basis of preliminary data obtained by echocardiography and was determined on the basis of the following assumptions: Type I error of 0.05 (two-sided), power of 80%, difference in end systolic volume of 0.78 ± 2.4 between patients with or without recurrent mitral regurgitation.

The calculated study population was 200. However 239 patients were recruited to allow for possible analytic problems while processing the eventualities potentially leading to patient attrition. Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous variables are presented as mean and standard deviation (SD), categorical variables as percentage of not-normally distributed variables as median and Irate bivariate association between the independent variables and LV reverse remodeling was assessed by the Student's t-test, Mann Whitney U test, χ^2 test and Fisher exact test were appropriate.

Echocardiographic variables over time were analyzed by means of ANOVA repeated measures followed by Tukey post-hoc test and Friedman test, where appropriate. Forty-nine demographic, clinical, operative and echocardiographic parameters were investigated for their predictive value of LVRR by univariable and multivariable models. To enhance the accuracy of the model, clustering method²⁶ was employed to reduce the number of variables²⁷.

Multivariable logistic regression analysis by means of a backward stepwise algorithm (cutoff for entry 0.05, for removal 0.10) was performed to select independent predictors of reverse remodeling. Categorical variables with more than two levels in the regression model were converted to dummy variables.

Model assumptions (linearity and additivity assumptions) were checked by piecewise cubic polynomials (spline functions) and pooled interaction test²⁸, respectively, and found to be satisfied. "Goodness of fit" of the final logistic regression models was assessed with the Hosmer–Lemeshow statistic^{27,28} and predictive accuracy was assessed by the concordance (c) index^{27,28}. Internal validation of predictors generated

by multivariable logistic regression was performed by means of bootstrapping techniques, with 1000 cycles and generation of OR and bias corrected 95% CI^{28,29}.

Optimal cutoff values were determined as the rounding cut-off that gives the maximum sum of sensitivity and specificity. This value should be the shoulder at the top left of the ROC (receiver operating characteristic curve). Bootstrapping techniques were employed to validate the results. A logistic regression analysis was carried out to evaluate the influence of the severity of preoperative regurgitation on recurrence of moderate/severe MR. Cumulative probability for death and reoperation were estimated by the Kaplan-Meier method. SPSS 12.0 (SPSS, Chicago, IL, USA) and Stats Direct 2.5.7 (StatsDirect, Sale, UK) were used for these calculations. Significance for hypothesis testing was set at the 0.05 two tailed level.

RESULTS

LEFT VENTRICULAR REVERSE REMODELING

Table 1 displays perioperative data. No difference was detected between Groups.

In responders (Figure 1 A), the mean end-systolic volume Index decreased significantly at discharge ($p<0.001$), early ($p<0.001$) and late controls ($p<0.001$). In contrast, in non-responders (Figure 1 B) ESVI reduced significantly at discharge ($p=0.01$), it was stable at early follow-up ($p=ns$) but increased again at late control ($p<0.001$). When the degree of LV reverse remodeling was compared further in the two groups, ESVI was reduced $\geq 10\%$ in ten (8.3%), $<10\%$ in 83 (69.2%), was relatively stable ($\pm 1\%$) in 15 (12.5%), and enlarged in 12 (10.0%) non-responders. Among responders, 79 (94.0%) had a reduction in ESVI of $15\% \leq 20\%$ and five (6.0%) a reduction $>20\%$. LVRR was not influenced by the type of ring employed (Figure 2).

CLINICAL ENDPOINTS AND MR

Early clinical outcome did not differ between Groups (Table 2). At late follow up, NYHA functional class was greater in non-responders ($p<0.001$).

During the follow-up 15 patients died; cause of death in responders ($n=2$) were: malignancy (55 months) sudden, unexplained death (22 months). Cause of death in responders ($n=13$) were: heart failure ($n=3$; 36, 45, and 54 months), myocardial infarction ($n=2$; 31 and 42 months), arrhythmia ($n=1$; 59 months), multi-organ failure ($n=1$; 6 months), respiratory failure ($n=1$; 14 months), infection ($n=2$; 3 and 8 months), stroke ($n=2$; 12 and 43 months) and malignancy ($n=1$; 59 months).

Table 1. Perioperative data (n=204)

	Responders n=84	Non-Responders n=120	p
Age (years)	68 ± 7.4	67 ± 7.6	0.26
Gender M/F	51/33(60.7/39.3)	78/42 (65.0/35.0)	0.55
NYHA class	3 [3-4]	3 [3-4]	0.72
Angina	40 (47.6)	54 (45.0)	0.69
CCS angina class	2 [1-3]	2 [1-3]	>0.9
Euroscore			
Additive	8.0 [5-9]	8.2 [5-8]	0.37
Logistic	14.8 [11-18]	15.1 [10-18]	0.8
Hypertension	32 (38.1)	48 (40.0)	0.86
Diabetes	24 (28.6)	34 (28.3)	0.9
COPD	12 (14.3)	17 (14.2)	0.9
Chronic renal disease	13 (15.5)	19 (15.8)	0.9
Cerebral vascular disease	11 (13.1)	18 (15.0)	0.51
Peripheral vascular disease	6 (7.1)	6 (5.0)	0.3
Familiar history	40 (47.6)	60 (50.0)	0.8
Myocardial infarction			
>3 months	62 (73.8)	99 (82.5)	0.15
≤3 months	22 (26.2)	21 (17.5)	0.12
Inferior/Posterior	40 (47.7)	60 (50.0)	0.77
Anterior/Septal	7 (8.3)	12 (10.0)	0.53
Lateral	18 (21.4)	24 (20.0)	0.8
Combined	19 (22.6)	24 (20.0)	0.8
Coronary vessel disease	2 [1-3]	2 [1-3]	0.8
Left Main	14 (16.7)	21 (17.5)	0.66
Medications			
Angiotensin-converting enzyme inhibitors	66 (78.6)	100 (83.3)	0.46
β-adrenergic blockers	46 (54.8)	62 (51.7)	0.56
Long-acting nitrates	42 (50.0)	54 (45.0)	0.14
Diuretics	71 (84.5)	105 (87.5)	0.32
Digitalis	18 (21.4)	28 (23.3)	0.8
Calcium antagonists	12 (14.3)	20 (16.7)	0.7
Preoperative IABP	3 (3.6)	5 (4.2)	0.8
Surgery			
Cardioplegia			
Antegrade	76 (90.5)	106 (88.3)	0.06
Antegrade and Retrograde	8 (9.5)	14 (11.7)	0.08
CPB time (min)	118 ± 28	128 ± 34	0.06
CCL time (min)	88 ± 18	96 ± 19	0.1

	Responders n=84	Non-Responders n=120	p
Surgical Approach			
Left atriotomy	70 (83.3)	101 (84.2)	0.6
Transseptal	8 (9.5)	10 (8.3)	0.4
Transseptal extended to LA roof	6 (7.2)	9 (7.5)	>0.9
CABG			
Anastomoses/patient	2[1-3]	2[1-2]	0.7
Arterial graft/patient	1 [1-2]	1 [1-2]	>0.9

Continuous variables are presented as mean $\pm$ standard deviation; Discrete variables are presented as percentage. Non-parametric variables were presented as median [Interquartile range].

Abbreviations: M/F=Male/Female; NYHA=New York Heart Association; CCS=Canadian Cardiovascular Society; COPD=Chronic obstructive pulmonary disease; IABP=Intaaortic balloon pump; CPB=Cardiopulmonary bypass; CCL=(Aortic)Cross-clamp; MR=Mitral regurgitation; CABG=Coronary artery bypass grafting.

Figure 1. Reduction in end systolic volume Index in responders (A) and non-responders (B) of left ventricular reverse remodeling. See text.

Overall, five-year actuarial survival was 83.2 ± 4.4 . It was significantly lower in non responders (Figure 3).

Data of mitral regurgitation are shown in Table 3. In responders, jet direction was posterior in the major part of patients whereas it was central or anterior in most of non-responders. In addition, TA ($p<0.001$), and CH ($p=0.02$) were preoperatively higher and CL ($p=0.04$) was shorter in non responders. No further significant difference between the two Groups was found regarding qualitative and quantitative MR data. At early control, the incidence of recurrent MR was 2.4% and 43.9% in responders and non-responders, respectively ($p<0.001$). At late control, recurrent MR was unchanged in responders, whereas showed a further increment in non-responders (67.3%, $p<0.001$ vs. responders). Whereas none of non responders showed a late recurrent MR ≥ 4 , 18 (15%) non-responders experienced moderate/severe recurrent MR. Interestingly, in the latter Group, among 28 patients with severe (4+) preoperative MR, seven (25%) developed severe and eleven (39.2%) moderate recurrent

Figure 2. Left ventricular reverse remodeling (LVRR) by ring type/size. The extent of remodeling was not significantly different between rings at different sizes.

MR. At logistic regression analysis, MR grade >3 was a predictive factor of recurrent moderate/severe MR (OR=5.2 [95% bias-corrected CI 2.4-6.3]; $p<0.001$). Among responders none underwent reoperation for failed repair. Contrastingly, four (3.7%) non responders had a re-MV repair and 13 (12.1%) underwent mitral valve replacement. Five-year freedom from reoperation for failed repair were 100% and $44 \pm 7\%$ in responders and non responders, respectively ($p<0.001$).

Finally, three (3.7%) non responders experienced cardiac-related events during the follow-up period ($p<0.001$ vs. responders [$n=0$]).

GLOBAL AND LOCAL LV REMODELING

Changes in end-diastolic volume Index and WMSI mirrored those of ESVI (Table 4). Left ventricular dimensions decreased, in responders, at any study point ($p<0.001$). In contrast, for non-responders, there was an initial reduction in LV dimensions at discharge ($p=0.01$) and early control ($p=0.02$ and $p=0.04$ for ESD and EDD, respectively), followed by a significant increase at late postoperative stage ($p<0.001$). Ejection fraction ($p=0.001$) and MPI ($p=0.01$) significantly improved at late follow-up only in responders, whereas remained unchanged in non-responders at any study point. Systolic and diastolic sphericity indexes improved in responders at discharge ($p<0.001$), early (SI_s , $p=0.02$ and SI_D , $p=0.03$, respectively) and late controls ($p<0.001$). In non-responders, there was an initial but not significant reduction in both systolic and diastolic sphericity indexes, with a late increase exceeding the preoperative value ($p<0.001$).

Non-responders had greater preoperative APM lateral and APM posterior, wider PM_s separation and larger APM WMSI. Contrastingly, PPM WMSI was higher in

Table 2. Clinical outcome (n=204)

	Responders n=84	Non-Responders n=120	p
ICU LoS (h)	22 [13-34]	26 [16 -40]	0.5
Time of MV (h)	9 [6-11]	11 [5-16]	0.08
Inotropes	7 (8.3)	11 (9.2)	0.8
Blood transfusion (Units)	5 [1-3]	3 [0-2]	0.09
Early Complications			
Rate	28.6	36.7	0.09
Bleeding	4(4.8)	8 (6.7)	
Low-output syndrome	1(1.2)	2 (1.7)	
IABP	1 (1.2)	2 (1.7)	
MI	1 (1.2)	3 (2.5)	
AF	8 (9.5)	13 (10.8)	
Permanent pacemaker	1 (1.2)	1(0.8)	
Renal failure	1(1.2)	1 (0.8)	
Respiratory failure	3 (3.6)	7 (5.8)	
CVA	-	1(0.8)	
Infection	3 (3.6)	6 (5.0)	
In-hospital LoS (days)	7 [5-8]	7 [4-9]	>0.9
NYHA class	2 [1-2]	3 [2-3]	<0.001
1	38 (45.2)	5 (4.1)	
2	39 (46.4)	32 (26.7)	
3	7 (8.3)	63 (52.5)	
4	-	20 (16.7)	
Late Complications			
Rate	4.8	2.5	0.38
Endocarditis	1(1.2)	-	
CVA	-	1(0.8)	
Others	3 (3.6)	2 (1.7)	

Discrete variables are presented as percentage (parentheses). Non-parametric data are shown as median [Interquartile range].

Abbreviations: ICU=Intensive Care Unit; LoS=Length of Stay; MV=Mechanical Ventilation (time of). IABP=Intaaortic balloon pump; MI=Myocardial infarction; AF=Atrial Fibrillation; CVA=Cerebrovascular accident documented by Computed Tomography; NYHA=New York Heart Association.

Table 3. Mitral regurgitation

	Responders				Non-Responders			
	Baseline	Discharge	Early	Late	Baseline	Discharge	Early	Late
MR								
Grade	3 [3-4]	0 [0-1]	0 [0-1]	0 [0-1]	3 [3-4]	0 [0-1]	1 [1-2]	2 [1-3]
None	-	72 (85.7)	76(90.5)	73(86.9)	-	79 (65.8)	37 (30.8)	12 (10.0)
1+	-	12 (14.3)	6 (7.1)	9 (10.7)	-	41 (34.2)	31 (25.8)	27 (22.5)
2+	13 (15.5)	-	2 (2.4)	2 (2.4)	20 (16.7)	-	30 (25.0)	61 (50.8)
3+	48 (57.1)	-	-	-	72 (60.0)	-	14 (11.7)	11 (10.0)
4+	23 (27.4)	-	-	-	28 (23.3)	-	8 (6.7)	7 (6.7)
Direction of regurgitant jet:								
Central	9 (10.7)	-	-	-	74 (61.7)	-	-	-
Anterior	10 (11.9)	-	-	-	10 (8.3)	-	-	-
Posterior	52 (61.9)	-	-	-	17 (14.2)	-	-	-
Complex	13 (15.5)	-	-	-	19 (15.8)	-	-	-
Carpentier's classification								
Type IIb	51 (60.7)	-	-	-	77 (64.2)	-	-	-
Type IIb + annular dilatation	33 (39.3)	-	-	-	43 (35.8)	-	-	-
Quantitative data								
TA	3.4 ± 1.1	1.9 ± 0.5	1.9 ± 0.5	1.9 ± 0.3	4.3 ± 1.1	1.9 ± 0.3	2.3 ± 0.3	2.9 ± 1.0
ERO	34 ± 10	-	-	-	38 ± 12	-	11 ± 7	26 ± 11
RF	43 ± 9	-	-	-	47 ± 13	-	17 ± 9	32 ± 15
RV	56 ± 11	-	-	-	59 ± 18	-	21 ± 12	38 ± 16
CH	1.0 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	1.3 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.4
CL	4.0 ± 0.5	7.4 ± 0.4	7.5 ± 0.4	7.5 ± 0.3	3.3 ± 0.3	3.1 ± 0.4	3.1 ± 0.3	3.1 ± 0.3
MA _s	4.1 ± 1.3	2.6 ± 0.7	2.6 ± 0.4	2.6 ± 0.7	4.2 ± 1.1	2.6 ± 0.7	2.5 ± 0.6	2.5 ± 0.6
MA _d	5.1 ± 1.2	3.3 ± 0.5	3.4 ± 0.6	3.4 ± 0.9	5.0 ± 1.2	3.4 ± 0.9	3.4 ± 0.8	3.3 ± 0.7
MAp	-	2.5 ± 0.5	2.4 ± 0.3	2.3 ± 0.3	-	2.3 ± 0.3	2.4 ± 0.3	2.4 ± 0.3

*†† Significance vs. preoperative discharge and early follow-up, respectively. § Significance vs. responders. Continuous variables are presented as mean ± standard deviation. Non-parametric variables were presented as median [Interquartile range]. Abbreviations: MR=Mitral Regurgitation; TA=Tenting area (cm²); ERO=effective regurgitant orifice (mm²); RF=Regurgitant fraction (%); RV=Regurgitant volume (ml); CH=Coaptation height (cm); CL=Coaptation length (mm);MA_s=(Systolic) Mitral annular area (cm²); MA_d=(Diastolic)Mitral annular area(cm²);MA_p=(Trans mitral diastolic gradient (mmHg).

Figure 3. Five-year actuarial Survival by Groups. See text.

responders, whereas PPM posterior, PPM lateral and PPM fibrosis were comparable in the two Groups.

At discharge, in responders, indexes of posterior and lateral displacement of papillary muscles, PM_s separation, PPM fibrosis and WMSIs were reduced significantly. All these index did not show any significant change afterwards. In non-responders, all the above indexes (except for APM WMSI which remained constant over time) showed a reduction, even not significant, at discharge, remained constant at early control showing a significant late increase.

PREDICTORS OF LVRR

At univariable analysis (Table 4), left ventricular diameters, sphericity indexes, LVEF, WMSI, MPI, APM posterior and lateral, PM separation and APM WMSI were predictors of LVRR. By multiple regression analysis (Table 6) baseline MPI, SI_s and WMSI resulted as independent predictors of LVRR.

Internal validation of such multivariable analysis by means of bootstrapping, including the same variables of standard logistic regression model, further confirmed the significant predictive of recurrent MR (bootstrap OR=2.4, 95% bias-corrected 95% CI=1.1-5.3). Finally, logistic regression model was reliable (Hosmer–Lemeshow test, $p=0.6$) and accurate (c index=0.8). ROC curve analysis to determine optimal cutoff values to predict reverse LV (Figures 4-6) showed that SI_s had 90% of sensitivity and specificity with an optimal cutoff <0.7 (95% CI by bootstrapping

Table 4. Global and local left ventricular remodeling

	Responders, n=84				Non-Responders, n=120			
	Baseline	Discharge	Early	Late	Baseline	Discharge	Early	Late
Global LV Remodeling								
EDD	59 ± 6	52 ± 7	48 ± 8 [†]	44 ± 6 [†]	65 ± 8 [§]	57 ± 7 [§]	50 ± 8 ^{†§}	59 ± 6 ^{§§}
ESD	49 ± 7	41 ± 6 [†]	37 ± 6 [†]	33 ± 5 [†]	56 ± 9 [§]	47 ± 6 [§]	40 ± 6 ^{†§}	49 ± 5 ^{§§}
LA	49 ± 6	48 ± 3	47 ± 2	45 ± 2	47 ± 7	46 ± 3	46 ± 2	44 ± 2
ESVI	66 ± 8	58 ± 8 [*]	52 ± 6 [†]	46 ± 5 [†]	77 ± 9 [§]	71 ± 8 ^{§§}	69 ± 9 [§]	80 ± 11 ^{§§}
EDVI	104 ± 12	93 ± 10 [*]	84 ± 10 [†]	79 ± 9 [†]	107 ± 16 [§]	100 ± 12 [§]	100 ± 14 [§]	109 ± 16 ^{§§}
LVEF	34 ± 12	37 ± 10	38 ± 11	42 ± 6 [†]	27 ± 11 [§]	28 ± 7 [§]	30 ± 9 [§]	29 ± 6 [§]
MPI	0.61 ± 0.1	0.58 ± 0.1	0.56 ± 0.1	0.50 ± 0.09 [†]	1.01 ± 0.1 [§]	0.95 ± 0.1 [§]	0.94 ± 0.1 [§]	0.95 ± 0.1 [§]
Systolic SPI	0.56 ± 0.1	0.42 ± 0.1 [*]	0.40 ± 0.1 [†]	0.35 ± 0.1 [†]	0.75 ± 0.1 [§]	0.72 ± 0.1 [§]	0.72 ± 0.1 [§]	0.78 ± 0.12 ^{§§}
Diastolic SPI	0.64 ± 0.1	0.52 ± 0.1 [*]	0.49 ± 0.1 [†]	0.44 ± 0.1 [†]	0.80 ± 0.1 [§]	0.76 ± 0.1 [§]	0.77 ± 0.1 [§]	0.81 ± 0.1 ^{§§}
WMSI	1.30 ± 0.5	1.16 ± 0.4 [*]	1.11 ± 0.5 [†]	1.09 ± 0.4 [†]	1.61 ± 0.7 [§]	1.42 ± 0.4 [§]	1.40 ± 0.5 [§]	1.59 ± 0.4 ^{§§}
Local LV Remodeling								
PPM posterior D (cm)	2.5 ± 0.6	2.2 ± 0.3 [*]	2.2 ± 0.3	2.2 ± 0.2	2.6 ± 0.5	2.5 ± 0.3 [§]	2.6 ± 0.3 [§]	2.7 ± 0.4 ^{§§}
APM posterior D(cm)	2.6 ± 0.4	2.3 ± 0.4 [*]	2.3 ± 0.4	2.4 ± 0.4	3.2 ± 0.5 [§]	3.1 ± 0.5 [§]	3.2 ± 0.5 [§]	3.4 ± 0.6 ^{§§}
PPM lateral D (cm)	2.0 ± 0.4	1.8 ± 0.3 [*]	1.7 ± 0.3	1.8 ± 0.3	1.9 ± 0.4	1.9 ± 0.3 [§]	1.9 ± 0.3 [§]	2.4 ± 0.3 ^{§§}
APM lateral D (cm)	1.2 ± 0.3	1.0 ± 0.2 [*]	1.0 ± 0.3	1.0 ± 0.3	1.5 ± 0.3 [§]	1.5 ± 0.4 [§]	15 ± 0.5 [§]	1.5 ± 0.4 ^{§§}
PM _s separation (cm)	3.3 ± 0.4	3.0 ± 0.4 [*]	3.0 ± 0.2	3.1 ± 0.2	3.7 ± 0.6 [§]	3.6 ± 0.6 [§]	3.6 ± 0.6 [§]	3.8 ± 0.7 ^{§§}
PPM-fibrosa D (cm)	6.6 ± 0.6	6.1 ± 0.5 [*]	6.2 ± 0.6	6.1 ± 0.5	6.6 ± 0.7	6.6 ± 0.5 [§]	6.5 ± 0.6 [§]	7.1 ± 0.7 ^{§§}
PPM WMSI	2.3 ± 0.5	2.1 ± 0.3 [*]	2.1 ± 0.4	2.2 ± 0.3	2.1 ± 0.4 [§]	2.0 ± 0.5 [§]	2.1 ± 0.6 [§]	2.4 ± 0.4 ^{§§}
APM WMSI	1.2 ± 0.1	1.0 ± 0.1 [*]	1.0 ± 0.1	1.0 ± 0.1	1.6 ± 0.4 [§]	1.4 ± 0.4 [§]	1.4 ± 0.36 [§]	1.4 ± 0.4 ^{§§}

^{*†‡} Significance vs. preoperative discharge and early follow-up, respectively. [§] Significance vs. responders. Continuous variables are presented as mean ± standard deviation.; Non-parametric variables were presented as median [Interquartile range].

Abbreviations: EDD=(Left ventricular) End diastolic diameter (mm); ESD=(Left ventricular) End systolic diameter (mm); LA=Left atrium (mm); ESVI=(Left ventricular) End systolic volume Index (ml/m²); EDVI=(Left ventricular) End diastolic volume Index (ml/m²); LVEF=Left ventricular ejection fraction (%); MPI=Myocardial performance index; SPI=Sphericity Index; WMSI=Wall motion Score Index; D=Distance (cm); PPM=Posterior papillary muscle; APM=Anterior papillary muscle; PM_s Papillary muscles; WMSI=Wall motion Score Index.

Table 5. Univariable predictors of LVRR

Variable	Odds Ratio	95% CI	p
MPI	5.82	1.84 - 7.26	<0.001
SI _s	9.51	4.60 - 12.4	<0.001
WMSI	3.04	0.52 - 3.59	0.001
APM posterior D	3.19	1.55 - 6.55	0.006
ESD	2.92	1.12 - 6.01	0.01
APM WMSI	3.82	1.84 - 7.26	0.01
PM _s separation	2.32	1.30 - 3.85	0.02
EDD	2.48	1.38 - 4.41	0.03
LVEF	2.56	1.22 - 5.33	0.03
SI _D	2.49	1.34 - 4.63	0.03
APM lateral D	2.63	1.11 - 3.40	0.04
MI localization	2.05	1.01 - 4.18	0.06
ESWS	1.66	0.79 - 3.48	0.15
Direction of jet	1.05	1.0 - 3.18	0.16
CCS angina class	0.55	0.27 - 1.13	0.21
Chronic renal disease	0.19	0.14 - 1.88	0.36
Cerebral vascular disease	0.64	0.24 - 1.56	0.36
COPD	1.41	0.60 - 3.01	0.37
Gender	1.72	0.49 - 5.76	0.38
MI <3 months	1.50	0.51 - 3.49	0.45
Number of diseased coronary arteries	1.44	0.50 - 5.12	0.47
NYHA class	1.28	0.62 - 1.62	0.48
Diseased left main coronary artery	1.55	0.85 - 2.81	0.52
Number of graft	1.29	0.57 - 2.64	0.53
Arterial graft	1.25	0.56 - 2.78	0.53
Age (years)	1.24	0.58 - 2.64	0.56
Smoking	0.58	0.10 - 2.51	0.56
Euroscore	1.32	0.44 - 3.50	0.57
Hypertension	0.61	0.10 - 2.62	0.6
Diabetes	1.38	0.42 - 4.65	0.61
Peripheral vascular disease	0.74	0.13 - 2.96	0.61
Familiar history	0.76	0.25 - 2.03	0.62
CCL time	1.22	0.48 - 2.91	0.61
CPB time	1.31	0.44 - 3.15	0.62
ERO	1.33	0.30 - 5.13	0.62
PPM - fibrosa D	0.82	0.33 - 2.06	0.63
PPM WMSI	1.28	0.50 - 3.60	0.64
MR	1.51	0.27 - 4.61	0.65
TA	0.78	0.26 - 2.01	0.73
Leaflet tethering	0.9	0.46 - 2.31	0.8
Preoperative medications	1.76	0.30 - 3.42	0.8
RF	1.27	0.26 - 3.57	0.8

Variable	Odds Ratio	95% CI	p
RV	1.09	0.52 - 2.27	0.82
Ring type	0.93	0.42 - 2.02	0.85
Ring size	0.94	0.59 - 1.50	0.82
LA	0.94	0.31 - 2.40	0.91
PPM posterior D	1.03	0.49 - 2.33	0.93
PPM lateral D	0.94	0.31 - 2.40	0.91

Abbreviations: LVRR=Left ventricular reverse remodeling; NYHA=New York Heart Association; CCS=Canadian Cardiovascular Society; COPD=Chronic obstructive pulmonary disease; MI=Myocardial infarction; CCL=Cross-clamp; CPB=Cardiopulmonary bypass; MR=(Grade of preoperative) Mitral regurgitation; TA=Tenting area; ERO=effective regurgitant orifice; RF=Regurgitant fraction; RV=Regurgitant volume; EDD=End diastolic diameter; ESD=End systolic diameter; LA=Left atrium; LVEF=Left ventricular ejection fraction (%); MPI=Myocardial performance index; SIS=Systolic sphericity Index; SID=Diastolic sphericity Index; WMSI=Wall motion Score Index; ESWS=End systolic wall stress; E=Peak trans-mitral flow velocity; A=peak late trans-mitral flow velocity; DT=Deceleration time at early diastolic filling (ms); IVRT=Isovolumetric relaxation time; PPM=Posterior papillary muscle; D=Distance; APM=Anterior papillary muscle; PMs=Papillary muscles; WMI=Wall motion index.

Table 6. Logistic regression for LVRR

Variable	Odds Ratio	p	Bias corrected 95% CI	
			Lower Limit	Upper Limit
SI _s	4.918	<0.001	2.107	5.993
MPI	4.753	<0.001	2.012	5.463
WMSI	2.612	0.003	0.903	3.841
APM posterior	1.625	0.06	0.871	2.433
SI _d	1.670	0.09	0.934	2.981
LVEF	1.612	0.1	0.954	2.666
APM WMSI	1.323	0.13	0.925	3.649
ESD	1.472	0.115	0.091	2.231
APM lateral	0.980	0.2	0.091	2.033
EDD	0.932	0.247	0.081	1.789
PM _s separation	1.01	0.3	0.096	2.012

Abbreviations: LVRR=Left ventricular reverse remodeling; EDD=End diastolic diameter; ESD=End systolic diameter; LVEF=Left ventricular ejection fraction; MPI=Myocardial performance index; SI_s=Systolic sphericity Index; SI_d=Diastolic sphericity Index; WMSI=Wall motion Score Index; DT=Deceleration time at early diastolic filling.

0.58-0.81). MPI with a cutoff <0.9 (95% CI by bootstrapping 0.75-0.96) had 100% of sensitivity and specificity. Finally, WMSI <1.5 (95% CI by bootstrapping 1.35-1.62) had 80% of sensitivity and 82% of specificity.

COMMENT

The most common surgical technique for CIMR is undersized mitral ring annuloplasty (UMRA)⁷. Although this procedure does not fully address the ventricular causes of CIMR, it is simple to perform and reproducible, and therefore has been widely adopted worldwide by cardiac surgeons. Nonetheless, after encouraging initial results⁸, different studies have revealed a significant proportion of patients developing recurrent MR during follow-up^{6,10} which has been mainly related to continued LV remodeling and persistent leaflet tethering^{9,30}. Thus left ventricular reverse geometric remodeling (LVR) is an important aim in the surgical treatment of CIMR.

Based on the same criterion used by Stellbrink et al¹⁶, in our study non-responders were observed in 58.8% of the study population which included 10% with further increase in ESVI. Braun and coworkers³¹ demonstrated 39.5% of non responders among 87 consecutive patients with CIMR undergoing restrictive mitral annuloplasty, considering a 10% reduction in LV end diastolic dimension as significant LVR. However, measurements of LV volumes have been demonstrated to be more reliable than LV diameters in assessing LV remodeling, especially in enlarged ventricles³².

In our experience, non-responders had a higher postoperative NYHA class ($p<0.001$), higher recurrence of mitral regurgitation ($p<0.001$) and higher reoperation rate for failed repair ($p<0.001$). In addition, 5-year survival was significantly lower in responders.

By comparing the two groups in our study, it appears evident that non-responders were preoperatively much more globally remodeled and that at late control they still showed more spherical, enlarged and dysfunctional left ventricle. Furthermore, the late increase in sphericity indexes in non-responders, exceeding the preoperative value, was consistent with further remodeling after UMRA, and reflects increased tethering on the mitral valve and greater displacement of PM_s . Furthermore, in our experience, non-responders had preoperatively a greater lateral and posterior displacement of the APM and a wider PM_s separation. Previous studies^{11,33} demonstrated that the local remodeling of the LV segments supporting PPM is a necessary condition for the development of MR and, accordingly, we found that PPM displacement occurred preoperatively in both Groups even, in non-responders, lateral and posterior displacement of APM were predominant.

In addition this Group had larger WMSI of the segments underlying the APM whereas PPM WMSI was higher in responders. These results support previous clin-

Figure 4. A,B Receiver operating characteristic (ROC) for systolic sphericity index to predict LV remodeling.

Figure 5. A,B. Receiver operating characteristic (ROC) for Myocardial Performance Index to predict LV remodeling.

Figure 6. A,B Receiver operating characteristic (ROC) for Wall Motion Score Index to predict LV remodeling.

ical findings reported by Agricola et al³⁴ who described two Groups of patients with CIMR according to tethering pattern. Likewise non-responder-patients in our study, their symmetric Group had prevalent posterior and lateral displacement of APM (both $p < 0.04$), PMs separation and APM WMSI (both < 0.0001).

Interestingly, this different distribution of local wall abnormalities did not reflect, in our experience, a different infarct localization and we cannot exclude that this different pattern of regional functional abnormalities is caused by progressive deterioration in contractile function with progressive recruitment of border zone myocardium into scar in patients with more dysfunctional LVs. Thus, the predominant displacement of APM and the larger APM WMSI might represent a sign of disease progression. Nonetheless, in our study, this pattern clearly identified subjects which are expected not to reverse-remodel after annuloplasty.

It would have been helpful to assess the regional viability of the regions associated with the anterior and posterior papillary muscles to confirm these findings.

After surgery, we showed that continued LV local remodeling occurs and it predominantly involves the region of the LV supporting the posterior papillary muscle whereas APM WMSI remained constant over time in both Groups.

Continued LV remodeling increases leaflets tethering leading to progressive lack of coaptation. In this setting the coaptation length gained at the end of procedure could play a significant role in preventing MR recurrence. The coaptation length should be sufficient to balance tethering forces secondary to postoperative remodeling thus another reason for these results might be the acceptance of a leaflet coaptation of only 5 mm at the end of the procedure which could not be adequate for all patients. Indeed, non responders showed a CL < 5 mm at any postoperative control and this value was significantly lower than responders ($p < 0.001$) even with comparable ring size between Groups ($p = ns$).

Thus, actually we believe that, in subjects who are expected not to reverse remodel, a minimum CL of 8 mm should be achieved³¹. Contrastingly, in patient with strongly tethered AML or with less tethered anterior leaflet but which is not sufficiently long to ensure a proper postoperative CL, regurgitation cannot be eliminated by ring annuloplasty. In these patients a chordal sparing mitral valve replacement technique should be considered.

A key point for achieving an appropriate leaflet coaptation and to ensure durable results is a true undersizing and, in this setting, a pivotal role can be played by the type of ring chosen. In the present experience we used only two rings (Carpentier's rigid or Physio semi-flexible rings). These two rings are not at all identical, thus, even we have undersized by two sizes both rings, we might have been less restrictive with the Physio ring than with the Classic ring. However, in our experience, the extent of LVRR was comparable between rings at any size. Furthermore neither ring type nor ring size were predictive of LVRR at logistic regression analysis.

Additionally, fifteen percent of non-responders experienced moderate/severe recurrent MR. Of interest, 64.2% of non responders with preoperative severe (4+) MR, developed a late recurrent MR $\geq 3+$ and preoperative MR grade >3 was a predictive factor of recurrent moderate/severe MR ($p < 0.001$). This finding deserves further investigation as these subjects might be not ideal candidates for UMRA and could more benefit from a chordal sparing mitral valve replacement.

Finally, at multivariable model, $SI < 0.72$, $MPI < 0.90$ and $WMSI < 1.59$ resulted independent predictors of LVRR. These results emphasize the importance of the extent of preoperative LV global remodeling as having a central role in predicting inadequate results after UMRA. Furthermore, these findings confirm that the increase of sphericity index at end of systole predicts recurrence of MR after restrictive annuloplasty⁹. A new finding in this study is that MPI predicts the likelihood of reverse remodeling, whereas LVEF was not significant. The myocardial performance Index is a simply measurable Doppler-derived index of combined systolic and diastolic performance which, differently from LVEF, is independent of LV loading conditions and heart rate¹⁹. It is the summation of isovolumetric contraction and relaxation time divided by the ejection time. MPI has a narrow range of values in subjects with normal left ventricular function (0.37 ± 5). Ventricular dysfunction prolongs isovolumetric relaxation and shortens ejection times, resulting in an increase of the index compared with normal subjects.

STUDY LIMITATIONS

Our study findings should be viewed in light of some inherent limitations.

- Evaluation of LVRR was based on volumes obtained by echocardiography; Volumetry by 2D echocardiography depends on geometric assumptions and is subject to image-plane positioning errors. Hence it is not accurate in shape distorted post-infarction left ventricles. However, this limitation belongs to most of published paper regarding this pathology.
- Viability testing was not performed in these patients. Therefore lack of LVRR in non responders might be also due to irreversible ischemic myocardial damage (non-viable myocardium). Furthermore, in relation to the papillary muscle displacement data presented, the revascularization of viable regions related to papillary muscle function might be the most important predictor of success with this operation. This issue deserves further investigation.
- Postoperative evaluation of the coronary status was not assessed. It would have been helpful to distinguish surgical failure from coronary disease progression.
- The issue of annulus re-shaping during annuloplasty has not been addressed. We employed only rigid/semi-flexible plane annuloplasty rings which may flatten the natural saddle shape causing greater tension on chordae and leaflets. Innovative

annular rings mimicking the shape of healthy mitral annulus have been recently introduced in the market³⁵⁻³⁷.

- Estimated cutoffs are known to be very susceptible to changes in the study population.

We employed bootstrapping techniques to validate the results, nonetheless, it has also been documented that the sensitivity/specificity associated with these cutoffs are overly optimistic.

STRENGTH OF THE STUDY

This is a large cohort reported with UMRA in CIMR patients with detailed (100% complete) echocardiographic follow-up. Furthermore our patient cohort was more homogeneous than in other study³⁸: all patients underwent associated CABG, they had no concomitant MV procedures, and the entire cohort was uniform regarding the MV ischemic leaflet dysfunction. Moreover, to assess results for MV repair, we studied true “recurrent” MR excluding those patients with “residual” MR in whom the insufficiency was presumably never eliminated at surgery. Additionally, we undertook valve sizing in a standardized fashion and the degree of undersizing was homogeneous over the 5-year-period of the study.

CLINICAL IMPLICATIONS

In our experience combined CABG and UMRA do not ensure successful and durable elimination of MR and significant LVRR in all patients. Those who can benefit from this approach could be preoperatively identified utilizing echo predictors. However, restrictive annuloplasty resulted to be ineffective in a large percentage of patients and results of this study suggest the need, in most of CIMR patients, for different approaches directly addressing ventricular tethering like second-order chordal cutting³, infarct placcation⁴, papillary muscle sling⁵, papillary muscle imbrication³⁹, PPM surgical relocation⁴⁰. Nonetheless, although these techniques appear promising, more data are required before they can be recommended for CIMR patients.

Additionally, the employment of support devices^{41,42} was introduced in the recent years in clinical practice, thus experiences with these techniques are actually in their preliminary phase.

Finally, mitral valve replacement, largely employed in the past in ischemic regurgitation, although eliminates the short-term risk of recurrent MR, is associated with poor long-term survival⁴³. Thus, in our actual policy, we do not consider MV replacement as a reasonable alternative to repair in all patients.

CONCLUSIONS

Our experience suggests that more information on possible echo predictors of an inadequate result may improve preoperative decision-making of CIMR patients for UMRA.

REFERENCES

1. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KL, Tajik AJ. Ischemic Mitral Regurgitation. Long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*. 2001;103(13):1759-64.
2. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation*. 2000;102(12):1400-6
3. Messas E, Guerrero JL, Handschumacher MD et al. Chordal cutting: a new therapeutic approach for ischemic mitral regurgitation. *Circulation*. 2001;104(16):1958-63.
4. Liel-Cohen N, Guerrero JL, Otsuji Y, et al. Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: insights from three-dimensional echocardiography. *Circulation* 2000; 101:2756-63.
5. Hvass U, Tapia M, Baron F, Pouzet B, Shafy A. Papillary muscle sling: a new functional approach to mitral repair in patients with ischemic left ventricular dysfunction and functional mitral regurgitation. *Ann Thorac Surg* 2003;75(3):809-11.
6. Tahta SA, Oury JH, Maxwell JM, Hiro SP, Duran CM. Outcome after mitral valve repair for functional ischemic mitral regurgitation. *J Heart Valve Dis*. 2002;11(1):11-8;
7. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;115(2):381- 6.
8. Bolling SF, Deeb GM, Bach DS. Mitral valve reconstruction in elderly, ischemic patients. *Chest* 1996;109(1):35- 40.
9. Bax JJ, Braun J, Somer ST et al. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation*. 2004;110(11 Suppl 1):II103-8.
10. McGee EC, Gillinov AM, Blackstone EH et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg*. 2004;128(6):916-24.
11. Hung J, Papakostas L, Tahta SA et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty. Continued LV remodelling as a moving target. *Circulation*. 2004 Sep 14;110(11 Suppl 1):II85-90.
12. Geidel S, Lass M, Schneider C et al. Downsizing of the mitral valve and coronary revascularization in severe ischemic mitral regurgitation results in reverse left ventricular and left atrial remodeling. *Eur J Cardiothorac Surg*. 2005;27(6):1011-6.
13. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. Edinburgh, Scotland: World Medical Association, October 2000. Available at: http://www.wma.net/e/policy/17-c_3.html. Accessed June 22, 2001.
14. Pfeffer MA, Braunwald E, Moye LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE investigators. *N Engl J Med* 1992;327(10):669-77.
15. Carpentier A. Cardiac valve surgery-The "French correction". *J Thorac Cardiovasc. Surg.* 1983; 86: 326-37.

16. Stellbrink C, Breithardt OA, Franke A et al. PATH-CHF (Pacing Therapies in Congestive Heart Failure) Investigators; CPI Guidant Congestive Heart Failure Research Group. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol*. 2001;38(7):1957-65.
17. Bland MJ, Altman DJ. Statistical method for assessing agreement between two methods of clinical measurements. *Lancet* 1986; 1:307-310.
18. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2(5):358.
19. Tei C, Ling LH, Hodge DO et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function a study in normals and dilated cardiomyopathy. *J Cardiol* 1995; 26(6):357-66.
20. Kono T, Sabbah HN, Rosman H, Alam M, Jafri S, Goldstein S. Left ventricular shape is the primary determinant of functional mitral regurgitation in heart failure. *J Am Coll Cardiol* 1992;20(7):1594-8.
21. Cerqueira MD, Weissman NJ, Dilsizian V et al. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105(4):539-42.
22. Gardin JM, Adams DB, Douglas PS et al. American Society of Echocardiography. Recommendations for a standardized report for adult transthoracic echocardiography: a report from the American Society of Echocardiography's Nomenclature and Standards Committee and Task Force for a
23. Standardized Echocardiography Report. *J Am Soc Echocardiogr*. 2002;15(3):275-90
24. Zoghbi WA, Enriquez-Sarano M, Foster E et al. American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; 16(7):777-802
25. Boltwood CM, Tei C, Wong M, Shah PM. Quantitative echocardiography of the mitral complex in dilated cardiomyopathy: the mechanism of functional mitral regurgitation. *Circulation* 1983; 68(3):498-508
26. Vijayaraghavan G, Boltwood CM, Tei C, Wong M, Shah PM. Simplified echocardiographic measurement of the mitral annulus. *Am Heart J* 1986; 112(5):985-91.
27. Romesburg HC. Cluster analysis for researchers. North Carolina: Lulu Press; 2004. 1-330.
28. Harrell FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modeling strategies for improved prognostic prediction. *Statistics in Medicine* 1984; 3:143-52.
29. Harrell FE Jr, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stats Med* 1996:361-87.

30. Hosmer DW, Lemeshow S. Applied Logistic regression. 2nd ed. New York, NY: Wiley-Interscience; 2000:143-202.
31. Kuwahara E, Otsuji Y, Iguro Y et al. Mechanism of recurrent/persistent ischemic/functional mitral regurgitation in the chronic phase after surgical annuloplasty: importance of augmented posterior leaflet tethering. *Circulation*. 2006 Jul 4;114(1 Suppl):I529-34.
32. Braun J, Bax JJ, Versteegh MI et al. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. *Eur J Cardiothorac Surg*. 2005;27(5):847-53.
33. Dujardin KS, Enriquez-Sarano M, Rossi A, Bailey KR, Seward JB. Echocardiographic assessment of left ventricular remodeling: are left ventricular diameters suitable tools? *J Am Coll Cardiol*. 1997 Nov 15;30(6):1534-41.
34. Gorman JH 3rd, Gorman RC, Plappert T et al. Infarct size and location determine development of mitral regurgitation in the sheep model. *J Thorac Cardiovasc Surg*. 1998;115(3):615-22.
35. Agricola E, Oppizzi M, Maisano F et al. Echocardiographic classification of chronic mitral regurgitation caused by restricted motion according to tethering pattern. *Eur J Echocardiography* 2004; 5: 326-34.
36. Votta E, Maisano F, Bolling SF, Alfieri O, Montecocchi FM, Redaelli A. The Geoform disease-specific annuloplasty system: a finite element study. *Ann Thorac Surg*. 2007;84(1):92-101.
37. Salgo IS, Gorman JH, Gorman RC, et al. Effect of Annular Shape on Leaflet Curvature in Reducing Mitral Leaflet Stress. *Circulation*. 2002; 106:711-717.
38. Jimenez JH, Yoganathan AP, et al. Effects of a saddle shaped annulus on mitral valve function and chordal force distribution: An in vitro Study. *Annals of Biomedical Engineering*. Vol. 31, pp. 1171-1181, 2003.
39. Adams DH, Anyanwu A. Pitfalls and limitations in measuring and interpreting the outcomes of mitral valve repair. *J Thorac Cardiovasc Surg*. 2006; 131(3):523-9.
40. Menicanti L, Di Donato M, Frigiola A, et al. Ischemic mitral regurgitation: intraventricular papillary muscle imbrication without mitral ring during left ventricular restoration. *J Thorac Cardiovasc Surg* 2005; 129: 440-2.
41. Kron IL, Green GR, Cope JT. Surgical relocation of the posterior papillary muscle in chronic ischemic mitral regurgitation. *Ann Thorac Surg* 2002;74:600-1.
42. Konertz W, Rombeck B, Hotz H. Short-term safety of the Acorn cardiac support device in patients with advanced heart failure. *J Am Coll Cardiol* 2000;35:182A.
43. Fukamachi K, McCarthy PM. Initial safety and feasibility clinical trial of the myosplint device. *J Card Surg*. 2005 Nov-Dec;20(6):S43-7
44. Gillinov AM, Wierup PN, Blackstone EH et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg*. 2001;122(6):1125-41.

4

Insights on Left Ventricular and Valvular Mechanisms of Recurrent Ischemic Mitral Regurgitation After Restrictive Annuloplasty and Coronary artery Bypass Grafting

Sandro Gelsomino, MD, Roberto Lorusso, MD, Ph.D, Sabina Caciolli, MD, Irene Capecchi, MD, Carlo Rostagno, MD, Marco Chioccioli, MD, Giuseppe De Cicco, MD, Giuseppe Billè, MD, Pierluigi Stefano, MD and Gian Franco Gensini, MD.

Published in: J Thorac Cardiovasc Surg. 2008; 136(2):507-18.

ABSTRACT

Background. We investigated leaflet and subvalvular configurations to identify mechanisms leading to recurrent mitral regurgitation after combined undersized mitral annuloplasty and coronary artery bypass and to preoperatively recognize patients who are unlikely to benefit from this approach.

Methods. Among 261 Subjects with chronic ischemic mitral regurgitation undergoing undersized annuloplasty and coronary bypass surgery in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and September 2007, thirty-one were excluded: 4 had intraoperative annuloplasty failure, 12 showed residual regurgitation and 15 had incomplete echoes available. The study population consisted of 230 patients who were divided in two Groups: patients without (Group 1, n=176) or with (Group 2, n=54) late recurrent mitral regurgitation. Fifty normal healthy subjects were controls. Serial echoes were performed preoperatively, at discharge and at follow up appointments (early, median 6 months [Interquartile range 5-6]; late, median 33 months [17-51]).

Results. Subjects with late regurgitation had preoperatively a more symmetric tethering ($p<0.001$), a more accentuated anterior mitral leaflet tethering ($p<0.001$) and a more restricted anterior leaflet excursion ($p=0.003$) than Group 1. Postoperatively, tethering of posterior leaflet increased ($p<0.001$) and it was predominant in both groups whereas the tethering of the anterior leaflet reduced at discharge ($p=0.01$ and $p=0.03$, respectively) remaining constant afterwards. Multivariable analysis showed anterior tethering angle $\geq 39.5^\circ$ ($p<0.001$), an anterior/posterior tethering angle ratio ≥ 0.76 ($p<0.001$), an anterior leaflet excursion angle $\leq 35^\circ$ ($p=0.001$) and a coaptation height ≥ 11 mm ($p=0.04$) to be predictors of recurrent mitral regurgitation.

Conclusions. Preoperative symmetric tethering with anterior mitral leaflet predominance was strongly associated with recurrence of MR. Measures of leaflet tethering resulted fundamental findings to identify ischemic patients who can really benefit from restrictive annuloplasty. Further larger studies are necessary to confirm our results.

INTRODUCTION

93

Chronic Ischemic Mitral Regurgitation (CIMR) results from a variable combination of infarction-induced subvalvular remodeling with subsequent leaflet tethering and annulus dilatation/flattening^{1,2}. An established therapeutic approach to relieve CIMR, in association with coronary artery bypass grafting (CABG), is an undersized mitral ring annuloplasty (UMRA) which, by reducing the septal-lateral dimensions and the valve area, brings both mitral leaflets into apposition³. Nonetheless, after encouraging initial results⁴, different studies have revealed a significant proportion of patients developing recurrent mitral regurgitation (MR) during follow-up⁵⁻⁷ which has been mainly related to continued left ventricular remodeling and persistent leaflet tethering^{7,8}. In our previous experience⁹, 72% of patients undergoing combined CABG and UMRA showed, at five-year control, recurrent MR. In addition, left ventricular reverse remodeling was observed only in 44.2% of the study population with 10.3% of patients showing further left ventricular dilatation. In the present study we investigated leaflet and subvalvular configurations before and after surgical annuloplasty to identify mechanisms leading to recurrent MR. Furthermore we attempted to determine whether preoperative tethering patterns and subvalvular configurations can accurately predict unsuccessful ischemic valve repair.

METHODS

PATIENTS POPULATION

Among 261 Subjects with CIMR undergoing combined CABG and UMRA in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and September 2007, thirty-one were excluded: 4 had intraoperative annuloplasty failure, 12 showed residual MR ($\geq 2+$ at discharge) and 15 had incomplete echoes available. Definition and inclusion criteria are as previously reported⁹. Therefore, the study population consisted of 230 patients who were divided in two Groups: patients without (Group 1, n=176) or with (Group 2, n=54) late recurrent MR (insufficiency $\geq 2+$ at late appointment in patients with no/trivial MR at discharge). Fifty normal healthy subjects with no history of cardiovascular disease and with normal Doppler echocardiographic examination and who had a gender distribution, age and average body surface area similar to study patients were controls. Patient profiles are summarized in Table 1. Following the World Medical Association guidelines concerning ethical principles for medical research involving human subjects¹⁰, the study was approved by Institutional Ethics Board. Furthermore, all patients gave their informed consent.

Table 1. Patients Profile

	All n=230	Group1 (MR-) n=176	Group1 (MR+) n=54	p
Age (years)	67 ± 7	68 ± 8	66 ± 7	0.87
Gender M/F	142/88 (63.1/36.9)	106/70 (60.2/39.8)	36/18 (66.6/33.4)	0.07
NYHA class	3 [3-4]	3 [3-4]	3 [3-5]	0.66
CCS angina class	2 [1-3]	2 [1-3]	2 [1-3]	>0.9
Euroscore				
Additive	8.1 [5-9]	8.0 [5-9]	8.2 [5-8]	0.8
Logistic	15 [10-18]	14.8 [11-18]	15.1 [10-18]	
Hypertension	89 (38.7)	67 (38.1)	22 (40.7)	0.6
Diabetes	66 (28.6)	50 (28.4)	16 (29.6)	0.81
COPD	31 (12.7)	23 (13.0)	8 (12.5)	0.9
Chronic renal disease	35 (15.2)	26 (14.8)	9 (16.6)	0.77
Cerebral vascular disease	25 (10.8)	18 (10.2)	7 (12.0)	0.63
Peripheral vascular disease	16 (6.9)	12 (6.8)	4 (7.4)	0.83
Familiar history	114 (49.5)	85 (48.3)	29 (53.7)	0.57
Myocardial infarction				
>3 months	175 (76.1)	132 (75.0)	43 (79.6)	
≤3 months	55 (23.9)	44 (25.0)	11 (20.4)	
Inferior/Posterior	121 (52.6)	98 (55.7)	23 (42.5)	0.8
Anterior/Septal	20 (8.7)	14 (7.9)	6 (11.1)	
Lateral	22 (9.6)	15 (8.6)	7 (12.9)	
Combined	67 (29.1)	49 (27.8)	18 (33.5)	
Coronary vessel disease				
1	2 [2-3]	2 [2-3]	2 [2-3]	
2	5 (2.2)	3 (1.8)	2 (3.8)	
≥3	103(44.7)	77 (43.7)	26 (48.1)	0.66
Left Main	122 (53.1)	96 (54.5)	26 (48.1)	
	43 (18.6)	32 (18.1)	11 (20.3)	
Medications				
Angiotensin-converting enzyme inhibitors	186(80.8)	141 (80.1)	45 (83.3)	
B-adrenergic blockers	124 (53.9)	96 (54.5)	28 (51.8)	
Long-acting nitrates	105 (45.6)	82 (46.6)	23 (42.5)	0.71
Diuretics	195 (84.7)	150 (85.2)	45 (83.3)	
Digitalis	49 (21.3)	38 (21.5)	11 (20.3)	
Calcium antagonists	35 (15.2)	26 (14.7)	9 (16.6)	
Preoperative IABP	14 (6.1)	11 (6.2)	3 (5.5)	0.6

	All n=230	Group1 (MR-) n=176	Group1 (MR+) n=54	p
Surgery				
Antegrade Cardioplegia	208 (90.4)	158 (89.7)	50 (92.5)	0.6
Antegrade and Retrograde Cardioplegia	22 (9.6)	18 (10.3)	4 (7.5)	0.16
CPB time (min)	108 [95-120]	105 [94-118]	110 [100-126]	0.09
CCL time (min)	90 [70-98]	81 [66-90]	95 [70-101]	0.06
Surgical Approach				
Left atriotomy	192 (83.4)	146 (82.9)	46 (85.2)	0.8
Transseptal	21 (9.2)	17 (9.7)	4 (7.4)	0.23
Transseptal extended to LA roof	17 (7.4)	13 (7.4)	4 (7.4)	>0.9
Mitral Ring				
*Carpentier Classic	123 (53.4)	93 (52.8)	30 (55.5)	0.7
*Physio	107 (46.6)	83 (47.2)	24 (44.5)	0.51
Ring size (mm)				
24 mm	28 [26-30]	28 [26-30]	28 [26-30]	>0.9
26 mm	12 (5.2)	9 (5.1)	3 (5.5)	
28 mm	87 (37.8)	68 (38.6)	19 (35.3)	
30 mm	88 (38.3)	67 (38.1)	21 (38.8)	
CABG	43 (18.7)	32 (18.2)	11 (20.4)	
Anastomoses/patient	2 [2-3]	2 [2-3]	2 [2-3]	>0.9
Arterial graft/patient	1 [1-2]	1 [1-2]	1 [1-2]	>0.9

Continuous variables are presented as mean $\pm$ standard deviation; Discrete variables are presented as percentage. Non-parametric variables were presented as median [Interquartile range]. Abbreviations: ns=not significant; M/F=Male/Female; NYHA=New York Heart Association; CCS=Canadian Cardiovascular Society; COPD=Chronic obstructive pulmonary disease; IABP=Intraaortic balloon pump; CPB=Cardiopulmonary bypass; CCL=(Aortic)Cross-clamp; MR=Mitral regurgitation; CABG=Coronary artery bypass grafting.*Edwards LifeSciences, Irvine,CA.

SURGERY

All patients underwent associated CABG. For the purpose of this study, complete revascularization was accomplished when, at least one graft was placed distal to an approximately 50% diameter narrowing in each of the three major vascular system in which arterial narrowing of this severity was noted in a vessel ≥ 1.5 mm of diameter. It was not considered necessary to bypass all obstructed diagonal branches

of the anterior descending or marginal branches of the circumflex coronary arteries for a classification of complete revascularization. Following this definition 100% patients underwent complete revascularization. The ring size was determined by standard measurements of the inter-trigonal distance and anterior leaflet height. A downsizing by two ring sizes was performed in all patients. After cardiopulmonary bypass (CPB), a transesophageal echocardiography (TEE) was performed to assess residual MR.

ECHOCARDIOGRAPHY

Serial trans-thoracic echoes (TTE) were performed preoperatively, at discharge and at follow up appointments (follow-up 100% complete). Median early follow up was 6 months (Interquartile range [IQR] 5-6), median late follow up was 33 months (IQR 17-51).

Echo examinations were carried out by two experienced echocardiographers (S.C. and M.C.) and stored on a magneto-optical disc for off-line analysis. Measurements were made off line by two cardiologists (I.C. and C.R.) blinded to severity of MR and to the time when the images were made. Measurements and calculations were carried out as previously reported⁹. The reliability of echocardiographic measurements was assessed by calculating inter-observer and intra-observer interval of agreements of main direct measures used in this study in a different group of 20 subjects (10 MR, Appendix 1)¹¹.

QUANTIFICATION OF MR

The following quantitative measurements were simultaneously employed to grade the severity of MR and final results were averages of measured values¹²⁻¹³: (1) Quantitative Doppler: mitral and aortic stroke volumes were calculated and regurgitant volume (RV) was the difference between these 2 stroke volumes. The effective regurgitant orifice (ERO) area was the ratio of RV to regurgitant time velocity integral (RTVI). (2) Proximal Isovelocity Surface Area (PISA) analyzed the proximal flow convergence and ERO was the ratio of regurgitant flow to regurgitant velocity. RV was the product of ERO by RTVI. For each measurement, minimum of three cardiac cycles were averaged. The severity of MR was graded on a scale of 1 to 4 according to American Society of Echocardiography Guidelines¹². In patients with no/trivial MR by color Doppler, RV, and ERO were used as calculated, and ERO was assumed as null. Mitral annular areas (MA_a) were obtained from mitral annular dimensions in apical long-axis, 4-chamber, and 2-chamber views, using an ellipsoid assumption¹⁴ and indexed by body surface area.

Figure 1. A) Papillary muscles displacement measured in the parasternal short axis view. B) PPM-fibrosa measured in long-axis view (see text).

Figure 2. A, a. Method to quantify mitral leaflet tethering in the parasternal long-axis view in mid-systole. CL=Coaptation length; d=coaptation distance; h= coaptation height; α' =Anterior mitral leaflet tethering angle; γ =Bending angle; β' =posterior mitral leaflet tethering angle; B, b. Diastolic parasternal long-axis view. α EX=Anterior mitral leaflet excursion angle; β EX=Posterior mitral leaflet excursion angle; AMLEX=Anterior mitral leaflet excursion; PMLEX=Posterior mitral leaflet excursion.

PAPILLARY MUSCLES DISPLACEMENT

The displacement of papillary muscles (PMs) was quantified as distances from well-defined anatomic landmarks at early and end systole¹⁵. The geometric chord defined by septal insertions and the mid-septal perpendicular line were used as references in the parasternal short-axis view (Figure 1A). Lateral and posterior displacements of anterior (APM) and posterior (PPM) papillary muscles were measured as distances from these fixed references. Separation between papillary muscles was directly measured. In the long axis view the apical displacement of the PPM was measured as the distance between the papillary muscle head and the fixed inter-valvular fibrosis (annular-papillar distance, Figure 1B). The wall motion score indexes (WMSIs) of the basal and mid-posterior and inferior segments for the PPM and of basal and mid-lateral and anterior segments for the APM were also calculated¹⁵.

MITRAL LEAFLET TETHERING

Mitral leaflets tethering in mid-systole was assessed in the parasternal long axis view (Figure 2). The mitral valve tenting area was calculated as the area enclosed between the annular line and the mitral valve leaflets. Posterior and apical displacement of the coaptation were measured as coaptation distance d and coaptation height h , respectively whereas coaptation length (CL) was directly measured. The AML tethering angle α' , the AML excursion angle α_{EX} and distance AML_{EX} , the PML tethering angle β' , the PML excursion angle β_{EX} and distance PML_{EX} and the bending angle γ were obtained as explained in Appendix 2. Tethering patterns were defined according to Agricola and coworkers¹⁵. The anterior/posterior tethering angle ratio α'/β' was a quantitative measurements of tethering: the more this ratio was approaching 1 the more symmetric was the tethering.

STATISTICAL ANALYSIS

Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data were expressed as mean $\pm$ standard deviation, non-parametric data were presented as median and interquartile range and frequencies as proportions.

Data were compared by the Student's t-test, Mann Whitney U test, χ^2 test and Fisher exact test where appropriate. Echocardiographic variables over time were analyzed by means of ANOVA repeated measures followed by Tukey post-hoc test. Kruskal Wallis and Friedman tests were used when variables were not normally distributed and the Dunn post-hoc test was employed for multiple comparisons.

Multivariable logistic regression analysis by means of a backward stepwise algorithm (cut-off for entry 0.05, for removal 0.10) was performed to select independent

predictors of recurrent regurgitation and forty demographic, clinical, and echocardiographic parameters were investigated for their predictive value. To enhance the accuracy of the model, the number of variables was reduced using variable clustering¹⁶ until the number of variables to use as candidate in the regression analysis was $\leq m/10$, where for binary outcomes m is the number of patients in the less frequent outcome category¹⁷.

Model assumptions (linearity and additivity assumptions) were checked by piecewise cubic polynomials (spline functions) and pooled interaction test¹⁸, respectively, and found to be satisfactory. Goodness of fit of the final logistic regression

Table 2. Preoperative Mitral Regurgitation

	Controls n=50	All n=230	Group1 (MR-) n=176	Group2 (MR+) n=54	p
MR					
Grade	-	3 [3-4]	3 [3-4]	3 [3-4]	>0.9

models was assessed with the Hosmer–Lemeshow statistic¹⁹ and predictive accuracy was assessed by the concordance index (c)¹⁸. Internal validation of predictors generated by multivariable logistic regression was performed by means of bootstrapping techniques, with 1000 cycles and generation of OR and bias corrected 95% CI¹⁸. Optimal cutoff values were determined as the rounding cut-off that gives the maximum sum of sensitivity and specificity. This value should be the shoulder at the top left of the ROC (receiver operating characteristic curve). Bootstrapping techniques were employed to validate the results.

SPSS 12.0 (SPSS, Chicago, IL, USA) and Stats Direct 2.5.7 (Stats Direct, Sale, UK) were used for these calculations. Significance for hypothesis testing was set at the 0.05 two-tailed level.

RESULTS

PREOPERATIVE MR, PM_s DISPLACEMENT LEAFLETS TETHERING.

There was no significant difference between Groups regarding qualitative and quantitative MR data (Table 2). However, in the Group 1 MR jet direction was posterior in the major part of patients, whereas it was central or anterior in most of patients in the Group 2. Furthermore, patients with recurrent mitral regurgitation had greater preoperative posterior and lateral displacement of the anterior papillary muscle (both, $p < 0.001$), a wider papillary muscle separation ($p = 0.007$) and a larger WMSI of the segments underlying the anterior papillary muscle ($p = 0.01$).

Table 3. Postoperative mitral regurgitation

	Controls n=50	Group 1 (MR-) n=176				Group 2 (MR+) n=54			
		Discharge	Early	Late	p	Discharge	Early	Late	p
MR Grade	-	0 [0-1]	0 [0-1]	0 [0-1]	>0.9	0 [0-1]	2 [2-3]*	3 [3-4]#	<0.001
None/Trace	-	176 (100)	176 (100)	176 (100)		54 (100)	5 (9.2)	-	
2+	-	-	-	-		-	24 (44.5)	12 (22.3)	
3+	-	-	-	-		-	24 (44.5)	34 (62.9)	
4+	-	-	-	-		-	1 (1.8)	8 (14.8)	
Quantitative data									
ERO	-	-	-	-	-	-	16 ± 7	32 ± 11	<0.001
RF	-	-	-	-	-	-	24 ± 5	44 ± 13	<0.001
RV	-	-	-	-	-	-	28 ± 5	56 ± 18	<0.001
Direction of regurgitant jet									
Central	-	-	-	-	-	-	-	-	-
Anterior	-	-	-	-	-	-	-	-	-
Posterior	-	-	-	-	-	-	52 (96.2)	52 (96.2)	
Complex	-	-	-	-	-	-	2 (3.8)	2 (3.8)	
Mitral Area									
MA _s	4.5 ± 0.4	4.9 ± 1.3*	4.9 ± 1.2	4.9 ± 1.3	0.6	5.0 ± 1.3*	5.1 ± 1.2	5.1 ± 1.3	0.7
MA _d	7.0 ± 0.6	6.4 ± 2.2*	6.4 ± 2.3	6.4 ± 2.3	0.5	6.3 ± 2.2*	6.3 ± 2.3	6.3 ± 2.0	>0.9
MA _{cont}	35 ± 8	23 ± 3*	23 ± 2	23 ± 3	0.34	20 ± 3*	19 ± 2	19 ± 3	0.79

	Controls n=50	Group1 (MR-) n=176			p	Group 2 (MR+) n=54			p
		Discharge	Early	Late		Discharge	Early	Late	
Papillary muscles displacement									
PPM posterior D	1.6 ± 0.2	2.2 ± 0.3*	2.2 ± 0.3	2.2 ± 0.2	>0.9	2.5 ± 0.3 ^s	2.4 ± 0.3 ^s	2.7 ± 0.4 ^{‡#}	<0.001
APM posterior D	2.0 ± 0.2	2.3 ± 0.4*	2.3 ± 0.4	2.3 ± 0.4	>0.9	3.1 ± 0.5 ^s	3.0 ± 0.5 ^s	3.4 ± 0.6 ^{‡#}	0.005
PPM lateral D	1.4 ± 0.2	1.8 ± 0.3*	1.7 ± 0.3	1.7 ± 0.3	0.88	1.8 ± 0.3	1.8 ± 0.3 ^s	2.4 ± 0.3 ^{‡#}	0.002
APM lateral D	0.9 ± 0.2	0.9 ± 0.2*	0.9 ± 0.3	0.9 ± 0.3	0.86	1.4 ± 0.4 ^s	1.4 ± 0.5 ^s	1.6 ± 0.4 ^{‡#}	0.02
PM ₃ separation	2.5 ± 0.4	3.0 ± 0.4*	2.9 ± 0.2	2.9 ± 0.2	0.9	3.6 ± 0.6 ^s	3.6 ± 0.6 ^s	3.8 ± 0.7 ^{‡#}	0.04
PPM-fibrosa D	5.1 ± 0.5	6.1 ± 0.5*	6.2 ± 0.6	6.1 ± 0.5	0.88	6.5 ± 0.5	6.4 ± 0.6	7.1 ± 0.7 ^{‡#}	<0.001
PPM WMSI	1.0 ± 0	2.1 ± 0.3*	2.2 ± 0.4	2.3 ± 0.3	0.69	1.9 ± 0.5 ^s	1.9 ± 0.6	2.4 ± 0.4 [‡]	0.02
APM WMSI	1.0 ± 0	1.2 ± 0.1*	1.2 ± 0.1	1.2 ± 0.1	>0.9	1.5 ± 0.4 ^s	1.5 ± 0.36	1.5 ± 0.4 [‡]	>0.9
Coaptation									
TA	0.8 ± 2	2.6 ± 1.1*	2.7 ± 1.0	2.7 ± 1.1	0.9	3.5 ± 1.1 ^s	3.6 ± 1.0 ^s	3.6 ± 1.1 [‡]	>0.9
CL	8.5 ± 0.4	8.4 ± 0.4*	8.5 ± 0.5	8.5 ± 0.3	0.8	5.1 ± 0.4 ^s	4.1 ± 0.3 ^{‡s}	3.0 ± 0.3 ^{‡#}	0.9
d	27.6 ± 6	31.1 ± 7*	32.8 ± 9	33.4 ± 6	0.08	33.1 ± 7 ^s	35.0 ± 9 ^s	38.4 ± 6 ^{‡#}	0.01
h	6.1 ± 2	7.3 ± 3*	7.5 ± 3	7.1 ± 3	0.06	11. ± 3 ^s	11.5 ± 3 ^s	11.1 ± 4 [‡]	>0.9
Mitral leaflets tethering									
α'	24.3 ± 3	25.5 ± 7*	23.2 ± 5	24.0 ± 6	0.6	37.4 ± 8 ^s	35.8 ± 8 ^s	35.2.0 ± 9 [‡]	0.79
γ	156.6 ± 12	151.2 ± 10*	150.3 ± 8	150.6 ± 9	0.9	124.1 ± 6 ^s	124.3 ± 6 ^s	120.1 ± 5 [‡]	0.8
β'	33.4 ± 5	62.0 ± 12*	64.3 ± 11	79.1 ± 14 [#]	0.001	62.3 ± 12 [‡]	66.2 ± 11 ^{‡s}	76.5 ± 14 [‡]	<0.001
α' / β' Ratio	0.72 ± 0.4	0.41 ± 0.1*	0.36 ± 0.1	0.30 ± 0.1	<0.001	0.60 ± 0.2 [‡]	0.54 ± 0.2 ^{‡s}	0.46 ± 0.1 ^{‡#}	<0.001

	Controls n=50	Group1 (MR-) n=176			p	Group 2 (MR+) n=54			p
		Discharge	Early	Late		Discharge	Early	Late	
Leaflets excursion									
α_{EX}	46.0 ± 7	40.3 ± 4*	41.0 ± 4	42.6 ± 5	0.7	34.0 ± 3 ^s	34.0 ± 3 ^s	34.1 ± 4*	>0.9
β_{EX}	28.6 ± 4	6 ± 2*	6 ± 2	4 ± 4 [#]	0.03	6 ± 3*	6 ± 2	4 ± 4 [#]	0.03
AML _{EX}	21.5 ± 5	19.4 ± 3*	19.6 ± 3	20.3 ± 4	0.64	16.6 ± 3 ^s	16.1 ± 3 ^s	16.2 ± 3*	0.9
PML _{EX}	9.5 ± 0.7	2.7 ± 0.3	2.7 ± 0.2	1.4 ± 0.2 [#]	0.001	3.4 ± 0.3*	3.1 ± 0.2	2.0 ± 0.2 [#]	<0.001

Continuous variables are presented as mean ± standard deviation. Non-parametric variables were presented as median [Interquartile range]. p=significance over time; *† Significance vs. preoperative discharge and early follow-up, respectively; ^s‡ Significance vs. Group 1 at discharge, early and late control, respectively. *Abbreviations:* MR=Mitral Regurgitation;ERO=effective regurgitant orifice(mm²); RF=Regurgitant fraction (%);RV=Regurgitant volume(ml/beat);MA_s=(Systolic) Mitral annular area(cm²);MA_d=(Diastolic)Mitral annular area(cm²);MA_{cont}=Mitral annular contraction(%);D=Distance (cm) PPM=Posterior papillary muscle;APM=Anterior papillary muscle;PM_s=(Separation of) Papillary muscles(cm);WMSI=Wall motion Score Index ;TA=Tenting area (cm²);CL=Coaptation length (mm);d=coaptation distance (mm);h=coaptation height (mm); α' =Anterior mitral leaflet tethering angle(°); β' =Posterior mitral leaflet tethering angle(°); α_{ex} =Anterior mitral leaflet excursion angle(°); β_{ex} =Posterior mitral leaflet excursion angle (°);AML_{ex}=Anterior mitral leaflet excursion (mm);PML_{ex}=Posterior mitral leaflet excursion (mm).

Table 4. Multivariable Analysis

Variable	Cutoff	*95% CI	Sensitivity	Specificity	AUC	95%CI	OR	Bias corrected p 95% CI
α'	≥39.5°	34.3°-41.2°	98%	97%	0.99	0.92-1	5.4	2.6-6.9 <0.001
α' / β'	≥0.76	0.68-0.81	87%	86%	0.93	0.89-0.95	4.8	2.0-6.3 <0.001
α_{ex}	≤35°	32°-39°	85%	83%	0.87	0.81-0.93	2.3	1.2-3.1 0.001
h	≥11 mm	8.7-11.9	81%	84%	0.89	0.83-0.95	1.8	0.8-2.3 0.04

Abbreviations: AUC=Area under curve; α' =Anterior mitral leaflet tethering angle; β' =Posterior mitral leaflet tethering angle(°); α_{ex} =Anterior mitral leaflet excursion angle; h=coaptation height. *95% CI by bootstrapping.

Contrastingly, WMSI of the segments underlying the posterior papillary muscle was higher in patients who did not show MR at postoperative control ($p=0.03$), whereas posterior and lateral displacement of the posterior papillary muscle were comparable in two Groups ($p>0.9$ and $p=0.7$, respectively). Moreover, tenting area ($p<0.001$) and coaptation height ($p=0.004$) were higher whereas coaptation length was lower ($p=0.006$) in patients with recurrent MR. Contrastingly, the coaptation distance was comparable between Groups ($p=0.7$). Additionally, both anterior tethering angle α' ($p=0.001$) and bending angle γ ($p=0.01$) were larger in Group 2, while the posterior tethering angle β' did not differ between groups ($p=0.66$). When the degree of tethering was compared further in the two Groups, patients without postoperative MR had a more pronounced posterior leaflet tethering (<0.001) with prevalent restriction of the posterior leaflet excursion ($p<0.001$). In contrast, patients who developed postoperative MR had a more accentuated anterior leaflet tethering ($p<0.001$), a more restricted excursion of the anterior leaflet ($p<0.001$) and a more symmetric tethering ($p<0.001$) when compared to Group 1.

POSTOPERATIVE MR, PMs DISPLACEMENT LEAFLETS TETHERING.

At postoperative control (Table 3) 96.2% of patients in the Group 2 showed a posterior MR whereas 3.8% had central or anterior regurgitation ($p<0.001$). Annular areas reduced from the preoperative value in both Groups ($p<0.001$) and remained constant over time. In patients with no recurrent MR, at discharge, indexes of posterior displacement (posterior papillary muscle, $p=0.03$; anterior papillary muscle, $p=0.001$) and lateral displacement (posterior papillary muscle, $p=0.02$; anterior papillary muscle, $p=0.03$) of both papillary muscles, PMs separation (<0.001), annular-papillar distance ($p=0.01$) and wall motion score indices (posterior papillary muscle, $p=0.02$, anterior papillary muscle, $p=0.04$) were reduced significantly. All these parameters remained constant in this Group afterwards. In Group 2, all indices of displacement of both papillary muscles as well as WMSI at level of the posterior papillary muscle showed a not significant reduction at discharge, remained stable at early control, increasing significantly at late examination. In contrast, WMSI of the LV segments underlying the anterior papillary muscle did not show any significant change over time.

Furthermore, the coaptation distance d reduced significantly in both Groups at discharge; however, whereas it kept constant in patients without recurrent MR, it significantly re-increased at late study in those with recurrent MR ($p=0.008$). Differently, coaptation height significantly decreased at discharge ($p<0.001$ and $p=0.03$ in Group 1 and 2, respectively) and kept constant afterwards in both Groups. Coaptation length raised in the Group 1 at discharge ($p<0.001$) remaining stable over time. In Group 2 CL increased at discharge ($p=0.02$) but reduced at early ($p=0.01$) and late ($p<0.001$) controls. However coaptation length was at any time higher in

Group 1 ($p < 0.001$) which showed 100% patients with $CL \geq 8$ mm at postoperative controls. At discharge, the anterior leaflet tethering angle α' significantly decreased ($p = 0.01$ and $p = 0.03$ in Groups 1 and 2, respectively), whereas the excursion angle α_{EX} ($p = 0.02$ and $p < 0.001$ in Group 1 and 2, respectively) and the excursion distance AML_{EX} of the anterior leaflet increased (both, $p = 0.02$). All these indices remained constant afterwards. In contrast, the posterior leaflet tethering angle β' raised at discharge (both, $p < 0.001$) whereas the excursion angle β_{EX} (both, $p < 0.001$) and excursion distance PML_{EX} (both, $p < 0.001$) reduced significantly in both Groups. These indices remained stable at early control, but, at late echocardiography, the tethering angle β' re-increased (both, $p < 0.001$) whereas the excursion angle β_{EX} (both 0.03) and the excursion distance PML_{EX} (both $p < 0.001$) further reduced without difference between Groups.

The bending angle γ significantly raised at discharge in patients without postoperative MR ($p = 0.03$) and kept constant at subsequent controls. Differently, the γ showed a significant decrease in patients with postoperative MR ($p = 0.008$) remaining constant afterwards. When the degree of tethering was examined further in the two Groups, it became progressively more asymmetric in both Groups (Group 1, $p < 0.001$ vs. preoperative, $p = 0.03$ vs. discharge, $p = 0.03$ vs. early; Group 2, $p < 0.001$ vs. preoperative, $p = 0.03$ vs. discharge, $p = 0.02$ vs. early).

VALVULAR AND SUBVALVULAR DETERMINANTS OF RECURRENT MR

Multivariable regression analysis (Table 4) identified an anterior tethering angle $\alpha' \geq 39.5^\circ$ ($p < 0.001$), an anterior/posterior tethering angle ratio $\alpha'/\beta' \geq 0.76$ ($p < 0.001$), an anterior leaflet excursion angle $\alpha_{EX} \leq 35^\circ$ ($p = 0.001$) and a coaptation height $h \geq 11$ mm ($p = 0.04$) as independent predictors of recurrent MR. Internal validation of such multivariable analysis by means of bootstrapping, including the same variables of standard logistic regression model, further confirmed the significant predictive of early death (bootstrap OR=1.7, 95% bias-corrected CI=0.6-3.8). Finally, logistic regression model was reliable (Hosmer–Lemeshow test, $p = 0.6$) and accurate (c-index=0.8).

DISCUSSION.

The main purpose of the present study was to investigate leaflets configurations in patients with CIMR before and after combined reductive annuloplasty and CABG and to identify characteristics of valvular as well as sub-valvular configurations responsible for recurrent ischemic regurgitation. Clinical data as well further treatment options offered for patients with discovery of residual/recurrent MR have been previously reported⁹ and have not been included in the present study.

SUBVALVULAR MECHANISM OF RECURRENT MR

105

Previous studies^{7,20} demonstrated that the local remodeling of the LV segments supporting the posterior papillary muscle is a necessary condition for the development of MR. Accordingly, we found that remodeling of the regions supporting the posterior papillary muscle occurred in both Group as demonstrated by WMSI_s of these regions which were higher than normal in all patients. Nonetheless, in our experience, patients with recurrent MR had preoperatively a greater local LV remodeling of the LV segments underlying the anterior papillary muscle, a greater lateral and posterior displacement of the anterior papillary muscle and a wider PM_s separation.

Interestingly, this different distribution of local wall abnormalities did not reflect, in our experience a different infarct localization confirming that mechanisms underlying CIMR are complex and not completely understood yet. However, our results support previous clinical findings reported by Agricola et al¹⁵ who described two Groups of patients with CIMR: likewise Group 2 in our study, their symmetric Group had prevalent posterior and lateral displacement of anterior papillary muscle (both $p < 0.04$), PM_s separation and WMSI of the regions supporting the anterior papillary muscle (both < 0.001).

After surgery, we showed that continued LV local remodeling occurs in both Groups and it predominantly involves the region of the LV supporting the posterior papillary muscle whereas the wall motion score index of segments underlying the anterior papillary muscle remained constant over time postoperatively in the entire patients cohort.

VALVULAR MECHANISM OF RECURRENT MR

This study has demonstrated different baseline leaflet configuration in patient with or without recurrent mitral regurgitation. Patients without postoperative MR had a more asymmetric tethering pattern with a more pronounced posterior mitral leaflet tethering and with a prevalent restriction of the posterior leaflet excursion. Contrastingly, patients who developed postoperative MR had a more symmetric tethering pattern, a more accentuated anterior leaflet tethering, a more restricted anterior leaflet excursion and a smaller bending angle γ . The different tethering pattern translated into different preoperative MR jet directions: predominantly posterior in Group 1, mainly central in Group 2. Postoperatively, the tethering of the posterior leaflet increased and it was predominant in both groups at any stage postoperatively. In contrast, the tethering of the anterior leaflet reduced and AML excursion angle increased significantly early after surgery, remaining constant afterwards in both Groups. This is consistent with that reported by Zhu et al²⁰ who observed a prevalent posterior leaflet tethering either in patients with (n=25)

or without ($n=6$) postoperative MR ($p<0.05$). Tethering of the posterior leaflet may be exacerbated by annuloplasty which, reducing annular size, can potentially shift the posterior annulus farther anteriorly, increasing its displacement relative to the papillary muscles without displacing the anterior annulus fixed at the aortic root²¹. However patients in Group 2 showed a mechanism of recurrent MR different from that of MR at baseline, with a tethering mechanism becoming progressively more asymmetric. In contrast with Kuwahara et al⁸ and Magne and coworkers²², in our experience, tethering of the posterior leaflet was not significant as a predictor of MR recurrence. However, these authors studied, recurrent/persistent and persistent MR, respectively, whereas, in our study residual MR was excluded. Persistent /residual MR is presumably due to immediate failure of the technique employed rather than LV remodeling²³ and it is not surprising that regurgitation persists at late follow up in these patients. Contrastingly, we found an anterior tethering angle $\alpha' \geq 39.5^\circ$ ($p<0.001$), an anterior/posterior tethering angle ratio $\alpha'/\beta' \geq 0.76$ ($p<0.001$), an anterior leaflet excursion angle $\alpha_{\text{ex}} \leq 35^\circ$ ($p=0.001$) and a coaptation height $h \geq 11$ mm ($p=0.04$) to be independent predictors of recurrent MR. Therefore, in accordance with Calafiore et al²⁴, a coaptation distance (in our study coaptation height) ≥ 11 mm was associated with a high risk of MR recurrence after UMRA. Nevertheless, as far as we know, this is the first demonstration that patients with predominant tethering of the anterior mitral leaflet had a higher likelihood to develop postoperative recurrent MR after reductive annuloplasty. We can postulate that patients with more accentuated AML tethering cannot guarantee a sufficiently long anterior leaflet to cover the whole antero-posterior diameter and this is worsened by the augmented postoperative tethering of the posterior leaflet which further displaces the coaptation point posteriorly. Green et al.²¹ have reported, in an ovine model, that annuloplasty produces a markedly impaired motion of a “frozen” posterior mitral leaflet, transforming the mitral valve in unicuspid valve where the mechanism closure is performed only by the anterior leaflet and Kuwahara et al⁸ concluded that an anterior leaflet longer than antero-posterior annular diameter is required in the presence of restricted posterior leaflet to ensure successful repair. However, in our opinion, a long anterior leaflet could not always be sufficient to balance tethering forces secondary to postoperative remodeling and the coaptation length gained at the end of procedure could play a significant role in preventing MR recurrence. Indeed, patients in Group 1 had larger coaptation length (CL, $p<0.001$) and 100% showed a CL ≥ 8 mm at postoperative controls. Interestingly, a subgroup of patients in the Group 2 showed postoperative MR even with a less tethered anterior mitral leaflet: in one of them the CL was small (2.6mm) whereas in two the apposition surface was absent and the AML closed against the annulus. Thus, on the basis of the actual experience, we believe that, in all subjects especially those who are expected not to reverse remodel, a minimum CL of 8 mm should be achieved, as suggested by other authors²⁵. Nonetheless, in patient with strongly tethered AML

or with less tethered anterior leaflet but not sufficiently long to ensure a postoperative CL ≥ 8 mm, mitral regurgitation cannot be presumably eliminated by ring annuloplasty. In these patients a technique directly addressing LV remodeling or a chordal sparing mitral valve replacement should be considered. Additionally, a key point for achieving an appropriate leaflet coaptation and to ensure durable results is a true undersizing and, in this setting, a pivotal role can be played by the type of ring chosen. In the present experience we used only two rings (Carpentier's rigid or Physio semi-flexible rings). These two rings are not at all identical, thus, even while we have undersized by two sizes both rings, we might have been less restrictive with the Physio ring than with the Classic ring. However, in our previous experience⁹, neither ring type nor ring size was predictive of recurrent MR.

Finally, patients with a more accentuated anterior mitral leaflet tethering and restrictive excursion could benefit from anterior basal chord cutting as a method of improving leaflet mobility and decreasing leaflet tethering. Nonetheless we have no experience with this technique and this issue deserves further investigation.

LIMITATIONS OF THE STUDY

Our study should be viewed in light of some inherent limitations. (1) Evaluation of mechanisms of recurrent ischemic mitral regurgitation were based on geometric assumptions and 2D echocardiographic measurements which are subject to image-plane positioning errors.

Hence it might be not accurate in shape distorted post-infarction left ventricles. The era of 3-D echocardiography has started potentially leading to new insights into LV remodeling, mitral apparatus shape and function²⁶. Nonetheless the 3-D method is still on its way and is far from being validated, standardized and widely applied in the clinical practice²⁷. (2) Viability testing was not performed in these patients. Therefore recurrence of MR might be also due to irreversible ischemic myocardial damage (not-viable myocardium). Furthermore, in relation to the papillary muscle displacement data presented, the revascularization of viable regions related to papillary muscle function might be the most important predictor of success with this operation. This limitation is shared with most of published papers. However, this issue deserves further investigation. (3) Postoperative evaluation of the coronary status was not assessed. It would have been helpful to differentiate between surgical failure (valve repair and CABG) and the progress of the coronary disease. (4) The issue of annulus re-shaping during annuloplasty has not been addressed. We employed only rigid/semi-flexible plane annuloplasty rings which may flatten the natural saddle shape causing greater tension on chordae and leaflets. Innovative annular rings have been recently introduced in the market which mimic the shape of healthy mitral annulus^{1,28-30}. (5) Estimated cutoffs are known to be very susceptible to changes in the study population. We employed bootstrapping techniques to validate the results,

nonetheless, it has also been documented that the sensitivity/specificity associated with these cutoffs are overly optimistic.

STRENGTH OF THE STUDY

The study does not display most of common clinical and methodological pitfalls that limit results from many studies of mitral valve repair²³. The patient cohort was large and the echocardiographic follow-up was detailed and 100% complete. In addition, our study population was more homogeneous than in other reports: all patients underwent associated CABG, they had no concomitant MV procedures and the entire cohort was uniform regarding the MV ischemic leaflet dysfunction. Moreover, only true “recurrent” MR was studied, excluding those patients with “residual” MR in whom the insufficiency was presumably never eliminated at surgery. Additionally, we undertook valve sizing in a standardized fashion and the degree of undersizing was homogeneous over the 5-year-period of the study. Finally, we employed only two rings (rigid and semi-flexible) which were equally distributed in the two groups.

CONCLUSIONS

Preoperative symmetric tethering with AML predominance was strongly associated with recurrence of MR. Measures of leaflet tethering, which are not systematically employed in the clinical practice, resulted, in our experience, fundamental findings to identify ischemic patients who can really benefit from restrictive annuloplasty. Further larger studies are necessary to confirm our findings.

REFERENCES

1. Gorman JH 3rd, Jackson BM, Enomoto Y, Gorman RC. The effect of regional ischemia on mitral valve annular saddle shape. *Ann Thorac Surg* 2004;77:544–8.
2. Otsuji Y, Handschumacher MD, Schwammenthal E, et al. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. *Circulation* 1997;96:1999–2008.
3. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;115(2):381–6.
4. Bolling SF, Deeb GM, Bach DS. Mitral valve reconstruction in elderly, ischemic patients. *Chest* 1996;109(1):35–40.
5. McGee EC, Gillinov AM, Blackstone EH et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 2004, 128(6):916–24.

6. Serri K, Bouchard D, Demers P et al. Is a good perioperative echocardiographic result predictive of durability in ischemic mitral valve repair? *J Thorac Cardiovasc Surg* 2006;131:523–529.
7. Hung J, Papakostas L, Tahta SA et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. *Circulation* 2004;110 (Suppl. II):II85–II90.
8. Kuwahara E, Otsuji Y, Iguro Y et al. Mechanism of recurrent/persistent ischemic/functional mitral regurgitation in the chronic phase after surgical annuloplasty: importance of augmented posterior leaflet tethering. *Circulation* 2006;114(Suppl.):I529–I534.
9. Gelsomino S, Lorusso R, De Cicco G et al. Five-year echocardiographic results of combined undersized mitral ring annuloplasty and coronary artery bypass grafting for chronic ischaemic mitral regurgitation. *Eur Heart J*. 2008 Jan;29(2):231-40.
10. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects.<http://www.wma.net/e/policy/b3.htm> (Accessed January 9, 2008).
11. Bland MJ, Altman DJ. Statistical method for assessing agreement between two methods of clinical measurements. *Lancet* 1986;1:307-310.
12. Zoghbi WA, Enriquez-Sarano M, Foster E et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16: 777–802.
13. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KL, Tajik AJ. Ischemic Mitral Regurgitation. Long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*. 2001;103(13):1759-64.
14. Vijayaraghavan G, Boltwood CM, Tei C, Wong M, Shah PM. Simplified echocardiographic measurement of the mitral annulus. *Am Heart J* 1986;112(5): 985-91.
15. Agricola E, Oppizzi M, Maisano F et al. Echocardiographic classification of chronic mitral regurgitation caused by restricted motion according to tethering pattern. *Eur J Echocardiography* 2004; 5: 326-34.
16. Romesburg HC. Cluster analysis for researchers. North Carolina: Lulu Press; 2004.1-330.
17. Harrel FE., Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. *Statistics in Medicine* 1984; 3: 143-52.
18. Harrel FE Jr, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stats Med* 1996:361-87.
19. Hosmer DW, Lemeshow S. Applied Logistic regression. 2nd ed. New York: Wiley-Interscience; 2000:143-202.
20. Zhu F, Otsuji Y, Yotsumoto G et al. Mechanism of persistent ischemic mitral regurgitation after annuloplasty: importance of augmented posterior mitral leaflet tethering. *Circulation*. 2005;112(Suppl):I396-401.
21. Green GR, Dagum P, Glasson JR et al. Restricted posterior leaflet motion after mitral ring annuloplasty. *Ann Thorac Surg*. 1999;68(6):2100-6.

22. Magne J, Pibarot P, Dagenais F, Hachicha Z, Dumesnil JG, Senechal M. Preoperative posterior leaflet angle accurately predicts outcome after restrictive mitral valve annuloplasty for ischemic mitral regurgitation. *Circulation*. 2007;115(6):782-91.
23. Adams DH, Anyanwu AC. Pitfalls and limitations in measuring and interpreting the outcomes of mitral valve repair. *J Thorac Cardiovasc Surg* 2006; 131:523-9.
24. Calafiore AM, Di Mauro M, Gallina S et al. Mitral valve surgery for chronic ischemic mitral regurgitation. *Ann Thorac Surg*. 2004;77(6):1989-97.
25. Braun J, Bax JJ, Versteegh MI et al. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. *Eur J Cardiothorac Surg*. 2005;27(5):847-53.
26. Tsukiji M, Watanabe N, Yamaura Y et al. Three-Dimensional Quantitation of Mitral Valve Coaptation by a Novel Software System with Transthoracic Real-Time Three-Dimensional Echocardiography. *J Am Soc Echocardiogr*. 2007; [Epub ahead of print].
27. Ryan LP, Jackson BM, Parish LM et al. Mitral valve tenting index for assessment of subvalvular remodeling. *Ann Thorac Surg*. 2007;84(4):1243-9.
28. Votta E, Maisano F, Bolling SF, Alfieri O, Montevicchi FM, Redaelli A. The Geoform disease-specific annuloplasty system: a finite element study. *Ann Thorac Surg*. 2007;84(1):92-101.
29. Salgo IS, Gorman JH, Gorman RC, et al. Effect of Annular Shape on Leaflet Curvature in Reducing Mitral Leaflet Stress. *Circulation*. 2002; 106:711-717.
30. Jimenez JH, Liou SW, Padala M et al. A saddle-shaped annulus reduces systolic strain on the central region of the mitral valve anterior leaflet. *J Thorac Cardiovasc Surg*. 2007;134(6):1562-8

APPENDIX 1

111

Bland –Altman limits of agreement for intra-observer and inter-observer variability

Variable		Mean difference	Standard deviation	95% limits of agreement
ESV(ml)	Intra-observer (IC)	1.3	1.6	-1.8-4.4
	Intra-observer (CR)	0.5	2.7	-4.8-5.8
	Inter observer	1.6	2.9	-4.0-7.3
LVEF (%)	Intra-observer (IC)	2.4	1.8	-1.1-6.0
	Intra-observer (CR)	2.5	2	-1.5-6.5
	Inter observer	2.3	2.8	-3.0-7.8
ERO (mm ²)	Intra-observer (IC)	0.4	2.1	-3.8-4.7
	Intra-observer (CR)	0.5	1.8	-3.1-4.1
	Inter observer	1.4	2.4	-3.4-6.2
h (mm)	Intra-observer (IC)	0.1	0.3	-0.4-0.7
	Intra-observer (CR)	0.1	0.2	-0.4-0.6
	Inter observer	0.2	0.4	-0.5-1.0
α' (°)	Intra-observer (IC)	1.4	1.9	-2.2-5.1
	Intra-observer (CR)	1.7	1.8	-1.8-5.2
	Inter observer	1.8	2.1	-2.3-6.0
β' (°)	Intra-observer (IC)	2.1	2.2	-2.2-6.4
	Intra-observer (CR)	1.5	2.2	-2.8-5.9
	Inter observer	1.4	3.5	-5.5-8.3

Intra-observer and inter-observer relative differences were <5% for all parameters. The Bland-Altman method showed excellent agreement between intra-observer and inter-observer measurements in both low and high values of echocardiographic parameters. Observers: observer 1: Irene Capecchi, (IC); observer 2: Carlo Rostagno (CR). Inter-observer (observer 1-observer 2).

Abbreviations: ESV=end systolic volume; LVEF=left ventricular ejection fraction; ERO=effective regurgitant orifice (area); h=coaptation height; α' =Anterior mitral leaflet tethering angle, β' =Posterior mitral leaflet tethering angle.

APPENDIX 2

TETHERING MEASUREMENTS.

The tethering angle of the anterior mitral leaflet (AML) α' was measured as follows:

$$\alpha' = \arcsin\left(\frac{BH}{BD}\right)$$

where BH was the bending height between the annular line and the bending angle γ created by tethering of intermediate or strut chordae in the body of the anterior leaflet, and BD was the bending distance between the bending point and the anterior annulus.

The AML excursion angle α_{ex} were obtained as:

$$\alpha_{\text{ex}} = \left[\left(\arcsin \frac{K}{AML_d} \right) - \left(\arcsin \frac{BH}{BD} \right) \right]$$

Where AML_d and K were the length of the anterior leaflet and the distance measured from the tip of the AML to the annular line, respectively, measured at the end of diastole.

Thus the anterior leaflet excursion AML_{ex} was calculated as:

$$AML_{\text{ex}} = AML * \sin \left[\left(\arcsin \frac{K}{AML_d} \right) - \left(\arcsin \frac{BH}{BD} \right) \right]$$

Similarly, the posterior mitral leaflet (PML) tethering angle β' was calculated as follows:

$$\beta' = \arcsin\left(\frac{PMLs}{l'}\right)$$

Where PML_s was the mid-systolic PML and l' was the distance between the PML coaptation point and the annular line.

Angle of PML excursion (β_{EX}) and excursion distance (PML_{EX}) were calculated as:

$$\beta_{EX} = \left[\left(\arcsin \frac{l}{PMLd} \right) - \left(\arcsin \frac{PML_s}{l'} \right) \right]; \quad PML_{EX} = PML \cdot \sin \left[\left(\arcsin \frac{l}{PML} \right) - \left(\arcsin \frac{PML_s}{l'} \right) \right]$$

Where $PMLd$ and l were length of the posterior leaflet and the distance measured from the tip of the PML to the annular line, respectively, measured at the end of diastole.

The α'/β' ratio was calculated to verify the tethering symmetry.

The bending angle (γ) was calculated as:

$$\gamma = 90^\circ + \arccos \left(\frac{BH}{BD} \right)$$

5

Impact of Anterior Leaflet Tethering on Recurrence of Ischemic Mitral Regurgitation after Restrictive Annuloplasty

Sandro Gelsomino, Giuseppe De Cicco, MD, Roberto Lorusso, MD, Ph.D, Giuseppe Billè, MD,
Irene Capecci, MD, Sabina Cacioli, MD, Marco Chioccioli, MD, Carlo Rostagno, MD,
Pierluigi Stefano, MD, and Gian Franco Gensini, MD

In press in: Ann Thorac Surg.

ABSTRACT

Background: We hypothesized that a specific leaflet configuration with anterior mitral leaflet (AML) tethering predominance is related to higher postoperative MR recurrence. Relationships between AML tethering and recurrent mitral regurgitation were investigated.

Methods: In 278 patients with surgical annuloplasty for chronic ischemic mitral regurgitation and 50 matched normal subjects, posterior and lateral displacement of papillary muscles (PMs), the AML and posterior mitral leaflet (PML) tethering angles and their ratio, coaptation length and the MR grade were quantified before and at follow up (median, 38 months [Interquartile range 15-60 months]). Patients were divided in 5 Groups on the basis of the preoperative AML tethering angle α' : Group 1, normal/slight AML tethering (n=33), Group 2, mild AML tethering (n=55), Group 3, moderate AML tethering (n=63), Group 4, moderate-severe AML tethering (n=64) and Group 5, severe AML tethering (n=63).

Results: Subjects with AML tethering $\geq$ moderate-severe had preoperatively a more symmetric tethering ($p < 0.001$), a more accentuated anterior papillary muscle displacement ($p < 0.001$) and a larger anterior local remodeling ($p = 0.02$). Recurrence of MR was significantly higher in patients with moderate-severe/severe AML tethering ($p < 0.001$). Postoperatively, tethering of posterior leaflet increased ($p < 0.001$) and it was predominant without difference between groups, resulting in a more asymmetric tethering in most of patients with recurrent MR ($p < 0.001$).

At multivariable logistic regression the AML tethering angle α' was the primary determinant of MR recurrence after adjustment of known risk factors ($p < 0.001$).

Conclusions: The grade of preoperative AML tethering was strongly associated with recurrence of MR. Assessment of leaflet tethering and PMs displacement by 2-D echocardiography should be incorporated into clinical risk assessment and prediction models.

INTRODUCTION

A standard therapeutic approach to relieve ischemic mitral regurgitation (IMR) is a ring annuloplasty which reduces mitral annular area by bringing the dilated posterior annulus anteriorly to shorten the anterior posterior dimension (or septal-lateral in anatomic terms) and bring the leaflet into apposition¹⁻⁵. Although often effective initially⁶, long term failures are increasingly recognized⁷⁻¹⁰. Green et al.¹¹ have reported in an ovine model that annuloplasty produces a markedly impaired motion of a “frozen” posterior mitral leaflet, transforming the mitral valve in unicuspid valve where the mechanism closure is performed only by the anterior mitral leaflet (AML) and Kuwahara et al¹² demonstrated that an AML longer than antero-posterior annular diameter is required in the presence of restricted posterior leaflet to ensure successful repair. Thus, the extent of preoperative anterior mitral leaflet (AML) tethering could play a crucial role in determining a successful repair. Nonetheless, little is known regarding the real impact of the AML tethering on postoperative recurrence of MR.

In our recent experience we have shown that annuloplasty failure is related to wider preoperative AML tethering¹³ and this hypothesis has been tested for recurrent MR late after surgery. However, the altered leaflet geometry and the recurrent MR could represent both the result of abnormal left ventricular (LV) function and geometry rather than the change in valve anatomy being primary.

Therefore, in the present study we investigated the “true” impact of AML tethering on unsuccessful ischemic valve repair in relation to other factors influencing MR recurrence and we tested the hypothesis that a specific leaflet configuration with AML tethering predominance is related to higher postoperative MR recurrence.

METHODS

SUBJECTS

Among 316 patients with chronic ischemic mitral regurgitation undergoing combined coronary artery bypass grafting (CABG) and undersized mitral ring annuloplasty (UMRA) in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and January 2008, thirty-eight were excluded: 4 had intraoperative annuloplasty failure, 14 showed residual MR ($\geq 2+$ at discharge) and 20 had incomplete echoes available. Therefore, the study population consisted of 278 patients. Fifty normal healthy subjects with no history of cardiovascular disease and with normal Doppler echocardiographic examination and who had a gender distribution, age and average body surface area similar to study patients were

controls. Definition, inclusion and exclusion criteria were as previously reported⁷. Median follow-up was 38 months (IQR 15-60).

Following the World Medical Association guidelines concerning ethical principles for medical research involving human subjects, the study was approved by Institutional Ethics Board. Furthermore, all patients gave their informed consent.

SURGERY

All patients underwent associated CABG. For the purpose of this study, complete revascularization was accomplished when, at least one graft was placed distal to an approximately 50% diameter narrowing in each of the three major vascular system in which arterial narrowing of this severity was noted in a vessel ≥ 1.5 mm of diameter. It was not considered necessary to bypass all obstructed diagonal branches of the anterior descending or marginal branches of the circumflex coronary arteries for a classification of complete revascularization. Following this definition 100% patients underwent complete revascularization. The ring size was determined by standard measurements of the inter-trigonal distance and anterior leaflet height. A downsizing by two ring sizes was performed in all patients.

ECHOCARDIOGRAPHIC MEASUREMENTS

Echo examinations were carried out preoperatively and at follow up appointment by two experienced echocardiographers (S.C. and M.C.) and all measurements were made off line as previously reported⁷ by to cardiologists (I.C. and C.R.) blinded to severity of MR and to the time when the images were made. The reliability of echocardiographic measurements was assessed by calculating inter-observer and intra-observer interval of agreements in a different group of 20 subjects (10 MR, Appendix 1)¹⁴.

PAPILLARY MUSCLES DISPLACEMENT

Lateral and posterior displacements of anterior (APM) and posterior (PPM) papillary muscles were measured as previously reported¹³. In the long axis view the apical displacement of the PPM was measured as the distance between the papillary muscle head and the fixed inter-valvular fibrosis (annular-papillar distance)¹⁵. The wall motion score indexes (WMSI_s) of the basal and mid-posterior and inferior segments for the PPM and of basal and mid-lateral and anterior segments for the APM were also calculated¹⁵.

MEASUREMENT OF LEAFLET TETHERING

119

Mitral leaflet configuration was quantified in the parasternal long-axis view in mid-systole and early diastole (Figure 1). The angles α' and β' , the bending angle γ , the leaflets excursion distances (PML_{EX} and AML_{EX} , respectively) and leaflets excursion angles (α_{EX} and β_{EX} , respectively) were calculated as previously reported¹³. The anterior/posterior tethering angle ratio α'/β' was a quantitative measurement of tethering: the more this ratio was approaching 1 the more symmetric was the tethering. The distances d and h representing posterior and apical displacement of the coaptation and the coaptation length were directly measured.

PATIENTS CLASSIFICATION

Patients were divided in quintiles with baseline α' values of $<27.2^\circ$ (Normal/slight AML tethering, Group 1, $n=33$), $27.2^\circ \leq 32.1^\circ$ (Mild AML tethering, Group 2, $n=55$), $32.2^\circ \leq 35.9^\circ$ (Moderate AML tethering, Group 3, $n=63$), $36.0^\circ \leq 39.5^\circ$ (Moderate-severe AML tethering, Group 4, $n=64$) and $>39.5^\circ$ (Severe AML tethering, Group 5, $n=63$), respectively. Patient characteristics are summarized in Table 1. No difference was found in preoperative and operative variables between Groups.

STATISTICAL ANALYSIS

Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data were expressed as mean $\pm$ standard deviation, non-parametric data were presented as median and interquartile range (IQR) and frequencies as proportions.

Variables were compared across α' categories with the ANOVA, Kruskal-Wallis and χ^2 tests with Tukey and Dunn post-hoc tests, where appropriate.

Multivariable logistic regression analysis was performed to assess the effect of preoperative AML tethering on recurrence of MR. Forty demographic, clinical, and echocardiographic parameters were investigated for their predictive value. To enhance the accuracy of the model, the number of variables was reduced using variable clustering^{16,17}. Model assumptions (linearity and additivity assumptions) were checked by piecewise cubic polynomials (spline functions) and pooled interaction test¹⁸, respectively, and found to be satisfied. Goodness of fit of the final logistic regression models was assessed with the Hosmer–Lemeshow statistic¹⁹ and predictive accuracy was assessed by the concordance index (c)¹⁸. For presentation purpose we first analyzed the main effect of preoperative AML tethering and then we investigated model with interactions between α' and other key risk factors selected on the basis of results of our previous experiences^{7,20}, and from data of published papers^{12,21}. A significance level of $p < 0.01$ was used as criterion for reporting interactions. Internal

Figure 1. Methods to quantify the mitral leaflet configurations in the parasternal long axis 2-dimensional echocardiogram (see text) in diastole (A) and systole (B). The angles α' and β' represent the grade of Anterior Mitral Leaflet (AML) and Posterior Mitral Leaflet (PML) tethering. The bending angle γ is the angle created by tethering of intermediate or strut chordae in the body of the anterior leaflet. Anterior and Posterior leaflet excursion angles (α_{EX} and β_{EX} , respectively) were calculated from systolic closure to diastolic maximal opening.

Abbreviations: d: coaptation distance; CL: Coaptation length.

validation of predictors generated by multivariable logistic regression was performed by means of bootstrapping techniques, with 1000 cycles and generation of OR and bias corrected 95% CI¹⁸.

SPSS 12.0 (SPSS, Chicago, IL, USA) and Stats Direct 2.5.7 (Stats Direct, Sale, UK) were used for these calculations.

RESULTS

MITRAL REGURGITATION

There was no significant difference between Groups regarding quantitative MR data in the preoperative period (Table 2). However, tenting area ($p < 0.001$) and coaptation height ($p = 0.03$) were higher in patients with severe or moderate-severe AML tethering. In addition, in these Groups, preoperative MR jet direction was central in most of patients, whereas it was posterior in the major part of patients of the other Groups (Figure 2A).

At follow-up 62 patients (22.3%) showed recurrent MR (insufficiency $\geq 2+$ in patients with no/trivial MR at discharge): it occurred in 47.6% patients with severe, 28.1% moderate-severe, 17.4% moderate and 10.9% mild preoperative AML tethering ($p < 0.001$). None in the normal/slight AML tethering Group showed recurrent MR. At postoperative control 90.3% of patients with MR recurrence had posterior jet without difference between Groups (Figure 2B).

Table 1. Patient profile differentiated by the anterior tethering angle (n=278)

	Group 1 Normal /Slight $\alpha' < 27.2^\circ$ n=33	Group 2 Mild $\alpha' 27.2^\circ \leq 32.1^\circ$ n=55	Group 3 Moderate $\alpha' 32.2^\circ \leq 35.9^\circ$ n=63	Group 4 Moderate-severe $\alpha' 36.0^\circ \leq 39.5^\circ$ n=64	Group 5 Severe $\alpha' > 39.5^\circ$ n=63	P
Age (years)	66 $\pm$ 6	65 $\pm$ 8	66 $\pm$ 4	65 $\pm$ 6	67 $\pm$ 7	0.7
Gender M/F	19 /14 (57.5/42.5)	32/23 (58.1/41.9)	35/28 (55.5/45.5)	34/30 (53.1/46.9)	34/29 (53.9/44.1)	0.8
Myocardial infarction						
>3 months	25 (75.7)	41 (74.5)	47 (74.6)	48 (75.0)	46 (73.0)	0.8
≤ 3 months	8 (24.3)	14 (25.5)	16 (25.4)	18 (25.0)	17 (27.0)	
Inferior/Posterior	17 (51.5)	29 (52.7)	33 (52.4)	32 (50.0)	35 (55.5)	0.6
Anterior/Septal	2 (6.1)	3 (5.5)	3 (4.7)	4 (6.3)	3 (4.7)	
Lateral	3 (9.1)	4 (7.3)	5 (7.9)	6 (9.3)	4 (6.4)	
Combined	11 (33.3)	19 (34.5)	22 (35.0)	22 (34.3)	21 (33.4)	
Coronary vessel disease						
Left Main	2 [2-3]	2 [2-3]	2 [2-3]	2 [2-3]	2 [2-3]	>0.9
	6 (18.1)	11 (20.0)	13 (20.6)	15 (23.4)	12 (19.0)	0.6
Surgery						
Antegrade Cardioplegia	30 (90.9)	49 (89.1)	58 (92.1)	58 (90.7)	59 (93.6)	0.6
Antegrade and Retrograde Cardioplegia	3 (9.1)	6 (10.9)	5 (7.9)	6 (9.3)	4 (6.4)	
CPB time (min)	108 [96-110]	105 [95-120]	109[98-115]	110 [100-126]	110 [100-130]	0.09
CCL time (min)	79 [60-98]	80 [62-100]	78 [64-89]	95 [75-106]	96 [70-115]	0.06

	Group 1 Normal /Slight $\alpha' < 27.2^\circ$ n=33	Group 2 Mild $\alpha' 27.2^\circ \leq 32.1^\circ$ n=55	Group 3 Moderate $\alpha' 32.2^\circ \leq 35.9^\circ$ n=63	Group 4 Moderate-severe $\alpha' 36.0^\circ \leq 39.5^\circ$ n=64	Group 5 Severe $\alpha' > 39.5^\circ$ n=63	P
Mitral Ring						
*Carpentier Classic	18 (54.5)	31 (56.3)	33 (52.4)	35 (54.6)	35 (55.5)	0.8
*Physio	15 (45.5)	24 (46.7)	30 (47.6)	29 (45.4)	28 (44.5)	
Ring size (mm)						
24 mm	28 [26-30]	28 [26-30]	28 [26-30]	28 [26-30]	28 [26-30]	
26 mm	2 (6.1)	3 (5.5)	3 (4.8)	3 (4.7)	4 (6.4)	0.7
28 mm	12 (36.3)	21 (38.0)	23 (36.5)	24 (37.5)	21 (33.4)	
30 mm	14 (42.4)	24 (43.7)	28 (44.4)	28 (43.7)	29 (46.0)	
	5 (15.2)	7 (12.8)	9 (14.3)	9 (14.1)	9 (14.2)	
CABG						
Anastomoses/patient	2 [2-3]	2 [2-3]	2 [2-3]	2 [2-3]	2 [2-3]	>0.9
Arterial graft/patient	1 [1-2]	1 [1-2]	1 [1-2]	1 [1-2]	1 [1-2]	>0.9

Continuous variable are presented as mean $\pm$ standard deviation; Discrete variables are presented as percentage. Non-parametric variables were presented as median [Interquartile range].

Abbreviations: ns=not significant, M/F=Male/Female; CPB=Cardiopulmonary bypass; CCL=(Aortic)Cross-clamp; CABG=Coronary artery bypass grafting. *Edwards LifeSciences, Irvine,CA.

The tenting Area reduced from preoperatively in Groups 1-3 (Table 3, $p < 0.001$) whereas it increased significantly in Groups 4 and 5 ($p < 0.001$). Furthermore, coaptation length increased in patients with preoperative AML tethering $\leq$ moderate ($p < 0.001$) whereas in the remnants it reduced significantly ($p < 0.001$). However coaptation length was at any time lower in Groups 4-5 ($p < 0.001$) which showed 100% patients with CL ≤ 8 mm at follow-up.

Additionally, the coaptation distance d reduced significantly in Groups 1-3 whereas it significantly re-increased at late study in the other Groups ($p = 0.001$). Finally, coaptation height significantly decreased in all Groups but remained higher in patients with preoperative moderate-severe /severe AML tethering.

PAPILLARY MUSCLE DISPLACEMENT

As shown in Figure 3A, patients with moderate-severe/severe AML tethering had greater preoperative posterior and lateral displacement of the anterior papillary muscle (both, $p < 0.001$), a wider papillary muscle separation ($p = 0.001$) and a larger WMSI of the segments underlying the anterior papillary muscle ($p = 0.02$). Contrastingly, WMSI of the segments underlying the posterior papillary muscle was higher in patients in Groups 1-3 ($p = 0.03$), whereas posterior and lateral displacement of the posterior papillary muscle as well as PPM fibrosis were comparable between Groups (Figure 3B).

At follow-up (Figure 3C), indices of posterior and lateral displacement of the anterior papillary muscle, PMs separation and WMSI of segments underlying the anterior papillary muscle, reduced significantly from the preoperative value only in Groups 1-3 ($p < 0.001$) whereas they remained stable in patients with moderate severe and severe AML tethering with values significantly higher compared to other Groups ($p < 0.001$).

In contrast, indexes of a posterior and lateral displacement of PPM as well as WMSI at level of the PPM reduced significantly in patients Groups 1-3. Contrastingly, all these indexes increased in patients with $\geq$ moderate-severe AML tethering ($p < 0.001$, Figure 3 D) with values significantly higher compared to other Groups ($p < 0.001$).

LEAFLET TETHERING

In the preoperative period, the excursion angle of the AML and the bending angle γ ($p < 0.01$) were lower in Groups 4-5 (Figure 4A, $p < 0.01$). Contrastingly, the PML tethering angle ($p = 0.66$) and the posterior leaflet excursion angle ($p = 0.52$) were not different between Groups (Figure 4B).

At follow up the excursion angle α_{ex} of the anterior leaflet increased (Figure 4C, $p < 0.001$) in patients of Groups 4-5. In Groups 1-3 this increment was not significant

Table 2. Preoperative Mitral Regurgitation differentiated by the anterior tethering angle

Controls	Group 1 Normal /Slight $\alpha < 27.2^\circ$ n=33	Group 2 Mild $\alpha 27.2^\circ \leq 32.1^\circ$ n=55	Group 3 Moderate $\alpha 32.2^\circ \leq 35.9^\circ$ n=63	Group 4 Moderate-severe $\alpha 36.0^\circ \leq 39.5^\circ$ n=64	Group 5 Severe $\alpha > 39.5^\circ$ n=63	P
MR	-	3 [3-4]	3 [3-4]	3 [3-4]	3 [3-4]	0.9
ERO	-	34 ± 8	36 ± 11	38 ± 12	38 ± 14	0.7
TA	0.8 ± 2	3.2 ± 1.0	3.1 ± 1.0	3.3 ± 1.1	3.4 ± 1.1	<0.001
CL	8.5 ± 0.4	3.3 ± 0.2	3.3 ± 0.2	3.5 ± 0.2	4.0 ± 0.3	0.057
d	27.6 ± 6	34.3 ± 6	35.2 ± 7	34.7 ± 5	37.6 ± 6	0.4
h	6.1 ± 2	11.4 ± 3	11.2 ± 3	12.3 ± 3	11.9 ± 4	0.03

Continuous variables are presented as mean ± standard deviation;Non-parametric variables were presented as median [Interquartile range]. p=significance between Groups;*significance vs. controls.

Abbreviations: MR=Mitral Regurgitation; ERO=effective regurgitant orifice (mm²); TA=Tenting area (cm²); CL=Coaptation length (mm);d=coaptation distance (mm); h=coaptation height (mm).

Table 3. Postoperative Mitral Regurgitation differentiated by the anterior tethering angle

	Group 1 Normal /Slight $\alpha < 27.2^\circ$ n=33	Group 2 Mild $\alpha 27.2^\circ \leq 32.1^\circ$ n=55	Group 3 Moderate $\alpha 32.2^\circ \leq 35.9^\circ$ n=63	Group 4 Moderate-severe $\alpha 36.0^\circ \leq 39.5^\circ$ n=64	Group 5 Severe $\alpha > 39.5^\circ$ n=63	P
MR	0 [0-1]*	0 [1-2]*	1 [1-2]*	3 [3-4]	3 [3-4]	0.003
ERO	-	-	-	30 ± 10	33 ± 11	<0.001
TA	2.4 ± 1.0	2.7 ± 1.1	2.7 ± 1.1	3.5 ± 1.1	3.6 ± 1.1*	0.03
CL	8.3 ± 0.3*	8.4 ± 0.4*	8.2 ± 0.3*	5.1 ± 0.2*	4.4 ± 0.1*	<0.001
d	31 ± 7*	32 ± 7*	34 ± 9*	38 ± 10*	40 ± 9*	0.02
h	7 ± 3*	8 ± 3*	8 ± 3*	12 ± 4*	12 ± 5	0.03

Continuous variables are presented as mean ± standard deviation;Non-parametric variables were presented as median [Interquartile range]. p=significance between Groups; *significance vs. preoperative value.

Abbreviations: MR=Mitral Regurgitation;ERO=effective regurgitant orifice (mm²); TA=Tenting area (cm²); CL=Coaptation length (mm); d=coaptation distance (mm); h=coaptation height (mm).

Figure 2. Regurgitant jet direction. (A) In the preoperative period, the regurgitant jet was predominantly posterior in patients in Group 1-3, whereas it was mainly central in those with moderate-severe / severe anterior mitral tethering. (B) In patients with recurrent mitral regurgitation at follow up, the jet direction was posterior in most subjects without differences between Groups.

Figure 3. Papillary muscle displacement. (A) Patients with moderate-severe/severe anterior mitral leaflet (AML) tethering had, at preoperative control greater posterior and lateral displacement of the anterior papillary muscle (APM post and APM lat, respectively) a wider papillary muscle separation (PMS) and a larger wall motion score index of the segments underlying the anterior papillary muscle (APM WMSI). (B) The wall motion score index of the segments underlying the posterior papillary muscle (PPM WMSI) was higher in patients in Groups 1-3. (C) At follow up APM post, APM lat, PMS and APM WMSI reduced significantly from the preoperative values only in Groups with AML tethering $\leq$ moderate. (D) PPM post, PPM lat, PMS fibrosis and PPM WMSI significantly decreased in patients with AML tethering $\leq$ moderate, whereas all these variables increased in patients with $\geq$ moderate-severe AML tethering at follow up control.

($p=0.06$). Differently, the bending angle γ significantly increased at follow-up in patients with AML tethering $\leq$ moderate; in contrast, the γ showed a significant decrease in patients with moderate severe/severe AML tethering ($p<0.01$). The posterior leaflet tethering angle β' (Figure 4D) increased whereas the excursion angle β_{EX} reduced at follow-up without differences between Groups (both, $p<0.001$).

Finally, when the degree of tethering was examined further in the Groups, it was more symmetric in Groups 4-5 before surgery (Figure 5A). However it became progressively more asymmetric at follow up control in all Groups (Figure 5B).

Figure 4. Mitral leaflet tethering. (A) At preoperative echocardiography the excursion angle of the anterior mitral leaflet (α_{ex}) and the bending angle γ were lower in with $\geq$ moderate-severe AML tethering. (B) The tethering angle and the excursion angle of the posterior mitral leaflet (β' and β_{ex} , respectively) were not different between Groups. (C) At follow up α_{ex} increased (Figure 4C, in patients with $\geq$ moderate-severe AML tethering whereas γ significantly decreased in patients with AML tethering $\geq$ moderate and reduced in patients with greater AML tethering. (D) β' increased at follow up control whereas the β_{ex} reduced without differences between Groups.

ASSOCIATION OF AML TETHERING WITH MR RECURRENCE

At multivariable regression analysis anterior tethering angle $\alpha' \geq 39.5^\circ$ (OR, 5.6 [bias-corrected 95% CI 2.6- 6.6], $p < 0.001$), an anterior/posterior tethering angle ratio $\alpha'/\beta' \geq 0.76$ (OR, 5.2 [bias-corrected 95% CI 2.7- 6.0], $p < 0.001$) an anterior leaflet excursion angle $\alpha_{ex} \leq 35^\circ$ (OR, 2.5 [bias-corrected 95% CI 1.2- 3.4], $p < 0.001$) and a coaptation height $h \geq 11$ mm (OR, 2.3 [bias-corrected 95% CI 1.1- 3.2], $p = 0.008$) were independent predictors of recurrent MR. The model resulted to be reliable (Hosmer–Lemeshow test, [H-L] $p = 0.7$) and accurate (c-index [c] = 0.8).

After we accounted for other clinical and echocardiographic risk factors AML tethering angle (adjusted OR, 4.9 [bias-corrected 95% CI 2.3- 5.8, $p < 0.001$), anterior/posterior tethering angle ratio (OR, 4.5 [bias-corrected 95% CI 3.3- 5.6], $p < 0.001$) anterior leaflet excursion angle (OR, 2.0 [bias-corrected 95% CI 1.5- 3.3], $p = 0.007$) and preoperative coaptation height (OR, 1.8 [bias-corrected 95% CI 0.9 - 3.2], $p = 0.03$) remained strong predictors of recurrent regurgitation (H-L = 0.7, c = 0.7).

Figure 5. Tethering pattern. (A) In the preoperative period the tethering pattern was more symmetric in Groups 4-5. (B) The tethering became progressively more asymmetric in all patients at follow up without significant differences between Groups

Compared with patients with posterior leaflet tethering ≥ 45 degrees²¹ (adjusted OR 1 [bias-corrected 95% CI 0.09- 1.2]), those with absent/slight or mild AML tethering had 22% and 76% higher odds for MR recurrence (adjusted OR_s 1.22 [bias-corrected 95% CI 1.06- 1.4] and 1.76 [bias-corrected 95% CI 1.2- 1.9], respectively). This rose to 2.5 times and 3 times higher MR recurrence in moderate (adjusted OR 2.5 [bias-corrected 95% CI 1.7- 3.2) and moderate-severe (adjusted OR 3.0 [bias-corrected 95% CI 2.1- 4.0) AML tethering, respectively. Finally, the increase in risk associated with severe AML tethering was > 4-fold (adjusted OR 4.2 [bias-corrected 95% CI 3.0- 6.1)

When we allowed for interaction between AML tethering and other significant risk factors, the effect of AML tethering was generally attenuated in higher-risk patients (Table 4). Significant interactions were found between AML tethering and systolic sphericity index, end-systolic volume, myocardial performance index, wall motion score index, coaptation height and α'/β' ratio (each $p < 0.001$).

Table 4. Adjusted Odds Ratios (95% bias corrected Confidence Intervals) of anterior mitral leaflet (AML) tethering* on recurrence of ischemic mitral regurgitation after interaction with other significant risk factors

	Group 1 Normal/slight $\alpha < 27.2^\circ$	Group 2 Mild $\alpha 27.2^\circ \leq 32.1^\circ$	Group 3 Moderate $\alpha 32.2^\circ \leq 35.9^\circ$	Group 4 Moderate-severe $\alpha 36.0^\circ \leq 39.5^\circ$	Group 5 Severe $\alpha > 39.5^\circ$
Systolic sphericity Index					
<0.7	1.6 (1.2-2.1)	2.0 (1.6-2.5)	2.9 (2.3-3.9)	4.3 (3.4-5.4)	5.0 (4.3-6.8)
≥ 0.7	1.4 (1.2-1.6)	1.8 (1.4-2.0)	2.1 (1.7-2.7)	2.7 (2.4-3.2)	3.9 (2.8-4.7)
End Systolic Volume (ml)					
<145	1.4 (1.2-1.5)	1.8 (1.4-1.9)	2.7 (2.3-3.1)	3.6 (3.2-4.4)	4.6 (4.0-5.6)
≥ 145	1.2 (1.0-1.4)	1.6 (1.4-1.8)	2.3 (1.4-3.1)	2.9 (2.3-3.8)	3.0 (2.5-3.7)
Myocardial Performance Index					
< 0.9	1.6 (1.5-1.8)	2.0 (1.9-2.2)	2.7 (2.4-3.0)	3.6 (3.1-4.2)	4.7 (3.3-5.4)
≥ 0.9	1.4 (1.2-1.6)	1.8 (1.6-2.0)	2.2 (1.6-2.7)	3.1 (2.8-3.5)	2.1 (2.8-3.4)
Wall motion Score Index					
<1.5	1.8 (1.5-2.0)	2.2 (1.9-2.4)	2.5 (2.2-2.9)	3.1 (2.5-3.6)	4.6 (4.0-5.6)
≥ 1.5	1.5 (1.3-1.7)	1.9 (1.7-2.1)	2.1 (1.7-2.7)	2.7 (2.2-3.4)	3.3 (2.9-3.7)
Coaptation height (mm)					
<11	1.7 (1.5-2.0)	2.1 (1.9-2.4)	3.1 (2.8-3.5)	3.2 (2.8-3.7)	4.5 (3.2-6.2)
≥ 11	1.5 (1.4-1.6)	1.9 (1.6-2.0)	2.6 (2.2-3.1)	2.7 (2.2-3.4)	3.7 (3.3-4.1)
α'/β'					
< 0.76	1.5 (1.3-1.7)	2.4 (2.1-2.8)	2.9 (2.3-3.3)	3.3 (2.7-4.0)	4.9 (4.1-6.2)
≥ 0.76	1.4 (1.1-1.7)	1.9 (1.5-2.4)	2.5 (1.7-3.1)	3.1 (2.8-3.4)	3.7 (2.6-4.4)

* Each Group was differentiated by the anterior tethering angle.

DISCUSSION

This report adds to a growing body of literature documenting recurrent ischemic mitral regurgitation after undersized mitral annuloplasty and coronary artery bypass grafting. The present study builds on these findings by examining the real impact of preoperative AML tethering on recurrence of MR after annuloplasty. Clinical data as well further treatment options offered for patients with discovery of recurrent MR have been previously reported^{7,20} and have not been included in the present study.

The main findings of this study can be summarized as follows:

First, preoperative assessment of AML tethering severity might be helpful to predict the recurrence of MR after undersized annuloplasty and coronary artery bypass grafting. To our knowledge our studies provide the first demonstration that MR recurrence can be predicted from the AML tethering pattern of the ischemic mitral valve on the preoperative echocardiographic evaluation. We previously demonstrated that preoperative AML tethering angle ≥ 39.5 degrees had a very high sensitivity and specificity to predict recurrent MR after operation whereas the PML tethering was not significant²⁰. Nonetheless, the influence of AML tethering could be secondary to other factors and the altered leaflet geometry and recurrent MR could represent both the result of abnormal left ventricular function and geometry which may be primary predictors. Therefore in this study multivariable models were adjusted for important risk factors of MR recurrence we had previously recognized^{7,20}. After we accounted for other clinical and echocardiographic key risk factors AML tethering angle remained a strong predictor of recurrent regurgitation. Indeed patients with moderate or moderate-severe preoperative AML tethering showed a 2.5 times and 3 times higher Odds for MR recurrence compared to those with significant PML tethering (PML angle ≥ 45 degrees²¹). This rose to > 4 fold in patient with severe AML tethering.

In contrast with our results, Kuwahara et al¹² showed that increased PML tethering was the primary determinant of late MR in 30 patients undergoing surgical annuloplasty for ischemic mitral regurgitation. In addition, Magne and coworkers²¹ identified a PML angle ≥ 45 degrees (sensitivity 100%, specificity 97%) to be a predictor of postoperative persistence of MR after annuloplasty.

However, these authors studied recurrent/persistent and persistent MR, respectively, whereas in our study residual MR was excluded. Persistent /residual MR is presumably due to immediate failure of the technique employed rather than LV remodeling²² and it is not surprising that regurgitation persists at late follow up in these patients. Furthermore, Matsunaga and coworkers²³ showed that the severity of the posterior papillary muscle displacement might be a predictor of ring annuloplasty failure. These authors, differently from us, employed in their patients a flexible ring (Duran ring, Medtronic, INC, Minneapolis, MN, US). In additions, they adopted the "PM angle" as an indirect measurement of tethering, defined as the

angle formed by the mitral annular plane and the line connecting the PM tips to the mitral annulus. It can be influenced by changes in LV geometry and dimension. In contrast we measured the angles between the mitral leaflets and the annulus which reflect directly the excursion of the leaflet and their effective tethering.

Second, our findings confirmed that patients with more accentuated AML tethering cannot guarantee a sufficiently long anterior leaflet to cover the whole antero-posterior diameter and this is worsened by the augmented tethering of the posterior leaflet occurring postoperatively in all patients which further displaces the coaptation point. In other words, the AML must be sufficiently long and mobile to ensure a proper surface of coaptation. In our experience, a coaptation length (CL) ≥ 8 mm at the end of the procedure guaranteed annuloplasty durability. Coaptation length was at any time lower in Groups 4-5 ($p < 0.001$) which showed 100% patients with CL ≤ 8 mm at follow-up.

Third, patients with higher preoperative AML tethering had a greater local LV remodeling of the segments of the anterior papillary muscle, a greater lateral and posterior displacement of the anterior papillary muscle and a wider PMs separation and a more symmetric tethering pattern. However patients with postoperative MR showed a mechanism different from that of MR at baseline, with a tethering pattern becoming progressively more asymmetric. This is due to continued remodeling that is mainly posterior in the postoperative period, whereas the LV remodeling in the area of the AML and, consequently, the anterior leaflet tethering, is maintained as in the preoperative situation.

These findings support previous clinical results reported by Agricola et al¹⁵ who described two Groups of patients with CIMR: likewise patients with more pronounced AML tethering, their symmetric Group had prevalent posterior and lateral displacement of anterior papillary muscle, PMs separation and WMSI of the regions supporting the anterior papillary muscle.

Fourth, continued LV remodeling occurs in all Groups in the postoperative period and it predominantly involves the region of the LV supporting the posterior papillary muscle. There was no continued anterior remodeling as demonstrated by wall motion score index of segments underlying the anterior papillary muscle which remained constant over time postoperatively in the entire patient cohort. This is in accordance with published data^{10,24} and confirms that tethering of the posterior leaflet may be exacerbated by annuloplasty which, reducing annular size, can potentially shift the posterior annulus farther anteriorly, increasing its displacement relative to the papillary muscles without displacing the anterior annulus fixed at the aortic root¹¹.

CLINICAL IMPLICATIONS

Anterior mitral leaflet tethering, irrespective of LV function and geometry, is a key factor to ensure durable MV-plasty. The possibility of allowing both leaflets into apposition depends on the ability of AML to move toward the annulus and to reach the posterior one. If this movement is insufficient the mitral leaflets never coapt no matter how much posterior annulus is reduced. The angle α' gives an accurate measure of AML tethering. Furthermore, the length of the AML can be estimated by the coaptation height which represents the depth of the AML during systole, in our opinion and according to Calafiore et al²⁵, when it is more than 11 mm, it is associated with a high risk of MR recurrence after reductive annuloplasty.

Thus we believe that in patients with severe ($\alpha' \geq 39.5^\circ$) or moderate-severe ($\alpha' 36.0^\circ \leq 39.5^\circ$) AML with a coaptation height >11 mm, the risk of performing UMRA must be carefully weighed against those risk associated with a chordal sparing mitral valve replacement.

It is arguable if patients with a more accentuated AML tethering and restrictive excursion could benefit from anterior basal chord cutting as a method of improving leaflet mobility and decreasing leaflet tethering. Nonetheless we have no experience with this technique and this issue deserves further investigation.

Another interesting point is that, in our experience, a long anterior leaflet was not always sufficient to balance tethering forces secondary to postoperative remodeling. Indeed, in a subgroup of patients with mild or moderate AML tethering who showed recurrent MR, the coaptation length was small (2.6mm) or completely absent, without any apposition surface and with the AML which closed against the annulus. Thus we believe that coaptation length (CL) gained at the end of procedure plays a significant role in preventing MR recurrence and in all subjects a minimum CL of 8 mm should be achieved, as suggested by other authors^{25,26}.

LIMITATIONS OF THE STUDY

There were several limitations of the present study. First, a viability testing was not performed in these patients. Therefore recurrence of MR might be also due to irreversible ischemic myocardial damage (not-viable myocardium). Furthermore, in relation to the papillary muscle displacement data presented, the revascularization of viable regions related to papillary muscle function might be the most important predictor of success with this operation. However, this limitation is shared with most of published papers and this issue deserves further investigation.

Second, evaluation of mechanisms of recurrent ischemic mitral regurgitation was based on geometric assumptions and 2D echocardiographic measurements which are subject to image-plane positioning errors. Hence it might be not accurate in shape distorted post-infarction left ventricles. The era of 3-D echocardiography

has started potentially leading to new insights into LV remodeling, mitral apparatus shape and function²⁷. Nonetheless the 3-D method is still on its way and is far from being validated, standardized and widely applied in the clinical practice²⁸.

Third, the issue of annulus re-shaping during annuloplasty has not been addressed. We employed only rigid/semi-flexible plane annuloplasty rings which may flatten the natural saddle shape causing greater tension on chordae and leaflets. Innovative annular rings have been recently introduced in the market which mimic the shape of healthy mitral annulus^{29,30}. This is object of an ongoing study.

Fourth, postoperative evaluation of the coronary status was not assessed. It would have been helpful to differentiate between surgical failure (valve repair and CABG) and the progress of the coronary disease.

CONCLUSIONS

This study has demonstrated that preoperative anterior mitral leaflet tethering is a powerful predictor of MR recurrence after annuloplasty, independently of LV function, dimensions and geometry. Measures of leaflet tethering should be incorporated into risk prediction model for unsuccessful MV plasty and might represent fundamental findings to identify ischemic patients who can really benefit from this kind of surgery. Further larger studies are necessary to confirm our findings.

REFERENCES

1. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;115(2):381–6.
2. Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg*. 2001; 122: 1125-41.
3. Miller DC. Ischemic mitral regurgitation redux--to repair or to replace? *J Thorac Cardiovasc Surg*. 2001;122(6):1059-62.
4. Grossi EA, Goldberg JD, LaPietra A, et al. Ischemic mitral valve reconstruction and replacement: comparison of long-term survival and complications. *J Thorac Cardiovasc Surg*. 2001;122(6):1107-24.
5. Adams DH, Filsoufi F, Aklog L. Surgical treatment of the ischemic mitral valve. *J Heart Valve Dis* 2002;11 Suppl 1:S21-5.
6. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;115(2):381–6.
7. Gelsomino S, Lorusso R, De Cicco G, et al. Five-year echocardiographic results of combined undersized mitral ring annuloplasty and coronary artery bypass grafting for chronic ischaemic mitral regurgitation. *Eur Heart J*. 2008;29(2):231-40.

8. Serri K, Bouchard D, Demers P, et al. Is a good perioperative echocardiographic result predictive of durability in ischemic mitral valve repair? *J Thorac Cardiovasc Surg* 2006;131:523–529.
9. McGee EC, Gillinov AM, Blackstone EH, et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 2004; 128(6):916–24.
10. Hung J, Papakostas L, Tahta SA, et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. *Circulation* 2004;110 (Suppl. II):II85–II90.
11. Green GR, Dagum P, Glasson JR, et al. Restricted posterior leaflet motion after mitral ring annuloplasty. *Ann Thorac Surg* 1999;68(6):2100–6.
12. Kuwahara E, Otsuji Y, Iguro Y, et al. Mechanism of recurrent/persistent ischemic/functional mitral regurgitation in the chronic phase after surgical annuloplasty: importance of augmented posterior leaflet tethering. *Circulation* 2006; 114(1 Suppl):I529–34.
13. Gelsomino S, Lorusso R, Caciolli S, et al. Insights on Left Ventricular and Valvular Mechanisms of Recurrent Ischemic Mitral Regurgitation After Restrictive Annuloplasty and Coronary Artery Bypass Grafting. *J Thorac Cardiovasc Surg* 2008;136(2): 507–18.
14. Bland MJ, Altman DJ. Statistical method for assessing agreement between two methods of clinical measurements. *Lancet* 1986;1:307–310.
15. Agricola E, Oppizzi M, Maisano F et al. Echocardiographic classification of chronic mitral regurgitation caused by restricted motion according to tethering pattern. *Eur J Echocardiography* 2004;5:326–34.
16. Romesburg HC. Cluster analysis for researchers. North Carolina: Lulu Press;2004:1–330.
17. Harrell FE., Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modeling strategies for improved prognostic prediction. *Statistics in Medicine* 1984;3:143–52.
18. Harrell FE Jr, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stats Med* 1996;361–87.
19. Hosmer DW, Lemeshow S. Applied Logistic regression. 2nd ed. New York: Wiley-Interscience; 2000:143–202.
20. Gelsomino S, Lorusso R, Capecchi I, et al. Left ventricular reverse remodeling after undersized mitral ring annuloplasty in patients with ischemic regurgitation. *Ann Thorac Surg*. 2008;85(4):1319–30.
21. Magne J, Pibarot P, Dagenais F, Hachicha Z, Dumesnil JG, Senechal M. Preoperative posterior leaflet angle accurately predicts outcome after restrictive mitral valve annuloplasty for ischemic mitral regurgitation. *Circulation*. 2007;115(6):782–91.
22. Adams DH, Anyanwu AC. Pitfalls and limitations in measuring and interpreting the outcomes of mitral valve repair. *J Thorac Cardiovasc Surg* 2006;131:523–9.
23. Matsunaga A, Tahta SA, Duran CMG. Failure of reduction annuloplasty for functional ischemic mitral regurgitation. *J Heart Valve Dis* 2004; 13:390–8.
24. Zhu F, Otsuji Y, Yotsumoto G, et al. Mechanism of persistent ischemic mitral regurgitation after annuloplasty: importance of augmented posterior mitral leaflet tethering. *Circulation*. 2005;112(Suppl):I396–401.

25. Calafiore AM, Di Mauro M, Gallina S, et al. Mitral valve surgery for chronic ischemic mitral regurgitation. *Ann Thorac Surg.* 2004;77(6):1989-97.
26. Braun J, Bax JJ, Versteegh MI, et al. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. *Eur J Cardiothorac Surg.* 2005;27(5):847-53.
27. Tsukiji M, Watanabe N, Yamaura Y, et al. Three-Dimensional Quantitation of Mitral Valve Coaptation by a Novel Software System with Transthoracic Real-Time Three-Dimensional Echocardiography. *J Am Soc Echocardiogr.* 2008;21(1):43-6.
28. Ryan LP, Jackson BM, Parish LM, et al. Mitral valve tenting index for assessment of subvalvular remodeling. *Ann Thorac Surg.* 2007;84(4):1243-9.
29. Votta E, Maisano F, Bolling SF, et al. The Geoform disease-specific annuloplasty system: a finite element study. *Ann Thorac Surg.* 2007;84(1):92-101.
30. Jimenez JH, Liou SW, Padala M, et al. A saddle-shaped annulus reduces systolic strain on the central region of the mitral valve anterior leaflet. *J Thorac Cardiovasc Surg.* 2007;134(6):1562-8.

APPENDIX 1

Bland –Altman limits of agreement for intra-observer and inter-observer variability.

Variable		Mean difference	Standard deviation	95% limits of agreement
α' (°)	Intra-observer (IC)	1.4	1.9	-2.2-5.1
	Intra-observer (CR)	1.7	1.8	-1.8-5.2
	Inter observer	1.8	2.1	-2.3-6.0
β' (°)	Intra-observer (IC)	2.1	2.2	-2.2-6.4
	Intra-observer (CR)	1.5	2.2	-2.8-5.9
	Inter observer	1.4	3.5	-5.5-8.3
h (mm)	Intra-observer (IC)	0.1	0.3	-0.4-0.7
	Intra-observer (CR)	0.1	0.2	-0.4-0.6
	Inter observer	0.2	0.4	-0.5-1.0

Intra-observer and inter-observer relative differences were <5% for all parameters. The Bland-Altman method showed excellent agreement between intra-observer and inter-observer measurements in both low and high values of echocardiographic parameters. Observers: observer 1: Irene Capecchi, (IC); observer 2: Carlo Rostagno (CR). Inter-observer (observer 1-observer 2).

Abbreviations: α' =Anterior mitral leaflet tethering angle, β' =Posterior mitral leaflet tethering angle; h: coaptation height;

6

Left ventricular diastolic function after restrictive mitral ring annuloplasty in chronic ischemic mitral regurgitation and its predictive value on outcome and recurrence of regurgitation

Sandro Gelsomino, MD, Roberto Lorusso, MD, PhD, Giuseppe Billè, MD, Carlo Rostagno, MD, Giuseppe De Cicco, MD, Stefano Romagnoli, MD, Cristina Porciani, MD, Cecilia Tetta, MD, Pierluigi Stefano, MD Gian Franco Gensini. MD.

ABSTRACT

Background. This study was aimed at exploring the predictive value of diastolic function on clinical outcome and recurrence of ischemic mitral regurgitation following combined undersized mitral annuloplasty (UMRA) and coronary artery bypass grafting (CABG). *Methods.* Two hundred-thirty-four patients with chronic ischemic mitral regurgitation (CIMR) who survived combined UMRA and CABG between September 2001 and September 2007, were divided into four groups on the basis of baseline Deceleration Time (DT) and systolic-diastolic pulmonary venous flow ratio (S/D): Group 1, normal ($n = 48$), Group 2, impaired relaxation ($n=61$), Group 3, pseudonormal ($n=60$) and Group 4, restrictive ($n=65$). Echocardiograms were performed, preoperatively, at discharge and at follow-up appointments (early, 6 months [interquartile range, IQR] 3-8 months; late, 38 months [IQR 17-53 months]). *Results.* Early mortality rate was highest in the restrictive group (9.2%, $p<0.001$). In addition 6-year actuarial survival was significantly lower in Group 4 ($p=0.025$). At late follow-up, among patients in group 4, 58.4% ($n=38$) had an MR grade ≥ 2 ($p<0.001$). Furthermore, DT <140 ms and S/D <0.80 were independent predictors of early ($p<0.001$ and 0.004, respectively) and late (both $p<0.001$) death. Finally DT <140 ms was the only diastolic independent predictor of MR recurrence ($p<0.001$). *Conclusions.* In patients with CIMR undergoing combined CABG and UMRA restrictive LV diastolic filling pattern is an important preoperative marker of high early and late death and recurrence of MR.

INTRODUCTION

Chronic Ischemic mitral regurgitation (CIMR) is a functional insufficiency of the mitral valve related to changes either in the left ventricle (LV) or valve geometry and performance, resulting from ischemic heart disease¹⁻². The incidence of MR following myocardial infarction (MI) is approximately 20% and is higher in patients with previous inferior MI^{3,4}. In subjects with coronary artery disease and concomitant ischemic LV dysfunction, MR is frequently found with notably 30% presenting severe MR⁵.

A standard surgical approach to relieve CIMR is undersized mitral ring annuloplasty (UMRA) aimed at improving both leaflet malcoaptation and LV shape (LV reverse remodeling, LVRR)^{6,7}.

Systolic dysfunction is an important predictor of early mortality and poor long-term outcome after combined mitral valve repair and coronary artery bypass grafting (CABG)⁸. Nonetheless, little is known about diastolic function and its influence on outcome and LVRR.

We sought to investigate the predictive value of preoperative impairment of diastolic function on early and late outcome and recurrence of mitral regurgitation in patients with Chronic ischemic mitral regurgitation (CIMR) undergoing combined UMRA and CABG.

METHODS

DEFINITIONS

CIMR was defined as the combination of mild-to-severe MR with 1) Prior myocardial infarction (MI) >16 days; 2) seventy-five percent or greater stenosis of at least one coronary vessel; 3) a corresponding regional wall motion abnormality; 4) type IIIb leaflet dysfunction following Carpentier's classification⁹ with or without annular dilatation.

Exclusion criteria were: 1) degenerative or other non-ischemic etiology; 2) ischemic isolated type I or type II dysfunction⁹; 3) additional mitral valve repair procedures; 4) other valvular or congenital heart diseases; 5) previous cardiac surgery/percutaneous transluminal coronary angioplasty; 6) atrial fibrillation or sinus rhythm with heart rate at rest >100 bts/min.

PATIENTS POPULATION

Among 270 Subjects with CIMR undergoing combined CABG and UMRA in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between

September 2001 and September 2007 and prospectively enrolled in the study, 36 were excluded: 4 had intraoperative annuloplasty failure, 12 showed residual MR (insufficiency $\geq 2+$ following valve repair documented at discharge) and 20 had incomplete data. The study population consisted of 234 patients. Clinical follow up information was obtained from all survivors through outpatient visits and phone calls and was 100% complete. Median early follow up was 6 months (interquartile range [IQR] 3-8), median late follow up was 38 months (IQR 17-53).

Following the World Medical Association guidelines concerning ethical principles for medical research involving human subjects, the study was approved by Institutional Ethics Board. Furthermore and all patients gave their informed consent. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

SURGERY

All patients underwent associated coronary artery bypass grafting. For the purpose of this study, complete revascularization was accomplished when, at least one graft was placed distal to an approximately 50% diameter narrowing in each of the three major vascular system in which arterial narrowing of this severity was noted in a vessel ≥ 1.5 mm of diameter. It was not considered necessary to bypass all obstructed diagonal branches of the anterior descending or marginal branches of the circumflex coronary arteries for a classification of complete revascularization. Following this definition 100% patients underwent complete revascularization.

The ring size was determined by standard measurements of the inter-trigonal distance and anterior leaflet height. A downsizing by two ring sizes was performed in all patients. After cardiopulmonary bypass (CPB), a transesophageal echocardiography (TEE) was performed to assess residual MR: leaflet coaptation ≥ 0.5 cm, MR ≤ 1 and systolic MV area > 2 cm² was assessed as successful repair.

ECHOCARDIOGRAPHIC STUDY

Echocardiographic studies were performed on Acuson Sequoia imaging device equipped with a 3.5-MHz ultrasound transducer (Acuson Corporation, Mountain View, CA) preoperatively, at discharge and at follow-up appointments. Echocardiographic measurements were averaged over three cardiac cycles. Inter-observer (I.C e C.R) and intra-observer variability for measurement of DT and end systolic volume (ESV) were $<5\%$ (range for intra-observer 0.7 to 3.1%, inter-observer 0.6 to 4.6%).

LV VOLUMES AND GEOMETRY

141

LV volume and left ventricular ejection fraction (LVEF) were assessed by the bi-apical Simpson disk method¹⁰. The sphericity index (SI) was obtained at end diastole and end systole (SI_D and SI_S , respectively) as the volume of the left ventricle divided by the volume of a sphere with a diameter equal to the longest axis of the left ventricle measured in the apical view¹¹. The wall motion score index (WMSI) was calculated according to a 17-segment model¹². According to Stellbrink et coworkers¹³ a decrease in LV end systolic volume >15% from baseline value was considered LVRR.

QUANTIFICATION OF MR

The following quantitative measurements were simultaneously employed to grade the severity of MR and final results were averages of measured values¹⁴⁻¹⁵: 1) Quantitative Doppler. (2) Proximal Isovelocity Surface Area (PISA). These methods were averaged, allowing calculation of regurgitant volume (RV), regurgitant fraction (RF) and effective regurgitant orifice (ERO). In patients with no or trivial MR by color Doppler, RV and RF were used as calculated, and ERO was assumed as null.

Recurrent MR was the insufficiency $\geq 2+$ at follow up appointments in patients with no/trivial MR at discharge.

LV DIASTOLIC FILLING PATTERNS

Diastole was evaluated by measuring transmitral flow. Peak early transmitral flow velocity (E), peak late transmitral flow velocity (A), E/A ratio and deceleration time of E velocity (DT) were obtained by pulsed Doppler¹⁶. The isovolumic relaxation time (IVRT) was obtained by continuous wave Doppler with the wave beam directed from the apical five-chamber view across the region between the aortic outflow tract and the inflow tract.

Finally, systolic and diastolic pulmonary venous flow and their ratio (S/D) were routinely assessed¹⁶.

PATIENT CLASSIFICATION

According to baseline S/D and DT, irrespective of filling profile, patients were assigned to one of four Groups¹⁶: Group 1 (n=48), normal pattern (S/D ≥ 1 ; DT <220 msec); Group 2 (n=61), impaired relaxation LV filling pattern (S/D ≥ 1 ; DT > 220 msec); Group 3 (n=60), pseudonormal LV filling pattern (S/D <1; DT 140-200 msec); Group 4 (n=65), restrictive LV filling pattern (S/D <1; DT <140msec). The 140 value was chosen because it unequivocally identifies patients with restrictive filling

and worse prognosis after myocardial infarction¹⁷. In restrictive and pseudonormal patients with E/A between 1 and 2, the Valsalva maneuver was performed to unmask the presence of impaired relaxation¹⁸. As reported in Table 1, preoperative demographic, clinical and intraoperative data were comparable in the four groups. Table 2 shows baseline echocardiographic findings: patients in the Group 4 had larger LV diameters and volumes and showed a more spherical and dysfunctioning left ventricle.

STATISTICAL ANALYSIS

The sample size was determined by GraphPad StatMate release 2.00 (GraphPad Prism Software, Inc, San Diego, CA) on the basis of preliminary data obtained by echocardiography and was determined on the basis of the following assumptions: Type I error of 0.05 (two-sided), power of 80%, difference in end systolic volume between patients with or without recurrent mitral regurgitation of 0.78, standard deviation of 2.4. The calculated study population was 300. However 270 patients were recruited to allow for possible analytic problems while processing the eventualities potentially leading to patient attrition. All data were analyzed with the SPSS for Windows, release 15.0 (SPSS, Inc, Chicago, IL) statistical package and with GraphPad Prism for Windows, release 4.0 (Graph-Pad Prism Software, Inc, San Diego, CA). Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data were expressed as mean $\pm$ SD and compared using repeated ANOVA with the Tukey post-hoc test for multiple groups comparison. Comparison of proportions was performed using contingency χ^2 analyses or Fisher's test, where appropriate. Non-normally distributed variables were presented as median and interquartile range. The Mann-Whitney and Kruskal-Wallis tests were used to compare non-parametric variables with Dunn's test for multiple comparisons. Cox Regression analysis was employed to identify multivariable predictors of late mortality. Multivariable logistic regression analysis, by means of a backward stepwise algorithm (cut-off for entry 0.05, for removal 0.10) was performed to identify predictors of early mortality and recurrence of MR. Forty-nine demographic, clinical and Doppler echocardiographic variables were investigated for their predictive value of LVRR. Categorical variables with more than two levels in the regression model were converted into dummy variables. To enhance the accuracy of the model, the number of variables were reduced using variable clustering^{19,20}. Model assumptions (linearity and additivity assumptions) were checked by piecewise cubic polynomials (spine functions) and pooled interaction test²¹, respectively, and found to be satisfied. Goodness of fit of the final logistic regression models was assessed with the Hosmer–Lemeshow statistic²⁰ and predictive accuracy was assessed by the concordance (c) index²¹. Internal validation of predictors generated by multivariable

Table 1. Patients profile (n=234)

	Group 1 n=48	Group 2 n=61	Group 3 n=60	Group 4 n=65	P
Age (years)	69 ± 7	68.5 ± 8	68 ± 5	69 ± 8	0.8
Gender M/F	31/17(64.6/35.4)	38/23(62.2/37.8)	37/23(61.6/38.4)	40/25(61.5/38.5)	0.9
Familiar history	22 (45.8)	28(45.9)	26 (43.3)	31 (47.6)	0.4
Systemic hypertension	20 (41.6)	24 (39.3)	23 (38.3)	27 (41.5)	0.6
Diabetes mellitus	14 (29.1)	17 (27.8)	17 (28.3)	20 (30.7)	0.4
Hyperlipidemia	20 (41.6)	25 (40.9)	26 (43.3)	27 (41.5)	0.8
Myocardial infarction					
Inferior/Posterior	25 (52.1)	29 (49.2)	28 (46.7)	31 (47.6)	
Anterior/Septal	4 (8.3)	5 (8.5)	6 (10.0)	6 (9.2)	
Lateral	9 (18.8)	11 (18.6)	11 (18.3)	12 (18.6)	0.5
Combined	10 (20.8)	14 (23.7)	15 (25.0)	16 (24.6)	
Angina	25 (52.0)	49 (47.5)	27 (45.0)	30 (46.1)	0.4
NYHA					
≤ II	11 (22.9)	13 (21.3)	14 (23.4)	14 (21.5)	
III	30 (62.5)	38 (62.3)	35 (58.3)	39 (60.0)	0.6
IV	7 (14.6)	10 (16.4)	11(18.3)	12 (18.5)	
Coronary vessel disease					
Left Main	2 [1-3]	2 [1-3]	2 [1-3]	2 [1-3]	>0.9
Left anterior descending	8 (16.6)	10 (16.3)	8 (13.3)	10 (15.3)	
Circumflex system	44 (91.7)	56 (91.8)	48 (80.0)	55 (84.6)	
Right coronary system	30 (62.5)	36 (59.0)	30 (50.0)	37 (56.9)	
	38 (79.1)	47 (77.0)	44 (73.3)	48(73.8)	

Therapy	Group 1 n=48	Group 2 n=61	Group 3 n=60	Group 4 n=65	P
Angiotensin-converting enzyme inhibitors	40 (83.3)	47 (77.1)	50 (83.3)	53 (81.5)	
B-adrenergic blockers	28 (58.3)	34 (55.7)	30 (50.0)	33 (50.7)	
Long-acting nitrates	23 (47.9)	30 (49.1)	27 (45.0)	30 (46.1)	0.7
Diuretics	39 (81.2)	54 (88.5)	52 (86.6)	59 (90.7)	
Digitalis	10 (20.8)	13 (21.3)	12 (20.0)	15 (23.1)	
Calcium antagonists	4 (8.3)	7 (11.4)	5 (8.3)	8 (12.3)	
Operative Data					
CPB time (min)	108 [95-120]	105 [94-118]	110 [100-126]	115 [106-133]	0.09
CCL Time	90 [70-98]	81 [66-90]	95 [70-101]	100 [80-107]	0.06
CABG					
Anastomoses/patient	2 [1-3]	2 [1-3]	2 [1-3]	2 [1-3]	>0.9
Arterial graft/patient	1 [1-2]	1 [1-2]	1 [1-2]	1 [1-2]	>0.9
Ring Size (mm)	28[26-30]	28[26-30]	28[26-30]	28[26-30]	
Carpentier Classic	26 (54.2)	35 (57.4)	32 (53.3)	36 (55.3)	>0.9
Physio	22 (45.8)	26 (42.6)	28 (46.7)	29 (44.7)	0.7

Continuous variables are presented as mean $\pm$ 1 standard deviation; Discrete variables are presented as n (percentage). Non-parametric variables are presented as median [interquartile range].

Abbreviations: M/F=Male/Female; NYHA=New York Heart Association functional class. CPB=Cardiopulmonary bypass; CCL=Cross-clamp; CABG=Coronary artery bypass grafting.

Table 2. Baseline echocardiography

	Group 1 n=48	Group 2 n=61	Group 3 n=60	Group 4 n=65	p
MR Grade	3 [3-4]	3 [3-4]	3 [3-4]	3 [3-4]	>0.9
MR Quantitative data					
TA	3.5 ± 1.1	3.7 ± 1.0	3.2 ± 1.1	3.5 ± 1.1	0.6
ERO	37 ± 12	36 ± 11	38 ± 14	40 ± 16	0.42
RF	46 ± 13	44 ± 12	47 ± 13	50 ± 18	0.55
RV	57 ± 17	56 ± 15	58 ± 18	60 ± 16	0.72
CH	1.0 ± 0.2	1.9 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	0.001
Left ventricular remodeling					
EDD	59 ± 6	60 ± 7	56 ± 7	65 ± 8	0.03
ESD	49 ± 7	51 ± 8	47 ± 7	56 ± 9	0.03
LA	49 ± 6	50 ± 7	48 ± 3	47 ± 7	0.7
ESV	109 ± 22	110 ± 24	112 ± 31	140 ± 26	<0.001
EDV	176 ± 37	165 ± 35	176 ± 28	194 ± 30	0.04
LVEF	38 ± 12	33 ± 12	36 ± 10	27 ± 11	0.007
SI _s	0.56 ± 0.1	0.55 ± 0.2	0.52 ± 0.1	0.75 ± 0.1	<0.001
SI _D	0.64 ± 0.1	0.62 ± 0.1	0.62 ± 0.1	0.80 ± 0.1	<0.001
WMSI	1.10 ± 0.5	1.14 ± 0.7	1.15 ± 0.6	1.71 ± 0.7	<0.001
Diastolic function					
E/A ratio	1.1 ± 0.3	0.6 ± 0.08	1.5 ± 0.3	1.9 ± 0.6	0.04
DT	215 ± 25	235 ± 28	200 ± 21	119 ± 12	<0.001
IVRT	95 ± 7	112 ± 9	95 ± 10	54 ± 10	0.02
S/D	1.1 ± 0.3	1.0 ± 0.2	0.93 ± 0.1	0.7 ± 0.1	<0.001

Continuous variables are presented as mean ± standard deviation; Non-parametric variables were presented as median [Interquartile range].

Abbreviations: MR=Mitral Regurgitation; TA=Tenting area (cm²); ERO=effective regurgitant orifice (mm²); RF=Regurgitant fraction (%); RV=Regurgitant volume (ml/beat); CH=Coaptation height (cm); EDD=(Left ventricular) End diastolic diameter (mm); ESD=(Left ventricular) End systolic diameter (mm); LA=Left atrium (mm); ESV=(Left ventricular) End systolic volume (ml); EDV=(Left ventricular) End diastolic volume (ml); LVEF=Left ventricular ejection fraction (%); SI_s=Systolic Sphericity Index ; SI_D=Diastolic Sphericity Index WMSI=Wall Motion Score Index; E=Peak trans-mitral flow velocity; A=peak late trans-mitral flow velocity; DT=Deceleration time at early diastolic filling (ms); IVRT=Isovolumetric relaxation time (ms); S/D Systolic to diastolic pulmonary venous flow ratio.

logistic regression was performed by means of bootstrapping techniques, with 1000 cycles and generation of OR and bias corrected 95% CI ²¹.

Optimal cutoff values were determined as the rounding cut-off that gives the maximum sum of sensitivity and specificity. This value should be the shoulder at the top left of the ROC (receiver operating characteristic curve). Bootstrapping techniques were employed to validate the results.

SPSS 12.0 (SPSS, Chicago, IL, USA) and Stats Direct 2.5.7 (Stats Direct, Sale, UK) were used for these calculations. Significance for hypothesis testing was set at the 0.05 two-tailed level.

RESULTS

CLINICAL ASSESSMENT

Early (30-day) mortality rates were 1.6% ($n=1$, respiratory failure), 2.5% ($n=1$, low-output syndrome) 3.3% ($n=2$, multiorgan failure, sepsis) and 9.2% ($n=6$, four low-output syndrome, two multiorgan failure) in Groups 1, 2, 3 and 4, respectively ($p<0.001$). Deceleration time was an independent predictor of early mortality at multivariable logistic regression (Table 3, $p<0.001$). Other independent predictors were SI_s ($p=0.001$), WMSI ($p=0.008$) and S/D ($p=0.004$) whereas the other diastolic variables were not significant.

Internal validation of such multivariable analysis by means of bootstrapping, including the same variables of standard logistic regression model, further confirmed the significant predictive of early death (bootstrap OR=2.6, 95% bias-corrected 95% CI=1.5-6.0). Finally, logistic regression model was reliable (Hosmer–Lemeshow test, $p=0.7$) and accurate (c index=0.8).

ROC analysis showed that DT had 100% of sensitivity and specificity with an optimal cutoff <140 ms (95% CI by bootstrapping 115-164 ms) [area under curve 1; 95% CI 0.70-1; $p<0.001$]. SI_s with a cutoff ≥ 0.7 (95% CI by bootstrapping 0.58-0.81) had 85% of sensitivity and 84% of specificity (area under curve 0.94; 95% CI 0.67-1; $p<0.001$). In addition, WMSI ≥ 1.5 (95% CI by bootstrapping 1.35-1.62) had 80% of sensitivity and 82% of specificity (area under curve 0.81; 95% CI 0.77-0.91; $p=0.002$). Finally, S/D <0.8 (95% CI by bootstrapping 0.63-0.91) had 90% of sensitivity and specificity (area under curve 0.78; 95% CI 0.65-0.87; $p=0.001$).

During the follow-up fifteen patients died: 1 in the normal Group (3 months, respiratory failure), 2 in the impaired relaxation Group (36 months, heart failure; 31 months, myocardial infarction) 3 in the pseudonormal Group (6 months, multiorgan failure; 8 months infection; 14 months respiratory failure) and 9 in the restrictive Group (stroke $n=2$ [12 and 22 months]; heart failure $n=2$ [45 and 54 months];

Table 3. Predictors of early and late death

Early			95% Bias corrected CI	
Variable	Odds Ratio	p	Lower Limit	Upper Limit
DT	3.05	<0.001	1.5	8.1
SI _s	2.40	0.001	1.4	3.9
WMSI	1.02	0.008	1.0	2.0
S/D	1.22	0.04	0.8	2.1

Late			95% Bias corrected CI	
Variable	Hazard Ratio	p	Lower Limit	Upper Limit
DT<140 ms	2.9	<0.001	1.6	4.2
S/D<0.8	2.4	<0.001	1.5	3.8
SI _s ≥0.7	1.9	0.001	1.1	3.3
WMSI≥1.5	1.6	0.003	1.1	2.2

Abbreviations: LV=Left Ventricle; DT=Deceleration time SI_s=Systolic Sphericity Index ; WMSI=Wall Motion Score Index; S/D Systolic to diastolic pulmonary venous flow ratio.

malignancy n=2 [55 and 59 months]; myocardial infarction, 42 months; arrhythmia, 59 months; sudden unexplained death, 22 months).

Six-year actuarial survival was $95.2 \pm 3.8\%$, $93.3 \pm 4.6\%$, $89.8 \pm 10.7\%$ and $64.2 \pm 6.6\%$ in Groups 1, 2, 3 and 4, respectively ($p=0.022$, Figure 1). A Cox regression analysis revealed that DT <140 ms ($p<0.001$) and S/D<0.8 ($p<0.001$) were independent predictor of late mortality (Table 3). Other predictors were SI ≥ 0.7 ($p=0.001$) and WMSI ≥ 1.5 ($p=0.003$). Other diastolic filling patterns were not significant.

At late control, mean NYHA class was 2.1 ± 0.3 , 2.3 ± 0.4 , 2.2 ± 0.4 and 3 ± 0.6 in Groups 1, 2, 3 and 4, respectively ($p<0.001$). 70.5% patients in the Group 4 had NYHA ≥ 3 vs. 33.3% in the pseudonormal group ($p<0.001$), 18.1% in the impaired relaxation group ($p<0.001$) and 4.6% in the normal Group ($p<0.001$).

POSTOPERATIVE DIASTOLIC FUNCTION

Indices of diastolic function (Figure 2A-D) remained stable over time in patients with baseline diastolic filling. In patients with impaired relaxation, E/A increased ($p=0.04$), whereas DT ($p=0.03$) and IVRT ($p=0.02$) reduced at discharge without further changes at subsequent controls. S/D did not show significant changes in this Group.

In patients with pseudonormal filling, E/A reduced ($p=0.001$) whereas DT ($p=0.03$), IVRT ($p<0.001$) and S/D ($p=0.03$) increased at discharge. All these values remained constant afterwards. Index of diastolic function did not modify over time in patients with restrictive filling pattern.

Figure 1. Six-year actuarial survival by group (see text).

Diastolic Function

Figure 2. A-D. Diastolic Function by Group (see text). Abbreviations: E/A= Peak trans-mitral flow velocity/ peak late trans-mitral flow velocity ratio; DT= Deceleration time at early diastolic filling; IVRT= Isovolumetric relaxation time; S/D= Systolic to diastolic pulmonary venous flow ratio.

RECURRENCE OF MITRAL REGURGITATION

149

Mitral regurgitation was significantly reduced at discharge in all groups ($p < 0.001$) and it did not change at following controls in Groups 1, 2 and 3 (Table 3). In contrast, in patients with restrictive filling pattern, it remained stable at early control, whereas it increased at further controls ($p < 0.001$). Indeed, at late follow-up, among patients in group 4, 58.4% ($n=38$) had an MR grade ≥ 2 vs. 8.3% ($n=4$), 9.8% ($n=6$) and 8.3% ($n=5$) in Groups 1, 2, and 3, respectively ($p < 0.001$).

Multivariable logistic regression analysis identified systolic sphericity Index (OR= 4.97, 95% bias corrected CI =2.11-6.40, $p < 0.001$), DT (OR= 4.66, 95% CI= 2.01-5.43, $p < 0.001$), end systolic volume (OR= 2.59, 95% bias corrected CI = 1.19-3.77, $p=0.003$) and wall motion score Index (OR= 1.99, 95% CI =0.88-2.37, $p=0.04$) as independent predictors of recurrent MR.

Internal validation of such multivariable analysis by means of bootstrapping, including the same variables of standard logistic regression model, further confirmed the significant predictive of recurrent MR (bootstrap OR=2.3, 95% bias-corrected 95% CI=1.1-5.2). Finally, logistic regression model was reliable (Hosmer–Lemeshow test, $p=0.8$) and accurate (c index= 0.78).

ROC analysis showed that SI_s had 100% of sensitivity and specificity with an optimal cutoff ≥ 0.7 (95% CI by bootstrapping 0.58-0.81) [area under curve 1; 95% CI 0.70-1; $p < 0.001$]. DT with a cutoff of < 142 (95% CI by bootstrapping 134-150) had 87% of sensitivity and 80% of specificity (area under curve 0.94; 95% CI 0.67-1; $p < 0.001$). In addition, $ESV \geq 145$ ml (95% CI by bootstrapping 134-155) had 90% of sensitivity and specificity (area under curve 0.87; 95% CI 0.80-0.94; $p < 0.001$). Finally, $WMSI \geq 1.5$ (95% CI by bootstrapping 1.35-1.62) had 80% of sensitivity and 82% of specificity (area under curve 0.81; 95% CI 0.77-0.91; $p=0.002$).

Echocardiographic Results

Table 4 shows postoperative echocardiography. In normal, impaired relaxation and pseudonormal groups, ESV decreased significantly at discharge ($p < 0.001$), early ($p < 0.001$) and late controls ($p < 0.001$). In contrast, in the restrictive group, ESV was significantly reduced at discharge ($p = 0.01$) and early follow up ($p = 0.02$) but increased again ($p < 0.001$) at late control. A 15% reduction in ESV , considered indicative of reverse remodeling¹³ occurred in 95.7%, 96.3%, 88.3% and 0% in Groups 1, 2, 3, and 4, respectively ($p < 0.001$). Changes in EDV , ESD , EDD and $WMSI$ mirrored those of ESV . Systolic and diastolic sphericity indexes improved in Groups 1, 2, and 3 at discharge ($p < 0.001$), early (Group 1, $p = 0.01$ for both SI_s and SI_D ; Group 2, $p < 0.001$ for SI_s and $p = 0.02$ for SI_D ; Group 3, $p = 0.04$ for both SI_s and SI_D) as well as at late control (Group 1, $p = 0.03$ for SI_s and $p = 0.01$ for SI_D ; Group 2, $p = 0.02$ for SI_s and $p = 0.01$ for SI_D ; Group 3, $p < 0.001$ for both SI_s and SI_D). In Group 4 there was an initial, but not significant, reduction in both the systolic and diastolic sphericity

Table 4. Postoperative mitral regurgitation

	Group 1 n=48			Group 2 n=61			Group 3 n=60			Group 4 n=65		
	Discharge	Early	Late	Discharge	Early	Late	Discharge	Early	Late	Discharge	Early	Late
MR	0 [0-1]*	0 [0-1]	0 [0-1]	0 [0-1]*	0 [0-1]	0 [0-1]	0 [0-1]*	0 [0-1]	0 [0-1]	0 [0-1]*	1 [1-2] †§#	2 [1-3] ‡§#
TA	1.9 ± 0.5*	1.9 ± 0.5	1.9 ± 0.3	1.9 ± 0.5*	1.9 ± 0.5	1.9 ± 0.3	1.9 ± 0.5*	1.9 ± 0.5	1.9 ± 0.3	1.9 ± 0.3*	2.3 ± 0.3 †§#	2.9 ± 1.0 †§#
ERO	-	-	-	-	-	-	-	-	-	-	11 ± 7 †§#	26 ± 11 †§#
RF	-	-	-	-	-	-	-	-	-	-	17 ± 9 †§#	32 ± 15 †§#
RV	-	-	-	-	-	-	-	-	-	-	21 ± 12 †§#	38 ± 16 †§#
CH	0.7 ± 0.7*	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.7*	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.7*	0.7 ± 0.2	0.7 ± 0.2	1.1 ± 0.2*	1.1 ± 0.2	1.6 ± 0.4 ‡§#

*†‡ Significance vs. preoperative discharge and early follow-up, respectively. §# Significance vs. Groups 1, 2 and 3, respectively.
Abbreviations: MR=Mitral regurgitation; TA=Tenting area (cm²); ERO=effective regurgitant orifice (mm²); RF=Regurgitant fraction (%); RV=Regurgitant volume (ml); CH=Coaptation height (cm).

Table 5. Echocardiographic results

	Group 1 n=48			Group 2 n=61			Group 3 n=60			Group 4 n=65		
	Discharge	Early	Late	Discharge	Early	Late	Discharge	Early	Late	Discharge	Early	Late
EDD	50 ± 6 [*]	50 ± 6 [†]	50 ± 6 [‡]	52 ± 8 [*]	50 ± 8 [†]	48 ± 6 [‡]	51 ± 7 [*]	49 ± 7 [†]	46 ± 6 [‡]	58 ± 7 ^{§§}	51 ± 8 ^{§§}	60 ± 6 ^{§§}
ESD	42 ± 6 [*]	37 ± 6 [†]	32 ± 6 [‡]	43 ± 7 [*]	37 ± 7 [†]	33 ± 5 [‡]	43 ± 5 [*]	36 ± 5 [†]	33 ± 6 [‡]	46 ± 6 ^{§§}	40 ± 6 ^{§§}	49 ± 5 ^{§§}
LA	48 ± 3	48 ± 3	48 ± 3	48 ± 3	47 ± 2	47 ± 2	49 ± 4	48 ± 4	48 ± 3	46 ± 3	46 ± 2	44 ± 2
ESV	112 ± 19 [*]	102 ± 18 [†]	90 ± 12 [‡]	122 ± 26 [*]	112 ± 20 [†]	92 ± 10 [‡]	118 ± 18 [*]	110 ± 16 [†]	91 ± 12 [‡]	141 ± 33 ^{§§}	132 ± 30 ^{§§}	147 ± 38 ^{§§}
EDV	176 ± 30 [*]	160 ± 21 [†]	150 ± 21 [‡]	182 ± 33 [*]	168 ± 24 [†]	154 ± 24 [‡]	179 ± 26 [*]	166 ± 24 [†]	150 ± 18 [‡]	191 ± 28 ^{§§}	181 ± 26 ^{§§}	196 ± 23 ^{§§}
LVEF	35 ± 10 [*]	35 ± 10	40 ± 10 [‡]	32 ± 10 [*]	33 ± 11	40 ± 6 [‡]	34 ± 8 [*]	33 ± 10	40 ± 11 [‡]	26 ± 7 ^{§§}	27 ± 9 ^{§§}	25 ± 6 ^{§§}
SPI _s	0.46 ± 0.1 [*]	0.41 ± 0.1 [†]	0.38 ± 0.1 [‡]	0.45 ± 0.1 [*]	0.39 ± 0.1 [†]	0.35 ± 0.1 [‡]	0.43 ± 0.1 [*]	0.41 ± 0.1 [†]	0.35 ± 0.1 [‡]	0.60 ± 0.1 ^{§§}	0.59 ± 0.1 ^{§§}	0.66 ± 0.12 ^{§§}
SPI _D	0.54 ± 0.1 [*]	0.49 ± 0.1 [†]	0.44 ± 0.1 [‡]	0.53 ± 0.1 [*]	0.49 ± 0.1 [†]	0.44 ± 0.1 [‡]	0.53 ± 0.1 [*]	0.51 ± 0.1 [†]	0.44 ± 0.1 [‡]	0.65 ± 0.1 ^{§§}	0.63 ± 0.1 ^{§§}	0.74 ± 0.1 ^{§§}
WMSI	1.15 ± 0.6 [*]	1.12 ± 0.6 [†]	1.09 ± 0.4 [‡]	1.14 ± 0.6 [*]	1.10 ± 0.4 [†]	1.08 ± 0.3 [‡]	1.15 ± 0.4 [*]	1.11 ± 0.4 [†]	1.09 ± 0.4 [‡]	1.22 ± 0.6 ^{§§}	1.19 ± 0.5 ^{§§}	1.25 ± 0.6 ^{§§}

**# Significance vs. preoperative discharge and early follow-up, respectively. †# Significance vs. Groups 1, 2 and 3, respectively.
Abbreviations: EDD=(Left ventricular) End diastolic diameter (mm); ESD=(Left ventricular) End systolic diameter (mm); LA=Left atrium (mm); ESV=(Left ventricular) End systolic volume (ml); EDV=(Left ventricular) End diastolic volume (ml); LVEF=Left ventricular ejection fraction (%); SPI_s=Systolic Sphericity Index ; SPI_D=Diastolic Sphericity Index WMSI=Wall motion Score Index, E=Peak trans-mitral flow velocity; A=peak late trans-mitral flow velocity; DT=Deceleration time at early diastolic filling (ms); IVRT=Isovolumetric relaxation time (ms) ; S/D Systolic to diastolic pulmonary venous flow ratio.

indexes, which remained stable at early follow-up with a late increase exceeding the preoperative value ($p<0.001$). In normal, impaired relaxation, and pseudonormal groups, LVEF significantly improved at discharge and at late follow-up, remaining unchanged at early control. In contrast, in the restrictive group it did not significantly change at any study point.

DISCUSSION

This study was aimed at exploring the predictive value of preoperative impairment of diastolic function on early and late outcome and recurrence of mitral regurgitation in patients with Chronic ischemic mitral regurgitation (CIMR) undergoing combined undersized mitral ring annuloplasty (UMRA) and coronary artery bypass grafting (CABG). For this purpose, patients of our cohort were divided into four Groups (normal diastolic pattern [$n=48$], impaired relaxation [$n=61$], pseudonormal [$n=60$], and restrictive [$n=65$]) according to baseline S/D and DT, irrespective of the filling profile. The study protocol included early and late clinical assessment, recurrent mitral regurgitation and left ventricular reverse remodeling assessed by echocardiography preoperatively, at discharge and at follow-up appointments.

The early (30-day) mortality rate was higher in the restrictive group (9.2%, $p<0.001$ vs. Groups 1, 2 and 3). In addition, Deceleration time <140 ms and S/D <0.8 were strong predictors of early mortality at multivariable logistic regression ($p<0.001$ and $p=0.004$, respectively) whereas the other diastolic variables were not significant.. Other independent predictors of late death were SI_s ($p=0.001$) and WMSI ($p=0.008$).

Furthermore, 6-year actuarial survival was significantly lower in Group 4 (log-rank=0.02) and Cox regression analysis identified DT <140 ms and S/D <0.8 ($p<0.001$) as independent predictors of late mortality. Other predictors were $SI \geq 0.7$ ($p=0.001$) and WMSI ≥ 1.5 ($p=0.003$). Other diastolic filling patterns were not significant. In addition, at late control, 70.5% patients in the Group 4 had NYHA ≥ 3 ($p<0.001$ vs. Groups 1-3).

Mitral regurgitation was significantly reduced at discharge in all groups ($p<0.001$) and it did not change at following controls in Groups 1, 2 and 3 whereas, in patients with restrictive filling pattern, it increased afterwards ($p<0.001$). However, at late follow-up, among patients in group 4, 58.4% ($n=38$) had a MR grade ≥ 3 . Multivariable logistic regression analysis identified DT ($p<0.001$), systolic sphericity index ($p<0.001$), end systolic volume ($p=0.003$) and wall motion score Index ($p=0.04$) as independent predictors of recurrence MR

Ereminiene et al²² demonstrated that diastolic restrictive filling pattern and deceleration time were independent predictors of death and residual moderate MR, late (12 months) after ischemic mitral valve repair in 55 patients. Nonetheless these

authors defined the restrictive filling pattern as an E/A ratio >2 or an E/A ratio 1-2 with DT <150 msec and IVRT <60 ms. E and E/A ratio are partially dependent on age, heart rate, loading conditions and degree of MR. In particular, mitral regurgitation may increase the E-wave velocity of transmitral flow, which resembles pseudonormal or restrictive patterns. Several studies have shown that a short DT, even not load independent, irrespective of the ratio of early and late filling velocity (E/A) ratio, is strongly related to pulmonary capillary wedge pressure^{23,24} and end-diastolic pressure²⁵, and it is an useful parameter for the serial assessment of LV diastolic function in post infarct patients also in those with MR²⁶. For this reason, we used DT as a means of assessing LV filling, irrespective of filling pattern. Nonetheless, in an attempt to overcome the limitations of transmitral flow Doppler indices, we used routinely the assessment of pulmonary venous flow. Furthermore, we employed the Valsalva maneuver to unmask the presence of impaired relaxation in pseudonormal and restrictive Groups.

Interestingly, LVEF did not provide any prognostic value thus indicating that LV diastolic dysfunction may be more sensitive than LV systolic dysfunction in predicting death and recurrence of MR after CABG and restrictive annuloplasty.

By comparing the four groups in our study, it appears evident that patients with preoperative restrictive filling pattern were much more globally remodeled at every study point; at late control they still showed a more spherical and enlarged LV. Particularly, the late increase in sphericity indexes in this group, which exceeded the preoperative value, was consistent with further remodeling after UMRA and reflects increased tethering on the mitral valve, thus translating into a significantly higher number of patients with late MR.

Finally, considering a 15% reduction in ESV indicative of reverse remodeling, it occurred in 95.7%, 96.3%, 88.3% and 0% in Groups 1, 2, 3, and 4, respectively ($p<0.001$).

STUDY LIMITATIONS

Our study findings should be viewed in light of some inherent limitations.

-Similarly to other studies²² we employed conventional indices of LV diastolic function.

Tissue Doppler imaging (TDI) would have been more useful in estimating LV diastolic filling pattern. Nonetheless, DT, even not load independent is strongly related to pulmonary capillary wedge pressure and end-diastolic pressure and it is an useful parameter for the serial assessment of LV diastolic function in post infarct patients, also in those with MR. Furthermore, in an attempt to overcome the limitations of transmitral flow Doppler indices, we used routinely the assessment of pulmonary venous flow.

An evaluation of diastolic function after UMRA and CABG, employing TDI will be ongoing to confirm these findings.

Evaluation of LVRR was based on volumes obtained by echocardiography; Volumetry by 2D echocardiography depends on geometric assumptions and is subject to image plane positioning errors. Hence it is not accurate in left ventricles that are distorted in shape such as after myocardial infarction. However, this limitation belongs to most of published papers regarding this pathology.

- Viability testing was not performed in these patients. Therefore lack of LVRR in non responders might be also due to irreversible ischemic myocardial damage (not-viable myocardium). This issue deserves further investigation.
- Postoperative evaluation of the coronary status was not assessed. It would have been helpful to differentiate between surgical failure (valve repair and CABG) and the progress of the coronary disease.
- Fifteen patients with late deaths were not included in the study. They could have benefited from serial echocardiograms possibly with different results.
- Estimated cutoffs are known to be very susceptible to changes in the study population.

We employed bootstrapping techniques to validate the results, nonetheless, it has also been documented that the sensitivity/specificity associated with these cutoffs are overly optimistic.

STRENGTH OF THE STUDY

This is a large cohort reported with UMRA in CIMR patients with detailed (100% complete) echocardiographic follow-up. Furthermore our patient cohort was more homogeneous than in other studies and does not display common clinical and methodological pitfalls that limit results from many studies of mitral valve repair²⁷: all patients underwent associated CABG, they had no concomitant MV procedures, and the entire cohort was uniform regarding the MV ischemic leaflet dysfunction. Moreover, to assess results for MV repair, we studied true “recurrent” MR excluding those patients with “residual” MR in whom the insufficiency was presumably never eliminated at surgery. Additionally, we undertook valve sizing in a standardized fashion and the degree of undersizing was homogeneous over the 5-year-period of the study. Finally, we used only two rings (Carpentier’s rigid or semi-flexible rings).

CLINICAL IMPLICATIONS.

In our experience combined CABG and UMRA do not ensure successful and durable elimination of MR and significant LVRR in all patients. Those who can benefit from this approach could be preoperatively identified utilizing echo predictors. However, restrictive annuloplasty resulted to be ineffective in a large percentage

of patients and results of this study suggest the need for different approaches directly addressing ventricular tethering in most of CIMR patients²⁸. These procedures, as well as the employment of support devices²⁹, were introduced in the recent years in clinical practice, thus our experience with these techniques is actually in the preliminary phase. Furthermore, mitral valve replacement, largely employed in the past in ischemic regurgitation, although eliminates the short-term risk of recurrent MR, it is associated with poor long-term survival³⁰. Thus, in our actual policy, we do not consider MV replacement as a reasonable alternative to repair.

Another interesting finding of our study, apart from the predictive value of DT on Outcome and MR recurrence, was that in patients with more advanced diastolic dysfunction, evidenced by a LV restrictive filling, UMRA associated to CABG did not cause improvement of diastolic function. Contrastingly, an improvement of diastolic function occurred in impaired relaxation and Pseudonormal patients. This suggest that an early surgical indication is advisable in patients with CIMR in less severe stages of disease. In presence of advanced diastolic dysfunction, patients should be considered poor candidates for this procedure and concomitant or alternative procedure should be contemplated.

CONCLUSIONS

On the basis of our experience and with the above-mentioned limitations, we suggest that the assessment of potential candidates for UMRA should include accurate evaluation of LV diastolic function to identify patients suffering from CIMR who could really benefit from restrictive annuloplasty. Our findings need to be confirmed by further larger studies.

REFERENCES

1. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KL, Tajik AJ. Ischemic Mitral Regurgitation. Long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001;103:1759-64.
2. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation* 2000;102:1400-6.
3. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. *Circulation* 1997; 96:827-33
4. Kumanohoso T, Otsuji Y, Yoshifuku S. Mechanism of higher incidence of ischemic mitral regurgitation in patient with myocardial infarction: quantitative analysis of left ventricular and valve geometry in 103 patients with prior myocardial infarction. *J Thorac Cardiovasc Surg* 2003;125:135-43.
5. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Card* 2003;91:538-43.
6. Bach DS, Bolling SF. Improvement following correction of secondary mitral regurgitation in end-stage cardiomyopathy with mitral annuloplasty. *Am J Cardiol*. 1996;78:966-69.
7. Tibayan FA, Rodriguez F, Langer F et al. Undersized mitral annuloplasty alters left ventricular shape during acute ischemic mitral regurgitation. *Circulation* 2004;110[suppl.II]:II 98-II102.
8. Hausmann H, Siniawski H, Hetzer R. Mitral valve reconstruction and replacement for ischemic mitral insufficiency: Seven years follow-up. *J Heart Valve Dis* 1999;8:536-42.
9. Carpentier A. Cardiac valve surgery-The "French correction". *J Thorac Cardiovasc. Surg.* 1983; 86: 326-37.
10. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2(5):358-67
11. Kono T, Sabbah HN, Rosman H, Alam M, Jafri S, Goldstein S. Left ventricular shape is primary determinant of functional mitral regurgitation in heart failure. *J Am Coll Cardiol* 1992;20:1594-98.
12. Cerqueira MD, Weissman NJ, Dilsizian V et al. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A Statement for Healthcare Professionals From the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105: 539-42.

13. Stellbrink C, Breithardt OA, Franke A, et al. PATH-CHF (Pacing Therapies in Congestive HeartFailure) Investigators; CPI Guidant Congestive Heart Failure Research Group. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol*. 2001; 38(7):1957-65.
14. Gardin JM, Adams DB, Douglas PS et al. American Society of Echocardiography. Recommendations for a standardized report for adult transthoracic echocardiography: a report from the American Society of Echocardiography's Nomenclature and Standards Committee and Task Force for a Standardized Echocardiography Report. *J Am Soc Echocardiogr* 2002;15 (3):275-90.
15. Enriquez-Sarano M, Tribouilloy C. Quantitation of mitral regurgitation: rationale approach and interpretation in clinical practice. *Heart* 2002, 88 (suppl IV):1-4.
16. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998; 32:865-75.
17. Moller JE, Pellikka PA, Hillis GS, Oh JK. Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. *Circulation*. 2006 Aug 1;114(5):438-44.
18. Rakowski H, Appleton C, Chan KL, et al. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: from the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. 1: *J Am Soc Echocardiogr*. 1996;9(5):736-60. 28) Romesburg HC. Cluster analysis for researchers. North Carolina: Lulu Press;2004.1-330.
19. Harrel FE., Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modeling strategies for improved prognostic prediction. *Statistics in Medicine* 1984;3:143-52.
20. Harrel FE Jr, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stats Med* 1996;361-87.
21. Hosmer DW, Lemeshow S. Applied Logistic regression. 2nd ed. New York, NY: Wiley-Interscience; 2000:143-202.
22. Ereminiene E, Vaskelyte J, Benetis R, Stoskute N. Ischemic mitral valve repair: predictive significance of restrictive left ventricular diastolic filling. *Echocardiography*. 2005;22(3):217-24
23. Giannuzzi P, Imparato A, Temporelli PL, et al. Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 1994;23:1630-7.
24. Appleton CP, Hatle LK, Popp RL. Relation of transmitral velocity patterns to
25. left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988;12:426-40.
26. Cerisano G, Bolognese L, Buonamici P, et al. Prognostic implications of restrictive left ventricular filling in reperfused anterior acute myocardial infarction. *J Am Coll Cardiol* 2001;37:793-9.
27. Braun J, Bax JJ, Versteegh MI et al. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. *Eur J Cardiothorac Surg* 2005;27(5):847-53.

28. Adams DH, Anyanwu AC. Pitfalls and limitations in measuring and interpreting the outcomes of mitral valve repair. *J Thorac Cardiovasc Surg* 2006; 131:523-9.
29. Borger MA, Alam A, Murphy PM, Doenst T, David TE. Chronic Ischemic Mitral Regurgitation: Repair Replace or Rethink? *Ann Thorac Surg* 2006; 81: 1153-61.
30. Konertz W, Rombeck B, Hotz H. Short-term safety of the Acorn cardiac support device in patients with advanced heart failure. *J Am Coll Cardiol* 2000;35:182A.
31. Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg*. 2001;122(6):1125-41.

7

Prognostic Value of Doppler-Derived Mitral Deceleration Time on Left Ventricular Reverse Remodeling after Undersized Mitral Annuloplasty

Sandro Gelsomino, MD, Roberto Lorusso, MD, PhD, Carlo Rostagno, MD, Sabina Cacioli, MD,
Marco Chioccioli, MD, Giuseppe Billè, MD, Giuseppe De Cicco, MD, Stefano Romagnoli, MD,
Cristina Porciani, MD, Pierluigi Stefano, MD and Gian Franco Gensini, MD

Published in: Eur J Echocardiogr. 2008; 9(5):631-40

ABSTRACT

Objective. This study was aimed at exploring the predictive value of Doppler-Derived Mitral Deceleration Time (DT) on left ventricular reverse remodeling (LVRR) in patients with chronic ischemic mitral regurgitation (CIMR) undergoing combined undersized mitral annuloplasty (UMRA) and coronary artery bypass grafting (CABG).

Methods. Two hundred and fifteen patients undergoing combined UMRA and CABG for CIMR between September 2001 and September 2007 in our Institution were divided into four groups on the basis of baseline DT: Group 1, normal ($n = 48$), Group 2, impaired relaxation ($n = 61$), Group 3, pseudonormal ($n = 50$) and Group 4, restrictive ($n = 56$). Echocardiograms were performed, preoperatively, at discharge and at follow-up appointments (100% complete, early, median 6 months [interquartile range 4-8 months]) and late, median 38 months (17-61months).

Results. LVRR, defined as a reduction in ESV $> 15\%$, occurred in 95.7%, 96.3%, 88.3% and 0% in Groups 1, 2, 3 and 4, respectively ($p < 0.001$). Logistic regression analysis showed that DT ≤ 125 ($p < 0.001$) was a strong predictor of LVRR after annuloplasty. *Conclusions.* Preoperative assessment of DT adds significant information to commonly used indexes of global and regional function, and represent a very easy and cost effective tool to accurately identify CIMR patients who can really benefit from annuloplasty.

INTRODUCTION

161

The usefulness of Doppler examination of left ventricular (LV) filling based on transmitral flow patterns has been demonstrated in various pathologic conditions¹⁻³. Indeed LV filling patterns were studied in patients with dilated cardiomyopathy, acute myocardial infarction and congestive heart failure⁴⁻⁸. In addition, its prognostic value has recently been demonstrated in patients undergoing coronary artery bypass (CABG)⁹.

Combined undersized mitral ring annuloplasty (UMRA) and CABG is a standard surgical approach to relieve chronic ischemic mitral regurgitation (CIMR)^{10,11}, although the efficacy is still controversial with many studies revealing a significant recurrence of mitral regurgitation (MR)¹²⁻¹⁵ mainly related to continued LV remodeling and persistent leaflet tethering. Therefore, left ventricular reverse remodeling (LVRR) is considered a significant postoperative target¹⁵. Doppler-Derived Mitral Deceleration Time (DT) has been demonstrated to be a strong predictor of LVRR and survival after myocardial infarction¹⁶. Nevertheless, the relationship between LV diastolic filling and its change over time and remodeling after reductive annuloplasty, as well as the prognostic impact of serial assessment of LV filling on postoperative LVRR, have not systematically addressed in a large population.

Therefore, the objective of this study was to evaluate the impact of LV filling on reverse remodeling after combined UMRA and CABG for CIMR.

METHODS

DEFINITIONS

CIMR was defined as the combination of mild-to-severe MR with 1) Prior myocardial infarction (MI)>16 days¹⁷; 2) seventy-five percent or greater stenosis of at least one coronary vessel; 3) a corresponding regional wall motion abnormality; 4) type IIIb leaflet dysfunction following Carpentier's classification³ with or without annular dilatation.

Exclusion criteria were: 1) degenerative or other non-ischemic etiology; 2) ischemic isolated type I or type II dysfunction¹⁸; 3) additional mitral valve repair procedures; 4) other valvular or congenital heart diseases; 5) previous cardiac surgery/percutaneous transluminal coronary angioplasty; 6) atrial fibrillation or sinus rhythm with heart rate at rest >100 bpm/min.

PATIENTS POPULATION

Among 270 Subjects with CIMR undergoing combined CABG and UMRA in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and September 2007 and prospectively enrolled in the study, 55 were excluded: 4 had intraoperative annuloplasty failure, 12 showed residual MR (insufficiency $\geq 2+$ following valve repair documented at discharge), 19 died (these were excluded because of unavailable complete data [4 early, 15 late]), and 20 had incomplete data. The study population consisted of 215 patients.

FOLLOW UP

Clinical follow up information was obtained from all survivors through outpatient visits and was 100% complete. Clinical information regarding New York Heart Association class, recurrence of angina, myocardial infarction, heart failure, reoperation for failed repair was recorded. Median early follow up was 6 months (interquartile range [IQR] 3-8), median late follow up was 38 months (IQR 17-53).

ETHICAL ISSUE

Following the World Medical Association guidelines concerning ethical principles for medical research involving human subjects, the study was approved by Institutional Ethics Board. Furthermore and all patients gave their informed consent. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

ECHOCARDIOGRAPHIC STUDY

The echocardiographic evaluation was as follows. A transthoracic (TTE) and a transesophageal (TEE) echocardiograms were performed within 5 days before surgery and serial TTE were performed at discharge and at follow-up appointments. Echocardiographic studies were performed on Acuson Sequoia imaging device equipped with a 3.5-MHz ultrasound transducer (Acuson Corporation, Mountain View, CA). Echocardiographic measurements were averaged over three cardiac cycles. Inter-observer (I.C e C.R) and intra-observer variability for measurement of DT, end systolic volume (ESV) and grade of MR were $<5\%$ (DT, intraobserver 0.7 -3.1%, interobserver 0.6 to 4.6% ; ESV, intraobserver 0.3-2.9%, interobserver 0.4-4.0; MR, intraobserver 0.4 -2.6%, interobserver 0.3 to 3.4%).

LV VOLUMES AND GEOMETRY

163

LV volume and left ventricular ejection fraction (LVEF) were assessed by the bi-apical Simpson disk method¹⁹. The sphericity index (SI) was obtained at end diastole and end systole (SI_D and SI_S, respectively) as the volume of the left ventricle divided by the volume of a sphere with a diameter equal to the longest axis of the left ventricle measured in the apical view²⁰. The wall motion score index (WMSI) was calculated according to a 17-segment model²¹.

QUANTITATION OF MR

The following quantitative measurements were simultaneously employed to grade the severity of MR and final results were averages of measured values²²⁻²³: 1) Quantitative Doppler. (2) Proximal Isovelocity Surface Area (PISA).

For each measurement, minimum of three cardiac cycles were averaged. The respective thresholds for mild, moderate, and severe MR were <30, 30–59 and ≥60 mL/beat for regurgitant volume (RV), <30, 30–49, and ≥50% for regurgitant fraction (RF), <20, 20–39, and ≥40 mm² for effective regurgitant orifice (ERO), respectively. In patients with no or trivial MR by color Doppler, RV, and RF were used as calculated and ERO was assumed as null. The tenting area (TA) was measured by the area enclosed between the annular plane and mitral leaflets from the parasternal long-axis view at mid-systole. The distance between leaflet coaptation and the mitral annulus plane at early and end systole measured displacement of mitral coaptation toward the LV apex. Recurrent MR was the insufficiency ≥2+ at follow up appointments in patients with no/trivial MR at discharge.

LV DIASTOLIC FILLING PATTERNS

Diastole was evaluated by measuring transmitral flow. Peak early transmitral flow velocity (E), peak late transmitral flow velocity (A), E/A ratio and deceleration time of E velocity (DT) were obtained by pulsed Doppler²⁴. The isovolumic relaxation time (IVRT) was obtained by continuous wave Doppler with the wave beam directed from the apical five-chamber view across the region between the aortic outflow tract and the inflow tract.

Finally, systolic and diastolic pulmonary venous flow and their ratio (S/D) were routinely assessed²⁴.

SURGERY

Indication for CABG surgery was given following AHA/ACC guidelines²⁵. Patients with CIMR showing an ERO >20mm² and RV > 30 ml were scheduled

for operation²⁶. When MR was 2/4, surgery was indicated: 1) in the presence of a dilated LV (end-diastolic volume >110 mL/m²) or low EF (<0.35%), as in the case of dilated cardiomyopathy²⁷; 2) in patients with an increase of ERO>13 mm² at TTE echocardiographic exercise test²⁸; 3) in ischemic patients with fluctuating MR showing a MR ≥3 after intraoperative loading test²⁹.

All patients underwent associated coronary artery bypass grafting. For the purpose of this study, complete revascularization was accomplished when, at least one graft was placed distal to an approximately 50% diameter narrowing in each of the three major vascular system in which arterial narrowing of this severity was noted in a vessel ≥1.5 mm of diameter. It was not considered necessary to bypass all obstructed diagonal branches of the anterior descending or marginal branches of the circumflex coronary arteries for a classification of complete revascularization. Following this definition 100% patients underwent complete revascularization.

The ring size was determined by standard measurements of the inter-trigonal distance and anterior leaflet height. A downsizing by two ring sizes was performed in all patients. After cardiopulmonary bypass (CPB), a transesophageal echocardiography (TEE) was performed to assess residual MR: leaflet coaptation ≥0.5cm, MR ≤1 and systolic MV area > 2cm² was assessed as successful repair.

PATIENT CLASSIFICATION

According to baseline S/D and DT, irrespective of filling profile, patients were assigned to one of four Groups²⁴: Group 1 (n=48), Normal pattern (S/D ≥1; DT <220 msec); Group 2 (n=61), impaired relaxation LV filling pattern (S/D ≥1; DT > 220 msec); Group 3 (n=50), pseudonormal LV filling pattern (S/D<1; DT 140-200 msec); Group 4 (n=56), restrictive LV filling pattern (S/D<1; DT<140 msec). The 140 value was chosen because it unequivocally identifies patients with restrictive filling and worse prognosis after myocardial infarction³⁰. In no-restrictive patients presenting E /A between 1 and 2, the Valsalva maneuver was performed to unmask the presence of impaired relaxation: the diagnosis of normal diastolic function was confirmed in the absence of reversal of the E/A below 1, during the strain phase of the maneuver³¹.

PRIMARY END-POINT

Based on the same criterion used by Stellbrink et al.³², patients were classified as responders of LVRR if the ESV was reduced > 15% compared with baseline volumes, and as non-responders if ESV was reduced ≤15% at late control following UMRA.

STATISTICAL ANALYSIS

165

The sample size was determined by GraphPad StatMate release 2.00 (GraphPad Prism Software, Inc, San Diego, CA) on the basis of preliminary data obtained by echocardiography and was determined on the basis of the following assumptions: Type I error of 0.05 (two-sided), power of 80%, difference in end systolic volume between patients with or without recurrent mitral regurgitation of 0.78, standard deviation of 2.4. The calculated study population was 200. However 270 patients were recruited to allow for possible analytic problems while processing the eventualities potentially leading to patient attrition. All data were analyzed with the SPSS for Windows, release 15.0 (SPSS, Inc, Chicago, IL) statistical package and with Graph-Pad Prism for Windows, release 4.0 (Graph-Pad Prism Software, Inc, San Diego, CA). Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data were expressed as mean $\pm$ SD and compared using repeated ANOVA with the Tukey post-hoc test for multiple groups comparison. Comparison of proportions was performed using contingency χ^2 analyses or Fisher's test, where appropriate. Non-normally distributed variables were presented as median and interquartile range. The Mann-Whitney and Kruskal-Wallis tests were used to compare non-parametric variables with Dunn's test for multiple comparisons.

Multivariable logistic regression analysis, by means of a backward stepwise algorithm (cut-off for entry 0.05, for removal 0.10) was performed to identify predictors of LVRR. Forty-nine demographic, clinical and Doppler echocardiographic variables were investigated for their predictive value of LVRR. To enhance the accuracy of the model, the number of variables was reduced using variable clustering³³ until the number of variables to use as candidate in the regression analysis was $\leq m/10$, where for binary outcomes, m is the number of patients in the less frequent outcome category³⁴.

Model assumptions (linearity and additivity assumptions) were checked by piecewise cubic polynomials (spline functions) and pooled interaction test³⁵, respectively, and found to be satisfied. Goodness of fit of the final logistic regression models was assessed with the Hosmer–Lemeshow statistic³⁶ and predictive accuracy was assessed by the concordance (c) index^{34,35}. Internal validation of predictors generated by multivariable logistic regression was performed by means of bootstrapping techniques, with 1000 cycles and generation of OR and bias corrected 95% CI³⁵.

Optimal cutoff values were determined as the rounding cut-off that gives the maximum sum of sensitivity and specificity. This value should be the shoulder at the top left of the ROC (receiver operating characteristic curve). Bootstrapping techniques were employed to validate the results.

Cumulative probability for death and re-operation were estimated by use of the Kaplan–Meier method.

SPSS 12.0 (SPSS, Chicago, IL, USA) and Stats Direct 2.5.7 (Stats Direct, Sale, UK) were used for these calculations. Significance for hypothesis testing was set at the 0.05 two-tailed level.

RESULTS

PATIENT BASELINE PROFILES

As reported in Table 1, preoperative demographic, clinical and intraoperative data were comparable in the four groups. Baseline echocardiographic characteristics of the study population according to preoperative LV diastolic pattern are reported in Table 2. There was no significant difference between the four Groups with respect to quantitative and qualitative MR data. In contrast, patients with restrictive pattern, as compared with those in the other Groups, had larger coaptation height ($p=0.001$), LV diameters ($p=0.03$) and volumes (ESV, $p<0.001$; EDV, $p=0.04$), a more spherical ($p<0.001$) and dysfunctioning LV (WMSI, $p<0.001$; LVEF, $p=0.04$). Furthermore, they had lower DT and S/D, by definition ($p<0.001$) with higher E/A ratio ($p=0.04$) and shorter IVRT ($p=0.02$).

CHANGES IN ECHOCARDIOGRAPHIC VARIABLES

Echocardiographic results are shown in Table 3. Mitral regurgitation was significantly reduced at discharge in all groups ($p<0.001$) and it did not change at following controls in Groups 1, 2 and 3. In contrast, in patients with restrictive filling pattern, it remained stable at early control, whereas increased significantly at late control ($p<0.001$). Indeed, at late follow-up, among patients in group 4, 59.1% ($n=26$) had an MR grade ≥ 2 vs. 8.3% ($n=4$), 9.8% ($n=6$) and 10% ($n=5$) in Groups 1, 2, and 3, respectively ($p<0.001$).

In normal, impaired relaxation and pseudonormal groups, ESV decreased significantly at discharge ($p<0.001$), early ($p<0.001$) and late controls ($p<0.001$). In contrast, in the restrictive group, ESV was significantly reduced at discharge ($p=0.01$) and early follow-up ($p=0.02$) but increased again ($p<0.001$) at late control. A 15% reduction in ESV (considered indicative of LVRR) occurred in 95.7%, 96.3%, 88.3% and 0% in Groups 1, 2, 3, and 4, respectively ($p<0.001$). A further comparison of the degree of LV reverse remodeling in the three groups showed that ESV was reduced 20% or more in 18 patients (40.0%) and $<20\%$ in 27 patients (60.0%) in Group 1. In Group 2, 33 patients (62.3%) had a reduction in ESV $<20\%$ and 20 patients (37.3%) had a reduction $\geq 20\%$. In addition, ESV was reduced 20% or more in 13 patients (34.2%) and $<20\%$ or less in 25 patients (65.8%) in Group 3 (between groups $p=0.71$). Finally, among patients with a restrictive pattern ESV was reduced

PROGNOSTIC VALUE OF DOPPLER-DERIVED MITRAL DECELERATION TIME

Table 1. Patients profile (n=215)

167

	Group 1 n=48	Group 2 n=61	Group 3 n=50	Group 4 n=56	p
Age (years)	69 ± 7	68.5 ± 8	68 ± 5	69 ± 8	0.8
Gender M/F	31/17 (64.6/35.4)	38/23 (62.2/37.8)	32/18 (64.0/36.0)	35/21 (62.5/37.5)	0.53
Family history	22 (45.8)	28(45.9)	23 (46.0)	27 (48.2)	0.82
Euroscore					
Additive	8.0 [5-9]	8.3 [6-11]	8.0 [5-9]	8.7 [5-8]	0.4
Logistic	14.8 [11-18]	14.6 [10-17]	15.0 [13-18]	15.1 [10-19]	0.8
COPD	10 (20.8)	8 (13.1)	9 (18.0)	9 (16.1)	0.07
Chronic renal disease	9 (18.7)	13 (21.3)	11 (22.0)	10 (17.8)	0.16
Cerebral vascular disease	6 (12.5)	9 (14.0)	8 (16.0)	6 (10.7)	0.43
Peripheral vascular disease	4 (8.3)	6 (9.8)	3 (6.0)	4 (7.1)	0.64
Familiar history	40 (47.6)				
Systemic hypertension	20 (41.6)	24 (39.3)	19 (38.0)	23 (41.0)	0.79
Diabetes mellitus	14 (29.1)	17 (27.8)	13 (26.0)	15 (26.7)	0.88
Hyperlipidemia	20 (41.6)	25 (40.9)	20 (40.0)	22 (39.2)	0.9
Myocardial infarction					
Inferior/Posterior	25 (52.1)	29 (49.2)	25 (50.0)	29 (51.7)	
Anterior/Septal	4 (8.3)	5 (8.5)	4 (8.0)	4 (7.1)	
Lateral	9 (18.8)	11 (18.6)	9 (18.0)	10 (17.9)	0.6
Combined	10 (20.8)	14 (23.7)	12 (24.0)	13 (23.3)	
Angina	25 (52.0)	49 (47.5)	23 (46.0)	28 (50.0)	0.46
CCS Angina class	2 [1-3]	2 [1-3]	2 [1-3]	2 [1-3]	>0.9
NYHA					
≤ II	11 (22.9)	13 (21.3)	10 (20.0)	11 (19.6)	
III	30 (62.5)	38 (62.3)	32 (64.0)	36 (64.3)	0.4
IV	7 (14.6)	10 (16.4)	8 (16.0)	9 (16.1)	
Coronary vessel disease	3 [1-3]	3 [1-3]	3 [1-3]	3[1-3]	>0.9
1	3 (6.3)	4 (6.6)	4 (8.0)	3 (5.4)	
2	19 (39.6)	23(37.7)	21(42.0)	25 (44.6)	
≥3	26 (54.1)	34 (55.7)	25 (50.0)	28 (50.0)	
Left Main	8 (16.6)	10 (16.3)	7 (14.0)	9 (16.0)	
Left anterior descending	44 (91.7)	56 (91.8)	44 (88.0)	52 (92.8)	
Circumflex system	30 (62.5)	36 (59.0)	27 (54.0)	33 (58.9)	
Right coronary system	38 (79.1)	47 (77.0)	39 (78.0)	43(76.7)	

	Group 1 n=48	Group 2 n=61	Group 3 n=50	Group 4 n=56	p
Therapy					
Angiotensin-converting enzyme inhibitors	40 (83.3)	47 (77.1)	41(82.0)	44(78.5)	0.9
B-adrenergic blockers	28 (58.3)	34 (55.7)	25 (50.0)	29 (51.7)	
Long-acting nitrates	23 (47.9)	30 (49.1)	23 (46.0)	26 (46.4)	
Diuretics	39 (81.2)	54 (88.5)	43 (86.0)	52 (92.8)	
Digitalis	10 (20.8)	13 (21.3)	10 (20.0)	13 (23.2)	0.06
Calcium antagonists	4 (8.3)	7(11.4)	4 (8.0)	7 (12.5)	
Preoperative IABP	6 (12.5)	8 (13.1)	8 (16.0)	11 (19.6)	
Operative Data					
CPB time (min)	108 [95-120]	105 [94-118]	110 [100-126]	115 [106-133]	0.09
CCL Time	90 [70-98]	81 [66-90]	95 [70-101]	100 [80-107]	0.06
CABG					
Anastomoses/patient	3 [1-3]	3 [1-3]	3 [1-3]	3 [1-3]	>0.9
Arterial graft/patient	1 [1-2]	1 [1-2]	1 [1-2]	1 [1-2]	>0.9
Ring size (mm)	28[26-30]	28[26-30]	28[26-30]	28[26-30]	>0.9
Carpentier Classic	26 (54.2)	35 (57.4)	27 (54.0)	31 (55.3)	0.7
Physio	22 (45.8)	26 (42.6)	23 (46.0)	25 (44.7)	

Continuous variables are presented as mean $\pm$ standard deviation;. Discrete variables are presented as n (percentage). Non-parametric variables were presented as median [Interquartile range].

Abbreviations: M/F=Male/Female; COPD=Chronic obstructive pulmonary disease; ; CCS=Canadian Cardiovascular Society; NYHA = New York Heart Association IABP=Intaaortic balloon pump; CPB=Cardiopulmonary bypass; CCL=(Aortic)Cross-clamp; MR=Mitral regurgitation;. CABG=Coronary artery bypass grafting.

Table 2. Baseline echocardiographic findings

	Group 1 n=48	Group 2 n=61	Group 3 n=50	Group 4 n=56	p
MR Grade	3 [3-4]	3 [3-4]	3 [3-4]	3 [3-4]	>0.9
2+	8 (16.6)	10 (16.4)	8 (16.0)	10 (17.8)	
3+	27 (56.3)	34 (55.8)	28 (56.0)	31 (55.4)	
4+	13 (27.1)	17 (27.8)	14 (28.0)	15 (26.8)	
MR Quantitative data					
TA	3.5 ± 1.1	3.7 ± 1.0	3.2 ± 1.1	3.5 ± 1.1	0.6
ERO	37 ± 12	36 ± 11	38 ± 14	40 ± 16	0.42
RF	46 ± 13	44 ± 12	47 ± 13	50 ± 18	0.55
RV	57 ± 17	56 ± 15	58 ± 18	60 ± 16	0.72
CH	1.0 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	0.001
Direction of regurgitant jet					
Central	15 (31.2)	19 (31.1)	16 (32.0)	19 (33.9)	0.7
Anterior	6 (12.5)	8 (13.1)	6 (12.0)	6 (10.7)	
Posterior	11 (22.9)	14 (23.0)	11 (22.0)	14 (25.1)	
Complex	16 (33.4)	68 (32.8)	17 (34.0)	17 (30.3)	
Carpentier's classification					
Type IIIb	30 (62.5)	39 (63.9)	31 (62.0)	37 (66.1)	0.9
Type IIIb + annular dilatation	18 (37.5)	22 (36.1)	19 (38.0)	19 (33.9)	>0.9
Systolic function and Geometry					
EDD	59 ± 6	60 ± 7	56 ± 7	65 ± 8	0.03
ESD	49 ± 7	51 ± 8	47 ± 7	56 ± 9	0.03
LA	49 ± 6	50 ± 7	48 ± 3	47 ± 7	0.7
ESV	109 ± 22	110 ± 24	112 ± 31	140 ± 26	<0.001
EDV	176 ± 37	165 ± 35	176 ± 28	194 ± 30	0.04
LVEF	38 ± 12	33 ± 12	36 ± 10	27 ± 11	0.007
SI _s	0.56 ± 0.1	0.55 ± 0.2	0.52 ± 0.1	0.75 ± 0.1	<0.001
SI _d	0.64 ± 0.1	0.62 ± 0.1	0.62 ± 0.1	0.80 ± 0.1	<0.001
WMSI	1.10 ± 0.5	1.14 ± 0.7	1.15 ± 0.6	1.71 ± 0.7	<0.001
Diastolic function					
E/A ratio	1.1 ± 0.3	0.6 ± 0.08	1.5 ± 0.3	1.9 ± 0.6	0.04
DT	215 ± 25	235 ± 28	200 ± 21	119 ± 12	<0.001
IVRT	95 ± 7	112 ± 9	95 ± 10	54 ± 10	0.02
S/D	1.1 ± 0.3	1.0 ± 0.2	0.93 ± 0.1	0.7 ± 0.1	<0.001

Continuous variables are presented as mean ± standard deviation; Non-parametric variables were presented as median [Interquartile range]. Abbreviations: MR=Mitral Regurgitation; TA=Tenting area (cm²); ERO=effective regurgitant orifice (mm²); RF=Regurgitant fraction (%); RV=Regurgitant volume (ml/beat); CH=Coaptation height (cm); MA_s=(Systolic) Mitral annular area (cm²); MA_d=(Diastolic) Mitral annular area (cm²); EDD=(Left ventricular) End diastolic diameter (mm); ESD=(Left ventricular) End systolic diameter (mm); LA=Left atrium (mm); ESV=(Left ventricular) End systolic volume (ml); EDV=(Left ventricular) End diastolic volume (ml); LVEF=Left ventricular ejection fraction (%); SI_s=Systolic Sphericity Index; SI_d=Diastolic Sphericity Index; WMSI=Wall motion Score Index; E=Peak trans-mitral flow velocity; A=peak late trans-mitral flow velocity; DT=Deceleration time at early diastolic filling (ms); IVRT=Isovolumetric relaxation time (ms); S/D Systolic to diastolic pulmonary venous flow ratio; ns=not significant.

Table 3. Postoperative Echocardiographic Results.

	Normal				Impaired Relaxation				Pseudonormal				Restrictive			
	Discharge	Early	Late		Discharge	Early	Late		Discharge	Early	Late		Discharge	Early	Late	
MR	0 [0-1]*	0 [0-1]	0 [0-1]		0 [0-1]*	0 [0-1]	0 [0-1]		0 [0-1]*	0 [0-1]	0 [0-1]		0 [0-1]*	1 [1-2] ^{†§§}	2 [1-3] ^{†§§}	
TA	1.9 ± 0.5*	1.9 ± 0.5	1.9 ± 0.3		1.9 ± 0.5*	1.9 ± 0.5	1.9 ± 0.3		1.9 ± 0.5*	1.9 ± 0.5	1.9 ± 0.3		1.9 ± 0.3*	2.3 ± 0.3 ^{†§§}	2.9 ± 1.0 ^{†§§}	
ERO	-	-	-		-	-	-		-	-	-		-	11 ± 7 ^{†§§}	26 ± 11 ^{†§§}	
RF	-	-	-		-	-	-		-	-	-		-	17 ± 9 ^{†§§}	32 ± 15 ^{†§§}	
RV	-	-	-		-	-	-		-	-	-		-	21 ± 12 ^{†§§}	38 ± 16 ^{†§§}	
CH	0.7 ± 0.7*	0.6 ± 0.2	0.6 ± 0.2		0.7 ± 0.7*	0.7 ± 0.2	0.7 ± 0.2		0.6 ± 0.7*	0.7 ± 0.2	0.7 ± 0.2		1.1 ± 0.2*	1.1 ± 0.2	1.6 ± 0.4 ^{†§§}	
EDD	50 ± 6*	50 ± 6 [†]	50 ± 6 [†]		52 ± 8*	50 ± 8 [†]	48 ± 6 [†]		51 ± 7*	49 ± 7 [†]	46 ± 6 [†]		58 ± 7 ^{†§§}	51 ± 8 ^{†§§}	60 ± 6 ^{†§§}	
ESD	42 ± 6*	37 ± 6 [†]	32 ± 6 [†]		43 ± 7*	37 ± 7 [†]	33 ± 5 [†]		43 ± 5*	36 ± 5 [†]	33 ± 6 [†]		46 ± 6 ^{†§§}	40 ± 6 ^{†§§}	49 ± 5 ^{†§§}	
LA	48 ± 3	48 ± 3	48 ± 3		48 ± 3	47 ± 2	47 ± 2		49 ± 4	48 ± 4	48 ± 3		46 ± 3	46 ± 2	44 ± 2	
ESV	112 ± 19*	102 ± 18 [†]	90 ± 12 [†]		122 ± 26*	112 ± 20 [†]	92 ± 10 [†]		118 ± 18*	110 ± 16 [†]	91 ± 12 [†]		141 ± 33 ^{†§§}	132 ± 30 ^{†§§}	147 ± 38 ^{†§§}	
EDV	176 ± 30*	160 ± 21 [†]	150 ± 21 [†]		182 ± 33*	168 ± 24 [†]	154 ± 24 [†]		179 ± 26*	166 ± 24 [†]	150 ± 18 [†]		191 ± 28 ^{†§§}	181 ± 26 ^{†§§}	196 ± 23 ^{†§§}	
LVEF	35 ± 10*	35 ± 10	40 ± 10 [†]		32 ± 10*	33 ± 11	40 ± 6 [†]		34 ± 8*	33 ± 10	40 ± 11 [†]		26 ± 7 ^{†§§}	27 ± 9 ^{†§§}	25 ± 6 ^{†§§}	
SPI _s	0.46 ± 0.1*	0.41 ± 0.1 [†]	0.38 ± 0.1 [†]		0.45 ± 0.1*	0.39 ± 0.1 [†]	0.35 ± 0.1 [†]		0.43 ± 0.1*	0.41 ± 0.1 [†]	0.35 ± 0.1 [†]		0.60 ± 0.1 ^{†§§}	0.59 ± 0.1 ^{†§§}	0.66 ± 0.12 ^{†§§}	
SPI _D	0.54 ± 0.1*	0.49 ± 0.1 [†]	0.44 ± 0.1 [†]		0.53 ± 0.1*	0.49 ± 0.1 [†]	0.44 ± 0.1 [†]		0.53 ± 0.1*	0.51 ± 0.1 [†]	0.44 ± 0.1 [†]		0.65 ± 0.1 ^{†§§}	0.63 ± 0.1 ^{†§§}	0.74 ± 0.1 ^{†§§}	
WMSI	1.15 ± 0.6*	1.12 ± 0.6 [†]	1.09 ± 0.4 [†]		1.14 ± 0.6*	1.10 ± 0.4 [†]	1.08 ± 0.3 [†]		1.15 ± 0.4 [†]	1.11 ± 0.4 [†]	1.09 ± 0.4 [†]		1.22 ± 0.6 ^{†§§}	1.19 ± 0.5 ^{†§§}	1.25 ± 0.6 ^{†§§}	
E/A	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3		1.1 ± 0.08*	1.1 ± 0.08	1.1 ± 0.08		1.1 ± 0.3*	1.1 ± 0.3	1.1 ± 0.3		1.9 ± 0.1 ^{†§§}	1.8 ± 0.1 ^{†§§}	1.8 ± 0.1 ^{†§§}	
DT	214 ± 25	220 ± 20	215 ± 18		210 ± 28*	212 ± 22	210 ± 24		230 ± 19*	228 ± 21	228 ± 21		128 ± 15 ^{†§§}	125 ± 11 ^{†§§}	125 ± 12 ^{†§§}	
IVRT	95 ± 7	93 ± 5	91 ± 5		98 ± 9*	96 ± 9	96 ± 6		110 ± 10*	110 ± 10	113 ± 10		56 ± 10 ^{†§§}	55 ± 8 ^{†§§}	55 ± 8 ^{†§§}	
S/D	1.1 ± 0.3	1.0 ± 0.3	1.0 ± 0.3		1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2		1.1 ± 0.1*	1.1 ± 0.1	1.1 ± 0.1		0.8 ± 0.1 ^{†§§}	0.7 ± 0.1 ^{†§§}	0.7 ± 0.1 ^{†§§}	

*† Significance vs. preoperative discharge and early follow-up, respectively. †§ Significance vs. Groups 1, 2 and 3, respectively.

Abbreviations: MR=Mitral regurgitation; TA=Tenting area (cm²); ERO=effective regurgitant orifice (mm²); RF=Regurgitant fraction (%); RV=Regurgitant volume (ml); CH=Coaptation height (cm); EDD=(Left ventricular) End diastolic diameter (mm); ESD=(Left ventricular) End systolic diameter (mm); LA=Left atrium (mm); ESV=(Left ventricular) End systolic volume (ml); EDV=(Left ventricular) End diastolic volume (ml); LVEF=Left ventricular ejection fraction (%); SPI_s=Systolic Sphericity Index ; SPI_D=Diastolic Sphericity Index WMSI=Wall motion Score Index, E=Peak trans-mitral flow velocity; A=peak late trans-mitral flow velocity; DT=Deceleration time at early diastolic filling (ms); IVRT=Isovolumetric relaxation time (ms) ; S/D Systolic to diastolic pulmonary venous flow ratio.

Table 4. Independent predictors of LV reverse remodeling.

171

Variable	Odds Ratio	p	95% Bias –corrected CI	
			Lower Limit	Upper Limit
DT	3.08	<0.001	1.54	5.90
SI _s	2.40	0.001	1.48	3.99
WMSI	1.02	0.008	1.00	2.02
S/D	1.22	0.06	0.87	2.13
SI _D	0.98	0.2	0.09	1.93
LVEF	0.93	0.24	0.08	1.78
ESD	0.81	0.33	0.09	1.01
EDD	0.87	0.11	0.09	1.23
E/A	0.67	0.62	0.07	1.0
IVRT	0.51	0.73	0.09	1.2

Abbreviations: LV=Left Ventricle; DT=Deceleration time SIS=Systolic Sphericity Index ; S/D Systolic to diastolic pulmonary venous flow ratio.; WMSI=Wall Motion Score Index; SI_D=Diastolic Sphericity Index; LVEF=Left ventricular ejection fraction; ESD=(Left ventricular) End systolic diameter (mm); EDD=(Left ventricular) End diastolic diameter; E=Peak trans-mitral flow velocity; A=peak late trans-mitral flow velocity; at early diastolic filling ; IVRT=Isovolumetric relaxation time.

10% or more in one patient (2.2%), <10% in 27 patients (61.4%), relatively stable ($\pm 1\%$) in four patients (9.1%), and enlarged in 12 patients (27.3%; mean increment $3.9 \pm 1.7\%$). Changes in EDV, ESD, EDD and WMSI mirrored those of ESV.

Systolic and diastolic sphericity indexes improved in Groups 1, 2, and 3 at discharge ($p < 0.001$), early (Group 1, $p = 0.01$ for both SI_s and SI_D; Group 2, $p < 0.001$ for SI_s and $p = 0.02$ for SI_D; Group 3, $p = 0.04$ for both SI_s and SI_D) as well as at late control (Group 1, $p = 0.03$ for SI_s and $p = 0.01$ for SI_D; Group 2, $p = 0.02$ for SI_s and $p = 0.01$ for SI_D; Group 3, $p < 0.001$ for both SI_s and SI_D). In Group 4 there was an initial, but not significant, reduction in both the systolic and diastolic sphericity indexes, which remained stable at early follow-up with a late increase exceeding the preoperative value ($p < 0.001$). In normal, impaired relaxation, and pseudonormal groups, LVEF significantly improved at discharge and at late follow-up, remaining unchanged at early control. In contrast, in the restrictive group it did not significantly change at any study point.

Indices of diastolic function remained stable over time in patients with baseline restrictive filling. In patients with pseudonormal filling E/A increased ($p = 0.03$) whereas DT ($p < 0.001$), IVRT ($p = 0.006$) and S/D ($p = 0.04$) reduced at discharge. All these values remained constant afterwards. In patients with impaired relaxation, E/A reduced ($p = 0.02$), whereas DT ($p = 0.001$) and IVRT ($p = 0.03$) raised at discharge without further changes at subsequent controls. S/D did not show significant changes in this Group. Index of diastolic function did not modify over time in patients with normal LV filling pattern.

Figure 1. Receiver operating characteristic (ROC) curve for Doppler-Derived Mitral Deceleration Time (DT) to predict LV remodeling.

Figure 2. Receiver operating characteristic (ROC) for systolic sphericity index (SI_s) to predict LV remodeling.

Figure 3. Receiver operating characteristic (ROC) for Wall Motion Score Index (WMSI) to predict LV remodeling.

PREDICTIVE VALUE OF DT ON LVRR

173

By multiple regression analysis baseline DT, SI_s and WMSI resulted as independent predictors of LVRR. Internal validation of such multivariable analysis by means of bootstrapping, including the same variables of standard logistic regression model, further confirmed the significant predictive of LVRR (bootstrap OR=2.2, 95% bias-corrected 95% CI=1.0-4.9). Finally, logistic regression model was reliable (Hosmer–Lemeshow test, $p=0.58$) and accurate (c index=0.77).

ROC curve analysis to determine optimal cutoff values (Figure 1-3) to predict reverse remodeling showed the following values: DT ≤ 125 ms (95% CI by bootstrapping 108-171 ms), SI_s had 90% of sensitivity and specificity with an optimal cutoff ≤ 0.7 (95% CI by bootstrapping 0.58-0.81), WMSI < 1.5 (95% CI by bootstrapping 1.35-1.62).

CLINICAL FOLLOW UP

At late control, mean NYHA class was 2.1 ± 0.3 , 2.3 ± 0.4 , 2.2 ± 0.4 and 3 ± 0.6 in Groups 1, 2, 3 and 4, respectively ($p < 0.001$). 70.5% patients in the Group 4 had NYHA ≥ 3 vs. 33.3% in the pseudonormal group ($p < 0.001$), 18.1% in the impaired relaxation group ($p < 0.001$) and 4.6% in the normal Group ($p < 0.001$).

Seventeen patients underwent re-operation for failed repair (four had a re-repair and 13 underwent mitral valve replacement): none in Group 1, two in Group 2, six in Group 3 and 9 in Group 4. Five-year freedom from reoperation for failed repair were 100%, $94 \pm 5\%$, $67 \pm 9\%$ and $43 \pm 7\%$ in Groups 1-4, respectively ($p < 0.001$). None of the patients developed clinical signs of angina. Furthermore, no myocardial infarction occurred in the postoperative period.

DISCUSSION

The present study demonstrates that a baseline restrictive filling pattern, as expressed by a short DT, identifies patients who are ultimately candidates to continued LV remodeling after UMRA leading to mitral repair failure and recurrence of mitral regurgitation. Ereminiene et al³⁷ demonstrated, in 55 patients, that diastolic restrictive filling pattern and deceleration time were independent predictors of death and residual moderate MR late (12 months) after ischemic mitral valve repair. Nonetheless these authors defined the restrictive filling pattern as an E/A ratio > 2 or an E/A ratio 1-2 with DT < 150 msec and IVRT < 60 ms. E and E/A ratio are partially dependent on age, heart rate, loading conditions and degree of MR. In particular, mitral regurgitation may increase the E-wave velocity of transmitral flow, which resembles pseudonormal or restrictive patterns. Several studies have shown that a

short DT, even not load independent, irrespective of the ratio of early and late filling velocity (E/A) ratio, is strongly related to pulmonary capillary wedge pressure^{38,39} and end-diastolic pressure⁴⁰ and it is an useful parameter for the serial assessment of LV diastolic function in post infarct patients also in those with MR⁴¹. For this reason, we used DT as a means of assessing LV filling, irrespective of filling pattern. Nonetheless, in an attempt to overcome the limitations of transmitral flow Doppler indices, we used routinely the assessment of pulmonary venous flow. On the basis of these two indices we classified patients in four Groups: Normal, impaired relaxation, pseudonormal and restrictive.

Furthermore, we employed the Valsalva maneuver in no-restrictive patients presenting E/A between 1 and 2, to unmask the presence of impaired relaxation.

Patients belonging to restrictive Group had larger distance between the coaptation point and the mitral annulus (coaptation height, $p=0.001$), which represents a quantitative estimate of incomplete mitral closure. In a recent study Karagiannis et al.⁴² showed a linear correlation between coaptation height and both measurements of left ventricular size and indices of systolic performance of the left ventricle. In our experience, subjects with restrictive diastolic pattern had larger diameters ($p=0.03$) and volumes (ESV, $p<0.001$; EDV, $p=0.04$) and a more dysfunctioning LV (LVEF, $p=0.04$) and this might explain the larger coaptation height found in this Group.

Cardiac remodeling is a well known important aspect of CIMR and myocardial disease progression responsible for recurrence of MR after annuloplasty^{13,14}. Thus left ventricular reverse remodeling (LVRR) is considered a primary postoperative target. Following the same criterion used by Stellbrink et al³¹, a reduction $>15\%$ in ESV compared with baseline volumes was considered LVRR. Other Groups⁴¹ considered LV end diastolic dimension as significant index of LVRR. Nonetheless, measurements of LV volumes have been demonstrated to be more reliable than LV diameters in assessing LV remodeling, especially in enlarged ventricles⁴³. On this basis, LV reverse remodeling occurred in 95.7%, 96.3%, 88.3% and 0% in Groups 1, 2, 3, and 4, respectively ($p < 0.001$). In addition, among restrictive patients, 12 (27.3%) showed continuous remodeling with a mean increment in ESV of $3.9 \pm 1.7\%$ at late examination.

Nonetheless, EDV and ESV decreased at early follow-up also in the restrictive group. Thus, increase in EDV and ESV at late follow-up could be related to the increasing or recurrence of a significant MR and all this might be inducing the restrictive pattern and not vice versa, since from the beginning the restrictive group has larger volumes and lower LVEF. A DT value $>125\text{ms}$ was the most powerful independent predictor of LVRR whereas, interestingly, LVEF did not provide any prognostic value thus indicating that LV diastolic dysfunction may be more sensitive than LV systolic dysfunction in predicting LVRR after CABG and restrictive annuloplasty. Nonetheless, the lack of improvement in LVEF in the restrictive group could be related to the changes in EDV and ESV in presence of a recurrence of MR.

In other words, the fact that LVEF did not show any prognostic value might be due to the presence of MR in this population.

Other predictors of LVRR were SI_s ($p < 0.001$) and WMSI ($p < 0.008$). By comparing the four groups in our study, it appears evident that patients with preoperative restrictive filling pattern were much more globally remodeled at every study point; at late control they still showed a more spherical and enlarged LV. Particularly, the late increase in sphericity indexes in this group, which exceeded the preoperative value, was consistent with further remodeling after UMRA and reflects increased tethering on the mitral valve, thus translating into a significantly higher number of patients with late significant MR in this group ($p < .001$).

STUDY LIMITATIONS

Our study findings should be viewed in light of some inherent limitations.

- Similarly to other studies³⁷ we employed conventional indices of LV diastolic function.
- Tissue Doppler imaging (TDI) would have been more useful in estimating LV diastolic filling pattern. Nonetheless, DT, even not load independent is strongly related to pulmonary capillary wedge pressure and end-diastolic pressure and it is an useful parameter for the serial assessment of LV diastolic function in post infarct patients also in those with MR. Furthermore, in an attempt to overcome the limitations of transmitral flow Doppler indices, we used routinely the assessment of pulmonary venous flow. An evaluation of diastolic function after UMRA and CABG, employing TDI will be ongoing to confirm these findings.
- Evaluation of LVRR was based on volumes obtained by echocardiography; Volumetry by 2D echocardiography depends on geometric assumptions and is subject to image-plane positioning errors. Hence it is not accurate in left ventricles that are distorted in shape such as after myocardial infarction. However, this limitation belongs to most of published paper regarding this pathology.
- Viability testing was not performed in these patients. Therefore lack of LVRR in non responders might be also due to irreversible ischemic myocardial damage (not-viable myocardium). This issue deserves further investigation.
- Postoperative evaluation of the coronary status was not assessed. It would have been helpful to differentiate between surgical failure (valve repair and CABG) and the progress of the coronary disease.
- Fifteen patients with late deaths were not included in the study. They could have benefited from serial echocardiograms possibly with different results.
- Estimated cutoffs are known to be very susceptible to changes in the study population.

We employed bootstrapping techniques to validate the results, nonetheless, it has also been documented that the sensitivity/specificity associated with these cutoffs are overly optimistic.

STRENGTH OF THE STUDY

This is a large cohort reported with UMRA in CIMR patients with detailed (100% complete) echocardiographic follow-up. Furthermore our patient cohort was more homogeneous than in other study and does not display common clinical and methodological pitfalls that limit results from many studies of mitral valve repair⁴⁴: all patients underwent associated CABG, they had no concomitant MV procedures, and the entire cohort was uniform regarding the MV ischemic leaflet dysfunction. Moreover, to assess results for MV repair, we studied true “recurrent” MR excluding those patients with “residual” MR in whom the insufficiency was presumably never eliminated at surgery. Additionally, we undertook valve sizing in a standardized fashion and the degree of undersizing was homogeneous over the 5-year-period of the study. Finally, we used only two rings (Carpentier’s rigid or semi-flexible rings).

CLINICAL IMPLICATIONS.

In our experience combined CABG and UMRA do not ensure successful and durable elimination of MR and significant LVRR in all patients. Those who can benefit from this approach could be preoperatively identified utilizing echo predictors. However, restrictive annuloplasty resulted to be ineffective in a large percentage of patients and results of this study suggest the need for different approaches directly addressing ventricular tethering in most of CIMR patients⁴⁵. These procedures were introduced in the recent years in clinical practice, thus our experience with these techniques is actually in the preliminary phase. Furthermore, mitral valve replacement, largely employed in the past in ischemic regurgitation, although eliminates the short-term risk of recurrent MR, it is associated with poor long-term survival⁴⁶. Thus, in our actual policy, we do not consider MV replacement as a reasonable alternative to repair.

Another interesting finding of our study, apart from the predictive value of DT on LVRR, was that in patients with more advanced diastolic dysfunction, evidenced by a LV restrictive filling, UMRA associated to CABG did not cause improvement of diastolic function. Contrastingly, an improvement of diastolic function occurred in no-restrictive patients. This suggest that an early surgical indication is advisable in patients with CIMR in less severe stages of disease. In the presence of advanced diastolic dysfunction, patients should be considered poor candidates for this procedure and concomitant or alternative procedure should be contemplated.

CONCLUSIONS

177

Preoperative assessment of DT adds significant information to commonly used indexes of global and regional function, and represents a very easy and cost effective tool to accurately identify CIMR patients who can really benefit from annuloplasty. Long term prospective studies on this controversial issue are encouraged.

REFERENCES

1. De Simone G, Greco R, Mureddu G et al. Relation of left ventricular diastolic properties to systolic function in arterial hypertension. *Circulation*. 2000;101(2):152-7.
2. Shingu Y, Shiiya N, Mikami T, Matsuzaki K, Kuniyama T, Matsui Y. Left ventricular diastolic dysfunction in chronic aortic dissection. *Ann Thorac Surg*. 2007;83(4):1356-60
3. Werner GS, Schaefer C, Dirks R, Figulla HR, Kreuzer H. Prognostic value of Doppler echocardiographic assessment of left ventricular filling in idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1994;73(11):792-8
4. Pinamonti B, Zecchin M, Di Lenarda A, Gregori D, Sinagra G, Camerini F. Persistence of restrictive left ventricular filling pattern in dilated cardiomyopathy: an ominous prognostic sign. *J Am Coll Cardiol*. 1997;29(3):604-12.
5. Whalley GA, Gamble GD, Dougherty RN. Restrictive diastolic filling predicts death after acute myocardial infarction: systematic review and meta-analysis of prospective studies. *Heart*. 2006 Nov;92(11):1588-94.
6. Quintana M, Edner M, Kahan T, Hjelm Dahl P, Sollevi A, Rehnqvist N. Is left ventricular diastolic function an independent marker of prognosis after acute myocardial infarction? *Int J Cardiol*. 2004;96(2):183-9.
7. Thohan V. Prognostic implications of echocardiography in advanced heart failure. *Curr Opin Cardiol*. 2004 May;19(3):238-49.
8. Samad BA, Olson JM, Alam M. Characteristics of left ventricular diastolic function in patients with systolic heart failure: a Doppler tissue imaging study. *J Am Soc Echocardiogr*. 2005 Sep;18(9):896-900
9. Liu J, Tanaka N, Murata K, Ueda K et al. Prognostic value of pseudonormal and restrictive filling patterns on left ventricular remodeling and cardiac events after coronary artery bypass grafting. *Am J Cardiol*. 2003;91(5):550-
10. Bach DS, Bolling SF. Improvement following correction of secondary mitral regurgitation in end-stage cardiomyopathy with mitral annuloplasty. *Am J Cardiol*. 1996; 78: 966-69.
11. Tibayan FA, Rodriguez F, Langer F et al. Undersized mitral annuloplasty alters left ventricular shape during acute ischemic mitral regurgitation. *Circulation* 2004; 110 [suppl.II]: II 98-II102.
12. McGee EC, Gillinov AM, Blackstone EH et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 2004, 128:916-24.

13. Hung J, Papakostas L, Tahta SA et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty. Continued LV remodeling as a moving target. *Circulation* 2004;110[suppl.II]:II 85-II 90.
14. Kuwahara E, Otsuji Y, Iguro Y et al. Mechanism of recurrent/persistent ischemic/functional mitral regurgitation in the chronic phase after surgical annuloplasty: importance of augmented posterior leaflet tethering. *Circulation* 2006, 114(Suppl I): I-529-I 534.
15. Geidel S, Lass M, Schneider C, et al. Downsizing of mitral valve and coronary revascularization in severe ischemic mitral regurgitation results in reverse left ventricular and left atrial remodeling. *Eur J Cardiothorac Surg* 2005;27:1011-16.
16. Temporelli PL, Giannuzzi P, Nicolosi GL et al. Doppler-Derived Mitral Deceleration Time as a Strong Prognostic Marker of Left Ventricular Remodeling and Survival After Acute Myocardial Infarction Results of the GISSI-3 Echo Substudy. *J Am Coll Cardiol* 2004;43:1646–53.
17. Pfeffer MA, Braunwald E, Moye LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE investigators. *N Engl J Med* 1992;327:669-77.
18. Carpentier A. Cardiac valve surgery-The “French correction”. *J Thorac Cardiovasc. Surg.* 1983;86(3): 326-37.
19. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2(5):358-67
20. Kono T, Sabbah HN, Rosman H, Alam M, Jafri S, Goldstein S. Left ventricular shape is primary determinant of functional mitral regurgitation in heart failure. *J Am Coll Cardiol* 1992;20:1594-98.
21. Cerqueira MD, Weissman NJ, Dilsizian V et al. American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A Statement for Healthcare Professionals From the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105: 539-42.
22. Gardin JM, Adams DB, Douglas PS et al. American Society of Echocardiography. Recommendations for a standardized report for adult transthoracic echocardiography: a report from the American Society of Echocardiography’s Nomenclature and Standards Committee and Task Force for a Standardized Echocardiography Report. *J Am Soc Echocardiogr* 2002;15 (3):275-90.
23. Enriquez-Sarano M, Tribouilloy C. Quantitation of mitral regurgitation: rationale approach and interpretation in clinical practice. *Heart* 2002, 88 (suppl IV):1-4.
24. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998; 32: 865-75.
25. Eagle KA, Guyton RA, Davidoff R et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 guidelines for coronary artery bypass graft surgery) *Circulation.* 1999;100(13):1464-80.

26. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation*.2001;103(13):1759-64.
27. Calafiore AM, Di Mauro M, Gallina S, Di Giammarco G, Iacò AL, Teodori G, Tavarozzi I. Mitral valve surgery for chronic ischemic mitral regurgitation. *Ann Thorac Surg*. 2004;77(6):1989-97.
28. Lancellotti P, Lebrun F, Pierard LA. Determinants of exercise-induced changes in mitral regurgitation in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol*. 2003;42(11):1921-8.
29. Byrne JG, Aklog L, Adams DH. Assessment and management of functional or ischaemic mitral regurgitation. *Lancet*.2000;355:1743-4.
30. Moller JE, Pellikka PA, Hillis GS, Oh JK. Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. *Circulation*. 2006;114(5):438-44.
31. Rakowski H, Appleton C, Chan KL, et al. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: from the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. 1: *J Am Soc Echocardiogr*. 1996;9(5):736-60.
32. Stellbrink C, Breithardt OA, Franke A et al. J; PATH-CHF (Pacing Therapies in Congestive Heart Failure) Investigators; CPI Guidant Congestive Heart Failure Research Group. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol*. 2001;38(7):1957-65.
33. Romesburg HC. Cluster analysis for researchers. North Carolina: Lulu Press; 2004.1-330.
34. Harrel FE., Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modeling strategies for improved prognostic prediction. *Statistics in Medicine* 1984; 3: 143-52.
35. Harrel FE Jr, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stats Med* 1996;361-87.
36. Hosmer DW, Lemeshow S. Applied Logistic regression. 2nd ed. New York, NY: Wiley-Interscience; 2000:143-202.
37. Ereminiene E, Vaskelyte J, Benetis R, Stoskute N. Ischemic mitral valve repair: predictive significance of restrictive left ventricular diastolic filling. *Echocardiography*. 2005;22(3):217-24.
38. Giannuzzi P, Imparato A, Temporelli PL, et al. Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 1994;23:1630-7.
39. Appleton CP, Hatle LK, Popp RL. Relation of transmitral velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988;12:426-40.
40. Cerisano G, Bolognese L, Buonamici P, et al. Prognostic implications of restrictive left ventricular filling in reperfused anterior acute myocardial infarction. *J Am Coll Cardiol* 2001;37:793-9.
41. Braun J, Bax JJ, Versteegh MI et al. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. *Eur J Cardiothorac Surg* 2005;27(5):847-53.

42. Karagiannis S E, Karatasakis G T, Koutsogiannis N, Athanasopoulos G D, Cokkinos D V. Increased distance between mitral valve coaptation point and mitral annular plane: significance and correlations in patients with heart failure. *Heart* 2003;89:1174–1178.
43. Dujardin KS, Enriquez-Sarano M, Rossi A, Bailey KR, Seward JB. Echocardiographic assessment of left ventricular remodeling: are left ventricular diameters suitable tools? *J Am Coll Cardiol*. 1997 Nov 15;30(6):1534–41.
44. Adams DH, Anyanwu AC. Pitfalls and limitations in measuring and interpreting the outcomes of mitral valve repair. *J Thorac Cardiovasc Surg* 2006; 131:523–9.
45. Borger MA, Alam A, Murphy PM, Doenst T, David TE. Chronic Ischemic Mitral Regurgitation: Repair Replace or Rethink? *Ann Thorac Surg* 2006; 81: 1153–61.
46. Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg*. 2001;122(6):1125–41,

8

Conclusions

Ischemic mitral regurgitation is mitral regurgitation due to complications of coronary artery disease, in particular, myocardial infarction, and not the fortuitous association of coronary artery disease with intrinsic valve disease such as rheumatic disease. In the acute phase of MI, IMR is frequent and appears to carry an adverse prognosis¹⁻³. However, the prognostic implications of IMR in the chronic post-MI phase are uncertain. In pioneering series that underscored the potential importance of IMR, patients were often included early after MI⁴, and decreased survival of patients with IMR may have been due to inclusion of acute MI^{2,3}. Furthermore, MR angiographic grade was not independently predictive of survival, and only a score combining MR grade with clinical data was a weak independent predictor of Outcome⁴. Therefore, the SAVE (Survival And Ventricular Enlargement) study data proved of major interest by suggesting that mild IMR was associated with high mortality⁵. However, because the study design excluded MR grade 3 or 4 and limited inclusion to 16 days after MI, the prognostic implications of IMR remain uncertain, particularly regarding specific implications of the full range of chronic IMR. Nevertheless, these pioneering series had the undisputed merit of raising the hypothesis that IMR, which affects 19% of patients after MI^{4,5}, may be a marker of poor outcome, suggesting that if observed in pure, chronic, definite IMR of all degrees, such an observation may have major prognostic and therapeutic implications.

Chronic Ischemic Mitral Regurgitation (CIMR) which can be due to one of the following reasons: (1) simple annular dilatation (secondary to left ventricular [LV] enlargement), which causes incomplete mitral leaflet coaptation associated with Carpentier type I (normal) leaflet motion; (2) local LV remodeling with papillary muscle displacement producing apical tethering or tenting of the leaflets (with Carpentier type III-b restricted systolic leaflet motion); or (3) both mechanisms⁶. Importantly, exhaustive analyses from the Mayo Clinic echocardiography laboratory^{7,8} have provided a great amount of insight into the mechanisms of ischemic mitral regurgitation and its clinical impact. Thanks to these investigators, we can now reliably measure leaflet tenting area and tenting height quantitatively from transthoracic echocardiograms in patients with LV dysfunction and CIMR, as well as estimate the effective regurgitant orifice⁷. Larger effective regurgitant orifice, or more leak, was directly and independently predicted by excess leaflet tenting and loss of systolic annular contraction, but it was not related to the degree of LV dysfunction. Adverse prognostic consequences were also clearly documented, moreover, as medium-term survival for patients with CIMR and LV dysfunction was strongly and independently related to calculated effective regurgitant orifice, even after statistical adjustment for all other variables⁸. Recently, Otsuji and associates⁹, experimenting with short-term canine and long-term sheep models and 3-dimensional echocardiographic imaging, also contributed new information concerning the mechanisms of IMR resulting from LV local remodeling. Now that we better understand what we

are talking about (and can actually measure it!), surgeons should be more aggressive and not ignore substantial degrees of IMR at the time of CABG. This policy should also apply to patients undergoing percutaneous coronary revascularization with percutaneous transluminal coronary angioplasty and stenting to optimize their prognosis, but such is unlikely since we do not live in a utopia and the interventional cardiologists have not figured out quite yet how to repair leaking mitral valves in the cardiac catheterization laboratory.

Although Undersized Ring Annuloplasty associated to CABG is effective in the treatment of CIMR¹⁰⁻¹², a considerable number of patients show recurrent/persistent MR¹³⁻¹⁵, which adversely affects mortality¹⁶ without established mechanism. Mitral leaflet tethering by the outward displacement of papillary muscles caused by LV remodeling is the basic mechanism of ischemic MR^{8,17-22}. Surgical annuloplasty, which may hoist the posterior annulus anteriorly without displacing the anterior annulus fixed at the aortic root, can potentially and specifically augment posterior leaflet (PML) tethering by increasing the distance between the PM tip and posterior annulus without affecting anterior leaflet (AML) tethering²³.

Thus, is UMRA reliable and effective, or better, is it effective for all CIMR patients? Does one do a ring annuloplasty or a more reliable chordal-preserving Mitral valve replacement? The answer is not a simple one. Historically, we have been handicapped by comparing very different cohorts of patients in attempting to assess whether repair offers a better outcome than does MVR. The patients receiving these two procedures were very dissimilar and not directly comparable, truly an apples versus oranges situation. Fallacious conclusions resulted from such comparisons.

Gillinov et al. analyzed 482 patients²⁴ using propensity score analysis and other sophisticated statistical methods to generate quintiles of patients undergoing either repair or MVR that were relatively well matched to answer the question whether one procedure is better than the other, and, if so, in which particular patient. This approach identified subsets of patients (unbalanced in numbers) that were reasonably well balanced in terms of risk factors. Bootstrap resampling (so-called "bagging") was also used to validate the results of the model and confirm that the results were generalizable. About 70% of patients -but not the sickest patients- were believed to benefit from repair. The amount of relative benefit of repair in terms of survival was less or actually erased if a thoracic artery was not used for CABG, a lateral LV wall motion abnormality was present, or the IMR jet was "complex." The sickest patients did equally poorly with either procedure, and in certain cases MVR was in fact associated with better predicted survival. Overall 5-year survival was still disappointing, regardless of whether the valve was repaired or replaced.

Grossi and associates²⁵ evaluated 223 patients with IMR; but, the New York University statisticians concluded that the marked imbalance in numbers of patients undergoing one procedure or another within the quintiles was such that the propensity score models did not provide an adequate fit to the data. Therefore, propen-

sity score adjustments were not used. Instead, the New York University group did multiple convoluted layers of multivariable analyses to adjust for the confounding effects of functional disability (New York Heart Association class), presence of angina, and particular operation performed, followed by separate Cox modeling within each of the two surgical groups. Those patients who underwent mitral repair at New York University were not as sick as those who required MVR (as was also the case in the Gillinov report²⁴); medium-term survival was suboptimal but roughly equivalent between the two types of procedures. Certain subsets of patients were identified who appeared to do better if they could undergo repair.

Therefore, even with methodological pitfalls²⁶ these articles show a superiority of mitral valve repair over replacement. Valve repair with an undersized annuloplasty ring works satisfactory in most cases of CIMR, but the surgeon needs to pay keen attention in interpreting clinical and echocardiographic data.

The aims of this thesis were: 1) to report long-term results of combined reductive annuloplasty and coronary artery bypass grafting in terms of recurrence of mitral regurgitation, left ventricular reverse remodeling, continued left ventricular remodeling, left ventricular dimensions and geometry. 2) to study modifications of LV and valvular conformation and geometry in chronic ischemic mitral regurgitation before and after annuloplasty. 3) to identify mechanisms (either ventricular or valvular) of recurrent mitral regurgitation 4) to recognize preoperative factors who can help to select patients who can really benefit from annuloplasty.

One of the main limitations of previous clinical studies on chronic IMR is the lack of a clear definition. Different descriptions have resulted in heterogeneous patient groups, which in turn complicate comparisons between studies. In the studies reported in this thesis care was taken in the selection of patients and clear definitions were adopted to ensure homogeneity of patient populations and facilitate comparisons between studies.

TRUE DEFINITION OF CIMR

Serri and colleagues²⁷ defined ischemic mitral regurgitation as “mitral regurgitation resulting from prior myocardial infarction associated with normal mitral valve leaflets and chordae.” This is an etiologic definition that fails to take into account the valve dysfunction or the lesions that actually result in the mitral regurgitation. What is a “normal mitral leaflet”? Carpentier’s pathophysiologic triad describes the interrelationship between leaflet motion (dysfunction), lesions, and etiology⁶. Carpentier’s classification of dysfunction is based on the opening and closing motions of the mitral leaflets in relation to the annular plane. Most patients with ischemic mitral regurgitation have type IIb leaflet dysfunction, with restricted leaflet motion in systole. Wall motion abnormalities, associated with left ventricular dilatation and lateral or apical papillary muscle displacement, result in this type

of valve dysfunction. The lesion associated with type IIIb dysfunction is primarily leaflet tethering, especially the posterior-medial scallop of the posterior leaflet (P3). Associated annular dilatation may be present, but leaflet tethering is considered the primary lesion. Type I dysfunction (normal leaflet motion) with isolated annular dilatation is less common but may occur in the setting of basal myocardial infarction. Some patients with ischemic mitral regurgitation have type II (excess leaflet motion) dysfunction. The lesions resulting in type II ischemic mitral regurgitation include an acutely ruptured papillary muscle or a previously infarcted fibrotic and elongated papillary muscle. In rare instances, isolated chordal rupture can also be seen following papillary tip ischemia.

We suggest a more uniform methodology to classify mitral valve cohorts not only on the basis of etiology but inclusive of dysfunctions and lesions. The importance of such an approach is well demonstrated in ischemic mitral regurgitation. The majority of patients have type IIIb dysfunction, and a remodeling annuloplasty must be undersized to overcorrect the septal-lateral dimension and achieve an adequate surface of leaflet coaptation. Patients with ischemic mitral regurgitation and leaflet restriction (type IIIb dysfunction) are more likely to have residual leaks compared with patients with type I dysfunction who have normal leaflet motion and are treated in a similar fashion. Furthermore, patients with ischemic mitral regurgitation and type II dysfunction have a better long-term prognosis than those with type IIIb dysfunction²⁴. Thus it is inadequate to describe a population of patients with ischemic mitral regurgitation solely on the basis of etiology. This point is equally valid in patients with a “degenerative” etiology of mitral valve disease. Prolapse (type II dysfunction) of the posterior leaflet due to a single ruptured chord (isolated lesion) has a markedly different repair rate and long-term freedom from recurrent mitral regurgitation compared with bileaflet prolapse with chordal rupture and/or elongation involving multiple leaflet segments. Definition of a population of mitral valve patients on the basis of etiology, dysfunction, and lesions is necessary to allow adequate comparison of outcomes, as all can impact clinical results.

WHICH RING?

To extrapolate the efficacy of a surgical technique, it is important that the reader determines whether the technique under evaluation was applied in a standardized and systematic manner that upholds current principles and understanding of pathophysiology. This is particularly relevant in mitral valve repair surgery, as the quality of the result judged by residual or recurrent mitral regurgitation is largely dependent on the manner in which the repair has been performed. Indeed valve sizing should be undertaken in a standardized and logical fashion to define the current efficacy of ischemic mitral valve repair. Because it is now widely accepted that use of an appropriately downsized ring is the single most important aspect

of mitral repair for ischemic mitral regurgitation, the absence of a precise sizing technique raises doubts regarding surgical approach and could explain suboptimal long-term results in some studies²⁷.

The use of incomplete flexible posterior annular bands further complicates interpretation of results²⁷. Recent articles have linked flexible posterior bands with significant recurrent ischemic mitral regurgitation^{13,14}. It is now well established that patients with ischemic mitral regurgitation can develop dilatation of the anterior annulus between the trigones^{28,29}. Because posterior flexible bands do not correct inter trigonal dilatation, they may not effectively ensure restoration of an adequate surface of leaflet coaptation.

In our studies we undertook valve sizing in a standardized fashion and the degree of undersizing was homogeneous over the 5-year-period of the study. Finally, we used only two rings (Carpentier's rigid or semi-flexible rings). Even these two rings are not at all identical, thus, if we have undersized by two sizes both rings, we might have been less restrictive with the Physio ring than with the Classic ring. However, in our experience, neither ring type nor ring size were predictive of recurrent MR. Recently, we have employed new rings which mimic the shape of healthy mitral annulus, and, in contrast with rigid/semi-flexible plane annuloplasty rings, do not flatten the natural saddle shape causing greater tension on chordae and leaflets, innovative annular rings mimic the shape of healthy mitral annulus³⁰.

PERSISTENT (RESIDUAL) VS. RECURRENT MITRAL REGURGITATION

Significant persistent (residual) mitral regurgitation following valve repair, documented either on postbypass transesophageal echocardiography (TEE) or pre-discharge transthoracic echocardiography, implies an immediate failure of the technique employed. In such cases the valve repair was really never successful, and it is not surprising that regurgitation persists into the long term. It would be incorrect to label such cases as "recurrent" mitral regurgitation in studies of long-term outcomes, as the mitral regurgitation was never eliminated at surgery. In the same way that recurrent cancer can only be defined when the primary tumor was successfully and completely resected, recurrent mitral regurgitation should be defined only when surgery initially eliminated the mitral regurgitation. These definitions are often not clarified, and residual mitral regurgitation may account for a substantial proportion of "recurrent" mitral regurgitation reported after ischemic mitral valve repairs. For example, Hung and colleagues¹⁵ studied 30 patients with "recurrent" mitral regurgitation after annuloplasty for ischemic mitral regurgitation in an attempt to understand the mechanisms of recurrence, yet 30% of these patients had moderate or severe mitral regurgitation on the early postoperative study and should have been categorized with residual mitral regurgitation. In addition Kuwahara et al³¹ and Magne and coworkers³² studied recurrent/persistent and persistent MR,

respectively, whereas, in our study residual MR was excluded. Indeed, persistent/residual MR is presumably due to immediate failure of the technique employed rather than LV remodeling³³ and it is not surprising that regurgitation persists at late follow up in these patients. In our opinion, surgeons generally should not accept any degree of mitral regurgitation other than trivial or mild on the postbypass TEE, as the freedom for need of reoperation, reverse ventricular remodeling, and resulting improvements in quality of life are at least in part dependent on elimination of mitral regurgitation. Significant degrees of residual mitral regurgitation (moderate to severe mitral regurgitation and sometimes even mild mitral regurgitation) should generally trigger a second bypass run and corrective action (for example, further ring downsizing, leaflet patch extension, correction of unrecognized prolapse, or valve replacement). This need for a second bypass run should be uncommon and probably not exceed 5% as mitral regurgitation should be eliminated in most patients with correct ring choice and sizing. Only in exceptional circumstances should patients leave the operating room with residual moderate mitral regurgitation; such as when a valve is deemed irreparable and nonreplacable (e.g., massive atrial/annular calcification) or when the risks of a second bypass run are thought to outweigh the benefits. Any study with a high degree of residual mitral regurgitation may be relied on to define perioperative but not long-term outcomes of mitral valve repair.

WHAT DID WE LEARN?

In our experience, 72% of patients undergoing combined CABG and UMRA showed, at five-year control, recurrent MR. In addition, left ventricular reverse remodeling was observed only in 44.2% of the study population with 10.3% of patients showing further left ventricular dilatation.

We clearly identified two categories of patients with CIMR referred to surgery: in one Group subjects showed a symmetric tethering pattern and a mainly posterior regurgitant jet. The second Group had a symmetrical tethering with a central jet. Whereas this difference did not reflect, in our experience, a different infarct localization, indeed a different pattern of local remodeling was responsible for this discrepancy: a more posterior local LV remodeling in the first group and an anterior-posterior LV remodeling with anterior predominance in the symmetric Group. Patients with higher preoperative AML tethering had a greater local LV remodeling of the segments of the anterior papillary muscle, a greater lateral and posterior displacement of the anterior papillary muscle and a wider PM_s separation and a more symmetric tethering pattern. However patients with postoperative MR showed a mechanism different from that of MR at baseline, with a tethering pattern becoming progressively more asymmetric. This is due to continued remodeling that is mainly posterior in the postoperative period, whereas the LV remodeling in the area

of the AML and, consequently, the anterior leaflet tethering, is maintained as in the preoperative situation.

These findings support previous clinical results reported by Agricola et al³⁴, who described two Groups of patients with CIMR: likewise patients with more pronounced AML tethering, their symmetric Group had prevalent posterior and lateral displacement of anterior papillary muscle, PM_s separation and WMSI of the regions supporting the anterior papillary muscle.

Continued LV remodeling occurs in all Groups in the postoperative period and it predominantly involves the region of the LV supporting the posterior papillary muscle. There was no continued anterior remodeling as demonstrated by wall motion score index of segments underlying the anterior papillary muscle which remained constant over time postoperatively in the entire patient cohort. This is in accordance with published data^{15,35} and confirms that tethering of the posterior leaflet may be exacerbated by annuloplasty which, reducing annular size, can potentially shift the posterior annulus farther anteriorly, increasing its displacement relative to the papillary muscles without displacing the anterior annulus fixed at the aortic root³⁶.

Thus our results showed the evidence that preoperative different pattern translated into different postoperative results with most of the symmetric tethering showing recurrent MR. Indeed this finding should be identified keeping in mind that these patients are more likely to develop MR. A key point is the length/ mobility of the anterior mitral leaflet evaluated either at echocardiography or at surgical inspection. We confirmed that an AML longer than A-P diameter is necessary but it could not suffice to ensure durability. The possibility of allowing both leaflets into apposition depends on the ability of AML to move toward the annulus and to reach the posterior one. If this movement is insufficient the mitral leaflets never coapt no matter how much posterior annulus is reduced. The length should allow gaining a postoperative coaptation length of at least 0.8 cm (better 1 cm) which ensures a proper coaptation for long time even in the presence of continued posterior remodeling. The role of the posterior leaflet is not “functional” but it is necessary to offer a “coaptation surface” to the AML, necessary for a proper valve closure. In fact we demonstrated that, even in the presence of a mobile, long AML, a proper continence is not ensured if the AML do not close against the PML.

The angle α' gives an accurate measure of AML tethering. Furthermore, the length of the AML can be estimated by the coaptation height which represents the depth of the AML during systole, in our opinion and according to Calafiore et al³⁷, when it is more than 11 mm, it is associated with a high risk of MR recurrence after reductive annuloplasty.

Thus patients with symmetric tethering and AML tethering predominance ($\alpha'/\beta' \rightarrow 1$), AML not mobile and more tethered ($\alpha \geq 39.5^\circ$ ($p < 0.001$), anterior leaflet excursion angle $\leq 35^\circ$) with a coaptation height ≥ 11 mm will not benefit from UMRA and these results suggest the need, in these subjects, for different approaches directly

addressing ventricular tethering or a chordae-sparing mitral valve replacement. To our knowledge our studies provide the first demonstration that MR recurrence can be predicted from the AML tethering pattern of the ischemic mitral valve on the preoperative echocardiographic evaluation. Nonetheless, the influence of AML tethering could be secondary to other factors and the altered leaflet geometry and recurrent MR could represent both the result of abnormal left ventricular function and geometry which may be primary predictors. This is why we carried out a study in which multivariable models were adjusted for important risk factors of MR recurrence. This study demonstrated that, after we accounted for other clinical and echocardiographic key risk factors AML tethering angle remained a strong predictor of recurrent regurgitation. Indeed patients with moderate or moderate-severe preoperative AML tethering showed a 2.5 times and 3 times higher Odds ratio for MR recurrence compared to those with significant PML tethering (PML angle ≥ 45 degrees³¹). This rose to > 4 fold in patient with severe AML tethering.

In contrast with our results, Kuwahara et al³¹ showed that increased PML tethering was the primary determinant of late MR in 30 patients undergoing surgical annuloplasty for ischemic mitral regurgitation. In addition, Magne and coworkers³² identified a PML angle ≥ 45 degrees (sensitivity 100%, specificity 97%) to be a predictor of postoperative persistence of MR after annuloplasty.

However, these authors studied recurrent/persistent and persistent MR, respectively, whereas in our study residual MR was excluded. Persistent /residual MR is presumably due to immediate failure of the technique employed rather than LV remodeling²² and it is not surprising that regurgitation persists at late follow up in these patients

FINAL CONSIDERATIONS

When I present my works at meetings/congresses worldwide I have very often to answer questions like this "I am a cardiac surgeon, how can I understand echocardiographic angles, excursions... ? These are of main interest to cardiologists"

My answer is: *"I am a cardiac surgeon too but I believe that it is much easier to ask for a couple of echocardiographic indexes rather than to re-plasty or replace an already repaired mitral valve"*

REFERENCES

1. Barzilai B, Gessler C Jr, Perez JE, et al. Significance of Doppler-detected mitral regurgitation in acute myocardial infarction. *Am J Cardiol.* 1988;61:220–223.
2. Lehmann KG, Francis CK, Dodge HT. Mitral regurgitation in early myocardial infarction: incidence, clinical detection, and prognostic implications: TIMI Study Group. *Ann Intern Med.* 1992;117:10–17.
3. Tcheng JE, Jackman JD Jr, Nelson CL, et al. Outcome of patients sustaining acute ischemic mitral regurgitation during myocardial infarction. *Ann Intern Med.* 1992;117:18–24.
4. Hickey MS, Smith LR, Muhlbaier LH, et al. Current prognosis of ischemic mitral regurgitation: implications for future management. *Circulation.* 1988;78:1-51–1-59.
5. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction: Survival And Ventricular Enlargement (SAVE) Investigators. *Circulation.* 1997;96:827–833.
6. Carpentier A. Cardiac valve surgery-The “French correction.” *J Thorac Cardiovasc Surg.* 1983;86:323-37.
7. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001;103(13):1759–64.
8. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation.* 2000;102:1400–1406.
9. Otsuji Y, Handschumacher MD, Liel-Cohen N, Tanabe H, Jiang L, chwammenthal E, et al. Mechanism of ischemic mitral regurgitation with segmental left ventricular dysfunction: three-dimensional echocardiographic studies in models of acute and chronic progressive regurgitation. *J Am Coll Cardiol.* 2001;37:641-8.
10. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg.* 1998;115:381–386; discussion 387–388.
11. Bax JJ, Braun J, Somer ST, Klautz R, Holman ER, Versteegh MI, Boersma E, Schalij MJ, van der Wall EE, Dion RA. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation.* 2004;110(Suppl II):II103–II108.
12. Calafiore AM, Gallina S, Di Mauro M, Gaeta F, Iaco AL, D'Alessandro S, Mazzei V, Di Giammarco G. Mitral valve procedure in dilated cardiomyopathy: repair or replacement? *Ann Thorac Surg.* 2001;71:1146–1152.
13. Tahra SA, Oury JH, Maxwell JM, Hiro SP, Duran CM. Outcome after mitral valve repair for functional ischemic mitral regurgitation. *J Heart Valve Dis.* 2002;11:11–18.
14. McGee Jr EC, Gillinov AM, Blackstone EH, Rajeswaran J, Cohen G, Najam F, Shiota T, Sabik JF, Lytle BW, McCarthy PM, Cosgrove DM. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg.* 2004;128:916–924.

15. Hung J, Papakostas L, Tahta SA, Hardy BG, Bollen BA, Duran CM, Levine RA. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: continued LV remodeling as a moving target. *Circulation*. 2004;110(Suppl II):II85–II90.
16. Dahlberg PS, Orszulak TA, Mullany CJ, Daly RC, Enriquez-Sarano M, Schaff HV. Late outcome of mitral valve surgery for patients with coronary artery disease. *Ann Thorac Surg*. 2003;76:1539–1548.
17. Godley RW, Wann LS, Rogers EW, Feigenbaum H, Weyman AE. Incomplete mitral leaflet closure in patients with papillary muscle dysfunction. *Circulation*. 1981;63:565–571.
18. Otsuji Y, Handschumacher MD, Schwammenthal E, Jiang L, Song JK, Guerrero JL, Vlahakes GJ, Levine RA. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. *Circulation*. 1997;96:1999–2008.
19. Gorman RC, McCaughan JS, Ratcliffe MB, Gupta KB, Streicher JT, Ferrari VA, St John-Sutton MG, Bogen DK, Edmunds LH Jr. Pathogenesis of acute ischemic mitral regurgitation in three dimensions. *J Thorac Cardiovasc Surg*. 1995;109:684–693.
20. Komeda M, Glasson JR, Bolger AF, Daughters GT 2nd, MacIsaac A, Oesterle SN, Ingels NB Jr., Miller DC. Geometric determinants of ischemic mitral regurgitation. *Circulation*. 1997;96(Suppl II): II128–II133.
21. Agricola E, Oppizzi M, Maisano F, De Bonis M, Schinkel AFL, Torracca L, Margonato A, Melissurgo G, Alfieri O. Echocardiographic classification of chronic ischemic mitral regurgitation caused by restricted motion according to tethering pattern. *Eur J Echocardiogr*. 2004;5:326–334.
22. Watanabe N, Ogasawara Y, Yamaura Y, Kawamoto T, Toyota E, Akasaka T, Yoshida K. Quantitation of mitral valve tenting in ischemic mitral regurgitation by transthoracic real-time three-dimensional echocardiography. *J Am Coll Cardiol*. 2005;45:763–769.
23. Green GR, Dagum P, Glasson JR, Nistal JF, Daughters GT 2nd, Ingels NB Jr., Miller DC. Restricted posterior leaflet motion after mitral ring annuloplasty. *Ann Thorac Surg*. 1999;68:2100–2106.
24. Gillinov AM, Wierup PN, Blackstone EH, Bishay ES, Cosgrove DM, White J, et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg*. 2001;122:1125–41.
25. Grossi EA, Goldberg JD, LaPietra A, Ye X, Zakow P, Sussman M, et al. Ischemic mitral valve reconstruction and replacement: comparison of long-term survival and complications. *J Thorac Cardiovasc Surg*. 122:1107–24.
26. Miller CD. Ischemic Mitral regurgitation. Redux-to repair or to replace. *J Thorac Cardiovasc Surg*. 122:1059–62.
27. Serri K, Bouchard D, Dernas P, Coutu M, Pellerin M, Carrier M, et al. Is good perioperative echocardiographic result predictive of durability in ischemic mitral valve repair. *J Thorac Cardiovasc Surg*. 2006;131:565–73.

28. Heub AC, Jatene FB, Moreira LF, Pomerantzeff PM, Kallas E, deOliveira SA. Ventricular remodeling and mitral valve modifications in dilated cardiomyopathy: new insights from anatomic study. *J Thorac Cardiovasc Surg.* 2002;124:1216-24.
29. Ahmad RM, Gillinov AM, McCarthy PM, Blackstone EH, Apperson-Hansen C, Qin JX, et al. Annular geometry and motion in human ischemic mitral regurgitation: novel assessment with three-dimensional echocardiography and computer reconstruction. *Ann Thorac Surg.* 2004;78:2063-8.
30. Votta E, Maisano F, Bolling SF, Alfieri O, Montevocchi FM, Redaelli A. The Geoform disease-specific annuloplasty system: a finite element study. *Ann Thorac Surg.* 2007;84(1):92-101.
31. Kuwahara E, Otsuji Y, Iguro Y et al. Mechanism of recurrent/ persistent ischemic/functional mitral regurgitation in the chronic phase after surgical annuloplasty: importance of augmented posterior leaflet tethering. *Circulation* 2006;114(Suppl.):I529-I534.
32. Magne J, Pibarot P, Dagenais F, Hachicha Z, Dumesnil JG, Senechal M. Preoperative posterior leaflet angle accurately predicts outcome after restrictive mitral valve annuloplasty for ischemic mitral regurgitation. *Circulation.* 2007;115(6):782-91.
33. Adams DH, Anyanwu A. Pitfalls and limitations in measuring and interpreting the outcomes of mitral valve repair. *J Thorac Cardiovasc Surg.* 2006; 131(3):523-9.
34. Agricola E, Oppizzi M, Maisano F et al. Echocardiographic classification of chronic mitral regurgitation caused by restricted motion according to tethering pattern. *Eur J Echocardiography* 2004;5:326-34.
35. Zhu F, Otsuji Y, Yotsumoto G, et al. Mechanism of persistent ischemic mitral regurgitation after annuloplasty: importance of augmented posterior mitral leaflet tethering. *Circulation.* 2005;112(Suppl):I396-401.
36. Green GR, Dagum P, Glasson JR, et al. Restricted posterior leaflet motion after mitral ring annuloplasty. *Ann Thorac Surg* 1999;68(6):2100-6.
37. Calafiore AM, Di Mauro M, Gallina S, et al. Mitral valve surgery for chronic ischemic mitral regurgitation. *Ann Thorac Surg.* 2004;77(6):1989-97.

9

Summary

Riassunto

Samenvatting

Curriculum Vitae

Summary

The aims of this thesis were: 1) to report long-term results of combined reductive annuloplasty and coronary artery bypass grafting in patients with chronic ischemic mitral regurgitation, in terms of recurrence of mitral regurgitation, left ventricular reverse remodelling, continued left ventricular remodelling, left ventricular dimensions and geometry 2) to study modifications of LV and valvular conformation and geometry in chronic ischemic mitral regurgitation before and after annuloplasty 3) to identify mechanisms (either ventricular or valvular) of recurrent mitral regurgitation 4) to recognize preoperative factors who can help to select patients who can really benefit from annuloplasty.

In Chapter 2 we present 5-year echocardiographic results of combined undersizing mitral ring annuloplasty and coronary artery bypass grafting in ischemic mitral regurgitation. Two-hundred-fifty-one patients were prospectively enrolled in the study. Serial echocardiograms were performed in 220 survivors at baseline, discharge and annually thereafter. MR remained stable at 1 year and re-increased at 3 years and 5 years. Five-year actuarial survival was $83.2 \pm 4.4\%$. Five-year freedom from reoperation for failed repair was $78.2 \pm 4.9\%$. Mean systolic and diastolic diameters decreased significantly at discharge and at early follow up but raised at 3 years and 5 years. Systolic and diastolic sphericity indexes improved at discharge, remained stable at 1-year but they re-increased at 3-year control with a late raise exceeding the preoperative value. Left ventricular reverse remodeling was observed in 44.2% of the study population with 10.3% of patients showing further left ventricular dilatation. At multivariable model, end-systolic volume ≥ 145 ml, systolic sphericity Index ≥ 0.7 , Myocardial performance Index ≥ 0.9 and wall motion score Index ≥ 1.5 were predictors of recurrent MR. Our findings emphasize the need for improved repair technique and better patient selection to identify patients with anticipated repair failure who could benefit more from valve replacement or other procedure directly addressing ventricular tethering.

In Chapter 3 We analyzed left ventricular reverse remodeling after combined coronary artery bypass grafting and undersized mitral ring annuloplasty examining the difference in the benefit of annuloplasty on clinical end points and recurrence of mitral regurgitation between responders and non-responders of left ventricular reverse remodeling. Study eligibility criteria were fulfilled by 204 patients with chronic ischemic mitral regurgitation who survived combined coronary artery bypass and reductive annuloplasty. Reverse remodeling was defined as a reduction in left ventricular end systolic volume Index $>15\%$. There were 84 (41.2%) responders of reverse remodeling and 120 (58.8%) non-responders. Non-responders had a higher recurrence of mitral regurgitation, higher reoperation rate for failed repair significantly larger left ventricular volumes and dimension at any study point with significant late increase of sphericity indexes exceeding preoperative values. At multivariable analysis baseline myocardial performance Index <0.90 , systolic sphericity Index <0.72 and wall motion score Index <1.59 resulted as independent predictors of

reverse remodeling. Our experience suggests that more information on possible echo predictors of an inadequate result may improve preoperative decision-making.

Chapter 4 investigates leaflet and subvalvular configurations of the mitral valve to identify mechanisms leading to recurrent mitral regurgitation after combined undersized mitral annuloplasty and coronary artery bypass. The study population consisted of 230 patients who were divided in two Groups: patients without (Group 1, n=176) or with (Group 2, n=54) late recurrent mitral regurgitation. Fifty normal healthy subjects were controls. Subjects with late regurgitation had preoperatively a more symmetric tethering, a more accentuated anterior mitral leaflet tethering and a more restricted anterior leaflet excursion than Group 1. Postoperatively, tethering of posterior leaflet increased and it was predominant in both groups whereas the tethering of the anterior leaflet reduced at discharge remaining constant afterwards. Multivariable analysis showed an anterior tethering angle $\geq 39.5^\circ$, an anterior/posterior tethering angle ratio ≥ 0.76 , an anterior leaflet excursion angle $\leq 35^\circ$ and a coaptation height ≥ 11 mm to be predictors of recurrent mitral regurgitation. Our results demonstrate that preoperative symmetric tethering with anterior mitral leaflet predominance is strongly associated with recurrence of mitral insufficiency. Measures of leaflet tethering results in fundamental findings to identify ischemic patients who can really benefit from restrictive annuloplasty.

In Chapter 5 we test the hypothesis that a specific leaflet configuration with anterior mitral leaflet tethering predominance is related to higher postoperative MR recurrence independently of left ventricular size and geometry. In 278 patients with surgical annuloplasty for chronic ischemic mitral regurgitation and 50 matched normal subjects, posterior and lateral displacement of papillary muscles the anterior leaflet and posterior leaflet tethering angles and their ratio, the coaptation length and the MR grade were quantified before and at follow up. Patients were divided in 5 Groups on the basis of the preoperative anterior mitral leaflet tethering angle: Group 1 (normal/slight tethering, n=33), Group 2, (mild tethering, n=55), Group 3 (moderate tethering, n=63), Group 4 (moderate-severe tethering, n=64) and Group 5 (severe tethering, n=63). Subjects with anterior mitral leaflet tethering $\geq$ moderate-severe had preoperatively a more symmetric tethering, a more accentuated anterior papillary muscle displacement and a larger anterior local remodeling. Recurrence of MR was significantly higher in patients with moderate-severe/severe anterior mitral leaflet tethering. Postoperatively, tethering of posterior leaflet increased and it was predominant without difference between groups, resulting in a more asymmetric tethering in the major part of patients with recurrent regurgitation. At multivariable logistic regression the anterior leaflet tethering angle was the primary determinant of regurgitation recurrence, even after adjustment of known risk factors. Our results confirm that the grade of preoperative anterior mitral leaflet tethering is strongly associated with recurrence of ischemic regurgitation.

The predictive value of diastolic function on clinical outcome and recurrence of ischemic mitral regurgitation following combined undersized mitral annuloplasty and coronary artery bypass grafting is reported in *Chapter 6*. Two hundred-thirty-four patients with chronic ischemic mitral regurgitation who survived combined restrictive annuloplasty and coronary bypass, were divided into four groups on the basis of baseline Deceleration Time and systolic-diastolic pulmonary venous flow ratio: Group 1, normal ($n = 48$), Group 2, impaired relaxation ($n=61$), Group 3, pseudonormal pattern ($n=60$) and Group 4, restrictive pattern ($n=65$). Early mortality rate was highest in the restrictive group (9.2%). In addition 6-year actuarial survival was significantly lower in Group 4. Furthermore, a deceleration time $<140\text{ms}$ and a systolic/diastolic pulmonary venous flow <0.80 were independent predictors of early and late death. Finally, a deceleration time $<140\text{ms}$ was the only diastolic independent predictor of recurrence of ischemic regurgitation. Restrictive left ventricular diastolic filling pattern is an important preoperative marker of high early and late death and recurrence of regurgitation in patients undergoing reductive annuloplasty for ischemic mitral regurgitation. In our experience left ventricular diastolic filling pattern is an important preoperative marker of high early and late death and recurrence of regurgitation.

In *Chapter 7* we explored the predictive value of Doppler-Derived Mitral Deceleration Time on left ventricular reverse remodeling in patients with chronic ischemic mitral regurgitation undergoing combined undersized mitral annuloplasty and coronary artery bypass grafting. Two hundred and fifteen patients undergoing combined undersized annuloplasty and coronary artery bypass were divided into four groups on the basis of baseline deceleration time: Group 1 (normal, $n = 48$), Group 2 (impaired relaxation, $n = 61$), Group 3 (pseudonormal pattern, $n = 50$) and Group 4 (restrictive pattern, $n = 56$). Left ventricular reverse remodeling, defined as a reduction in end systolic volume Index $> 15\%$, occurred in 95.7%, 96.3%, 88.3% and 0% in Groups 1, 2, 3 and 4, respectively. Logistic regression analysis showed that a deceleration time $\leq 125\text{ms}$ was a strong predictor of reverse remodeling after annuloplasty. Preoperative assessment of this parameter adds significant information to commonly used indexes of global and regional function, and represents a very easy and cost effective tool to accurately identify those patients who can really benefit from annuloplasty.

We can conclude that undersized mitral annuloplasty can safely be employed in a restricted number of patients with chronic ischemic mitral regurgitation. These patients can be preoperatively recognized on the basis of echocardiographic characteristics.

Patients with symmetric tethering with anterior leaflet tethering predominance and/or enlarged and more spherical left ventricles and/or advanced diastolic dysfunction, do not benefit from undersized annuloplasty.

Riassunto

Gli scopi della presente tesi sono: 1) Riportare i risultati a distanza (5 anni) della anuloplastica restrittiva associata a bypass aorto-coronarico in pazienti con insufficienza mitralica post-ischemica, in termini di insufficienza mitralica ricorrente, remodelling e remodelling-inverso del ventricolo sinistro, dimensioni e geometria ventricolari 2) Studiare le modificazioni a livello ventricolare, valvolare e sottovalvolare nell'ischemico cronico prima e dopo l'intervento di plastica mitralica 3) Identificare i meccanismi che determinano la ricomparsa di insufficienza mitralica 4) Identificare i fattori preoperatori che possono essere d'aiuto per selezionare quei pazienti che possono realmente beneficiare di un anuloplastica sottodimensionata.

Nel Capitolo 1 abbiamo presentato i risultati ecocardiografici a 5 anni della anuloplastica restrittiva associata a bypass aortocoronarico. Duecentocinquantuno pazienti sono stati arruolati per lo studio ed un controllo ecocardiografico è stato effettuato nei 220 sopravvissuti all'intervento chirurgico. Globalmente, l'insufficienza è rimasta invariata a 1 anno mentre è aumentata significativamente ai controlli a 3 e 5 anni. La sopravvivenza attuariale a 5 anni è stata di $83.2 \pm 4.4\%$ mentre la libertà da reintervento è stata $78.2 \pm 4.9\%$. I diametri ventricolari hanno mostrato una significativa riduzione al controllo alla dimissione ed ai controlli precoci, con significativi aumenti a 3 e 5 anni. Gli indici di sfericità (sistolico e diastolico) si sono ridotti alla dimissione, rimanendo stabili ad 1 anno e ri-aumentando significativamente a 3 e 5 anni. L'incidenza di rimodellamento inverso è stata di 44.2% con il 10% dei pazienti che hanno mostrato un ulteriore incremento del volume telesistolico. All'analisi multivariata, un volume telesistolico ≥ 145 ml, un indice di sfericità sistolico ≥ 0.7 , un indice di performance miocardica ≥ 0.9 ed un wall motion score Index ≥ 1.5 sono risultati predittori di insufficienza mitralica postoperatoria. I nostri risultati enfatizzano la necessità di un'accurata selezione preoperatoria dei pazienti, che ci aiuterà a riconoscere quelli che non beneficiano di una plastica valvolare e per i quali è necessario un intervento alternativo che corregga direttamente il tethering a livello ventricolare o una sostituzione valvolare mitralica.

Nel capitolo 3 abbiamo analizzato il rimodellamento inverso dopo anuloplastica riduttiva e bypass aortocoronarico esaminando in particolare la differenza di risultato, in termini di outcome clinico e ricomparsa di insufficienza mitralica, tra responders e non-responders al rimodellamento ventricolare sinistro inverso. Duecentoquattro pazienti sopravvissuti all'intervento di anuloplastica riduttiva, sono stati oggetto dello studio. È stato considerato rimodellamento inverso una riduzione del volume telesistolico ventricolare sinistro indicizzato $>15\%$. Ottantaquattro pazienti (41.2%) hanno mostrato rimodellamento inverso mentre in 120 (58.8%) non si è riscontrato una riduzione del volume telesistolico $>15\%$. I non-responders hanno mostrato una maggiore ricorrenza di insufficienza mitralica postoperatoria, una più alta frequenza di reintervento per fallimento della procedura, un volume ventricolare e dimensioni ventricolari significativamente maggiori a tutti i controlli con un indice di sfericità che hanno raggiunto al follow up valori più alti di quello basale. L'analisi multivariata

ha identificato come predittori indipendenti di rimodellamento inverso i seguenti fattori: un valore di indice di performance miocardica <0.90 , un indice di sfericità sistolica <0.72 ed un wall motion score Index <1.59 . La nostra esperienza suggerisce che un maggior numero di informazioni su i possibili predittori ecocardiografici di rimodellamento inverso possono decisamente migliorare la selezione dei pazienti in fase preoperatoria, indirizzando all'intervento quelli che realmente beneficiano di una anuloplastica riduttiva

Nel Capitolo 4 abbiamo studiato la configurazione a livello valvolare e sottovalvolare per identificare i meccanismi che determinano la ricomparsa di insufficienza mitralica ischemica dopo anuloplastica riduttiva. La popolazione dello studio è consistita in 230 pazienti divisi in due gruppi: pazienti senza insufficienza mitralica postoperatoria (Gruppo 1, $n=176$) e pazienti con insufficienza mitralica dopo l'intervento (Gruppo 2, $n=54$). Cinquanta soggetti sani hanno rappresentato il Gruppo di controllo. I pazienti con insufficienza mitralica postoperatoria avevano nel preoperatorio un tethering più simmetrico, un tethering del lembo anteriore più accentuato, una escursione del lembo anteriore maggiormente ridotta. Nel postoperatorio, il tethering del lembo posteriore è aumentato significativamente mentre quello del lembo anteriore si è ridotto alla dimissione, rimanendo costante successivamente. La regressione logistica ha identificato un angolo di tethering del lembo anteriore $\geq 39.5^\circ$, un rapporto angolo di tethering anteriore / angolo di tethering posteriore ≥ 0.76 , un angolo di escursione del lembo anteriore $\leq 35^\circ$ ed un'altezza di coaptazione ≥ 11 mm come predittori indipendenti di insufficienza mitralica postoperatoria. I nostri risultati suggeriscono che la presenza di tethering simmetrico prevalentemente anteriore è una controindicazione alla anuloplastica riduttiva.

Nel Capitolo 5 abbiamo testato l'ipotesi che una specifica configurazione di tethering nel preoperatorio, caratterizzata da tethering simmetrico prevalentemente anteriore, è legato alla ricomparsa di insufficienza mitralica postoperatoria, indipendentemente dal volume e dalla geometria del ventricolo sinistro. Abbiamo misurato il dislocamento posteriore e laterale dei muscoli papillari, gli angoli di tethering dei lembi mitralici a gli indici di coaptazione in 278 pazienti sottoposti ad anuloplastica riduttiva per insufficienza mitralica cronica post-ischemica, ed in 50 soggetti normali. I pazienti sono stati divisi in 5 Gruppi in base all'entità del tethering del lembo anteriore: assente/lieve (Gruppo 1, $n=33$), medio (Gruppo 2, $n=55$), moderato (Gruppo 3, $n=63$), moderato-severo (Gruppo 4, $n=64$) e severo (Gruppo 5, $n=63$). I pazienti con tethering anteriore $\geq$ moderato-severo mostravano, all'eco preoperatorio, una maggiore dislocazione del papillare anteriore and un maggiore rimodellamento nella zona anteriore. Una insufficienza mitralica residua è stata riscontrata in percentuale significativamente maggiore in pazienti con tethering anteriore moderato-severo o severo. Dopo l'intervento, il tethering del lembo posteriore è aumentato in tutti i Gruppi ed i pazienti con insufficienza mitralica postoperatoria mostravano un tethering prevalentemente asimmetrico. La regressione logistica ha

individuato nel angolo di tethering del lembo anteriore il fattore determinante per la ricomparsa di insufficienza nel postoperatoria. Questo risultato veniva confermato anche dopo avere corretto la regressione per quei fattori determinanti la ricomparsa di insufficienza mitralica. I nostri risultati confermano che il tethering anteriore è determinante per la ricomparsa di insufficienza mitralica, indipendentemente dalla geometria e dalle dimensioni del ventricolo.

Nel Capitolo 6 abbiamo studiato l'influenza della funzione diastolica sui risultati postoperatori e sulla ricomparsa di insufficienza mitralica dopo anuloplastica riduttiva. Per questo 234 pazienti con insufficienza mitralica cronica post-ischemica sono stati divisi in 4 Gruppi sulla base del tempo di decelerazione e del rapporto tra flusso venoso polmonare sistolico e diastolico: Gruppo 1 (funzione normale, n = 48), Gruppo 2 (alterato rilasciamento, n=61), Gruppo 3 (pattern pseudonormale, n=60) e Gruppo 4 (pattern restrittivo, n=65). La mortalità precoce è stata maggiore nel Gruppo con pattern restrittivo (9.2%). Inoltre, la sopravvivenza a 6 anni è stata significativamente più bassa nel Gruppo 4. Un tempo di decelerazione <140ms ed un rapporto sisto-diastolico del flusso venoso polmonare <0.80 si sono rivelati fattori predittivi di morte precoce ed a distanza mentre il solo tempo di decelerazione <140ms predice la ricomparsa di insufficienza mitralica nel postoperatorio. La disfunzione diastolica, ed in particolare la presenza di un pattern restrittivo, rappresenta un indice predittivo di mortalità e di ricorrenza di insufficienza mitralica. Lo studio della funzione diastolica dovrebbe, perciò, essere effettuato regolarmente durante lo screening preoperatorio del paziente.

Nel Capitolo 7 abbiamo studiato il valore predittivo del tempo di decelerazione sul rimodellamento inverso nei pazienti con insufficienza mitralica cronica post-ischemica sottoposti ad anuloplastica riduttiva e bypass aorto-coronarico. Sono stati studiati 215 pazienti, divisi in 4 Gruppi in base al valore del tempo di decelerazione: Gruppo 1 (funzione normale, n = 48), Gruppo 2 (alterato rilasciamento, n = 61), Gruppo 3 (pattern pseudonormale, n = 50) e Gruppo 4 (pattern restrittivo, n = 56). L'incidenza di rimodellamento inverso (definito come una riduzione del volume telesistolico ventricolare sinistro $ESV > 15\%$) nei Gruppi 1- 4 è stato 95.7%, 96.3%, 88.3% e 0%, rispettivamente. L'analisi multivariata ha confermato che un valore di tempo di decelerazione ≤ 125 rappresenta un fattore predittivo di rimodellamento dopo anuloplastica. Questi risultati confermano che la funzione diastolica, ed in particolare il tempo di decelerazione, sono informazioni indispensabili per una corretta valutazione preoperatoria del paziente ed una corretta indicazione chirurgica.

Possiamo concludere che l'anuloplastica riduttiva può essere utilizzata con successo in un piccolo numero di pazienti con insufficienza mitralica cronica post-ischemica. Un accurata valutazione preoperatoria è indispensabile ed aiuta ad identificare questi pazienti.

I pazienti con tethering simmetrico prevalentemente anteriore e/o con ventricolo sinistro aumentato di volume e sferico e/o con disfunzione diastolica non beneficiano di questa procedura. Per questi pazienti deve essere valutato un intervento alternativo che corregga il tethering a livello ventricolare oppure una sostituzione valvolare mitralica.

Samenvatting

Ischemische mitraal klep regurgitatie (MR) is een relatief veel voorkomend verschijnsel bij coronair ziekten, en treedt op na een acuut myocard infarct (MI), of als een chronisch aandoening, en minder vaak bij plaatselijke intermitterende ischemie. Chronische ischemische mitraal klep regurgitatie (CIMR) is een functionele regurgitatie, in tegenstelling tot anatomische MR, omdat de klepbladen er normaal uitzien. CIMR heeft wel een veel slechtere prognose na een doorgeemaakt myocard infarct en coronair revascularisatie (1-5), en is een veel voorkomende oorzaak van hartfalen. CMIR komt voor bij 10 tot 20% van alle patiënten met een coronair arterie aandoening (8-10).

De doelstellingen van dit proefschrift waren: 1) om de lange termijn resultaten te presenteren van een gecombineerde behandeling bestaande uit coronaire bypass chirurgie (CABG) en reductieve annuloplastie in patiënten met chronische ischemische mitraal klep regurgitatie. Als parameters zijn gekozen de terugkeer van mitraal klep regurgitatie, linker ventrikel reverse remodeling, en meer algemeen de linker ventrikel dimensies en geometrie. 2) om de veranderingen te beschrijven in de bouw en de vorm van de linker ventrikel en mitraal klep die optreden na annuloplastie, bij patiënten met CIMR. 3) om *die* mechanismen te herkennen die betrokken zijn bij het terugkomen van mitraal klep regurgitatie, zij het ventriculair of valvulair. 4) om preoperatief eigenschappen te herkennen zodat patiënten beter kunnen worden geselecteerd die potentieel voordeel hebben bij annuloplastie.

In *hoofdstuk 2* worden de resultaten gepresenteerd van het echo-onderzoek 5 jaar na een gecombineerde CABG en mitraal klep annuloplastie, in patiënten met CIMR. 251 Patiënten werden prospectief in de studie opgenomen. In 220 overlevende patiënten werd een echocardiogram gemaakt voor de operatie, bij ziekenhuis ontslag, en daarna jaarlijks.

MR bleef stabiel na het eerste jaar, maar nam weer toe na het derde en vijfde jaar. De overleving na 5-jaar was $83,2 \pm 4,4\%$. De 5-jaars vrijheid van reoperatie doordat de hersteloperatie onvoldoende resultaat opleverde was $78,2 \pm 4,9\%$. De gemiddelde LV systolische en diastolische diameter waren bij ontslag uit het ziekenhuis en na het eerste jaar significant afgenomen, maar namen weer toe na 3 en na 5 jaar. De systolische en diastolische index voor de LV bolvorm was verbeterd bij ontslag, bleef vervolgens het eerste jaar stabiel, maar nam weer toe bij de controle na 3 jaar, en later zelfs meer wat tot een grotere index leidde dan voor de ingreep. Linker ventrikel reverse remodeling werd waargenomen bij 44,2% van de studie groep, terwijl in 10,3% een verdere dilatatie werd gemeten. Uit multivariate logistische analyse bleken verschillende factoren de terugkeer van MR te kunnen voorspellen: Eind systolisch volume ≥ 145 ml, LV systolische bolindex $\geq 0,7$, Hart functie index $\geq 0,9$ en index voor de wall motion score $\geq 1,5$.

De uitkomsten van deze studie benadrukken de noodzaak van een betere chirurgische herstel techniek van de mitraal klep, en een betere patiënten selectie, om patiënten te kunnen herkennen met een voorspelbare klepherstel ingreep zonder

resultaat, die meer baat zouden kunnen hebben bij klepvervanging of een andere procedure waardoor de ventriculaire aanhechtingen worden verbeterd.

In *hoofdstuk 3* is linker ventrikel reverse remodeling bestudeerd na een gecombineerde ingreep die bestond uit CABG, en een onderbemeten mitraalklep annuloplasty. Hierbij is gekeken naar het verschil in verbetering door de annuloplastie op klinische eindpunten en op terugkeer van MR, tussen patiënten die wel of juist niet linker ventrikel reverse remodeling lieten zien. Voor deze studie kwamen 204 patiënten in aanmerking, die de gecombineerde ingreep overleefden van de CABG en de reductieve annuloplastie. Reverse remodeling was gedefinieerd als een vermindering in LV eind-systole volume index $> 15\%$. Er waren 84 (41,2%) responders van reverse remodeling, en 120 (58,8%) non-responders. Bij deze non-responders kwam terugkeer van MR meer voor, was er een grotere mate van reoperaties en significant grotere LV dimensies en volumina op ieder tijdstip, met significante late toename van de bolvorm index, tot zelfs groter dan de waarde voor de chirurgie. Bij multivariate analyse bleken vooraf gemeten hart functie index $< 0,90$, systolische bolvorm index $< 0,72$, en wall motion score $< 1,59$ onafhankelijke voorspellers van reverse remodeling.

Onze ervaring suggereert dat echo data als mogelijke voorspellers van eindresultaat, de preoperatieve patiënten selectie en de keuze van het type ingreep zou kunnen verbeteren.

In *hoofdstuk 4* wordt een onderzoek beschreven naar de mitraal klep bladen en subvalvulaire structuren, om mechanismen te herkennen die leiden tot het terugkeren van MR, in de fase na een CABG en mitraal annuloplastie.

De onderzoeks groep bestond uit 230 patiënten die in twee groepen werden verdeeld: Groep 1 (n=176) zonder late MR, en Groep 2 (n=54) met late terugkerende MR. Een groep van 50 gezonde vrijwilligers werd genomen als controle.

Patiënten in Groep 2 bleken preoperatief een meer symmetrische tethering te hebben, een meer benadrukte anterior mitraal klep tethering, en een meer beperkte anterior klep blad excursie, in vergelijking met Groep 1. Postoperatief nam de tethering van het posterior klepblad toe, zowel in groep 1 als in groep 2, terwijl de tethering van het anterior klepblad verminderd was bij ontslag, en daarna onveranderd bleef. Multivariate analyse liet zien welke variabelen voorspellers waren van het terugkomen van MR: anterior tethering hoek $> 39,5^\circ$, een anterior/posterior tethering hoek verhouding $> 0,76$, een anterior klepblad excursie hoek $< 35^\circ$, en een coaptatie hoogte $> 11\text{mm}$.

Onze resultaten laten zien dat preoperatieve symmetrische tethering met overheersend anterior mitraal klepblad sterk is geassocieerd met het terugkeren van MR.

In *hoofdstuk 5* wordt de hypothese getoetst die stelt dat een specifieke vorm van het klepblad met een versterkte anterior klepblad tethering, is gerelateerd aan een hogere mate van postoperatieve terugkeer van MR, onafhankelijk van de linker

ventrikel grootte en vorm. In 278 patiënten met chirurgische annuloplastie voor de behandeling van CIMR, en in 50 geselecteerde normale personen, werden voor de ingreep en tijdens de follow up verschillende variabelen bestudeerd; posterior en laterale verplaatsing van de papilaire spieren, de tethering hoek en hun ratio van de anterior en de posterior klep bladen. De patiënten werden verdeeld in 5 groepen op basis van de hoek van tethering van het anterior mitraal klepblad voor de operatie. Groep 1 (normale/geringe tethering, n=33), groep 2 (matige tethering, n=55), groep 3 (middelmatige tethering, n=63), groep 4 (middelmatige tot ernstige tethering, n=64) en groep 5 (ernstige tethering, n=63). Het bleek dat patiënten met een tethering van het anterior mitraal klepblad van meer dan middelmatig, preoperatief een meer symmetrische tethering hadden, een meer versterkte anterior papilaire spierverplaatsing en een grotere remodeling van de linker ventrikel voorwand. Terugkeer van MR was significant vaker in patiënten met middelmatige tot ernstige anterior mitraal klepblad tethering.

Postoperatief nam de tethering van het posterior klepblad toe, maar de mate waarin verschilden niet tussen de groepen. Het resulteerde in een meer symmetrische tethering bij de meeste patiënten met terugkerende MR. Multivariate logistische regressie toonde aan dat de tethering hoek van het anterior klepblad de primaire voorspeller was van terugkerende MR, zelfs na aanpassen van bekende risicofactoren. Onze resultaten bevestigen dat de mate van preoperatief anterior mitraal klepblad tethering sterk is geassocieerd met de terugkeer van ischemische MR.

In *hoofdstuk 6* wordt de voorspellende waarde beschreven van diastolische hartfunctie op de klinische outcome en op het terugkeren van ischemische MR, bij 234 patiënten die behandeld zijn met een onderbemeten mitraal annuloplastie en een CABG. De patiënten werden verdeeld in 4 groepen op basis van deceleration time en de systolische/diastolische longvene flowratio: Groep 1, normaal (n=48), Groep 2, verminderde relaxatie (n=61), Groep 3, pseudonormaal patroon (n=60), en Groep 4, restrictief patroon (n=65). De sterfte direct na de ingreep was het hoogst in groep 4 (9.2%), de groep met een restrictief patroon. Daarnaast bleek ook de 6 jaars overleving lager in groep 4. Ook bleek dat een deceleratie tijd van < 140 ms, en een systolisch/diastolisch longvene flow ratio van < 0.80 , onafhankelijke voorspellers waren van het terugkeren van ischemische MR. Een restrictief diastolisch vullings patroon van de linker ventrikel is een belangrijke preoperatieve marker voor een hoge vroege en late mortaliteit.

In *hoofdstuk 7* wordt de voorspellende waarde besproken die de deceleratietijd van de mitraal klep heeft op de reverse remodeling van de linker ventrikel, in patiënten met CIMR, na een chirurgische behandeling. Deze behandeling bestond uit CABG gecombineerd met undersized mitraal annuloplastie, en werd uitgevoerd in 215 patiënten. Deze patiënten werden in 4 groepen ingedeeld, analoog als in hoofdstuk 6. De linker ventrikel reverse remodeling werd gedefinieerd als een vermindering van de LV eind systolisch volume index $>15\%$, en bleek sterk

te verschillen tussen de groepen (Groep 1 : 95,7% , Groep 2 : 96,3%, Groep 3 : 88,3% , Groep 4 : 0%). Logistische regressie analyse liet zien dat een decelleratie tijd van ≤ 125 ms een sterke voorspeller was voor reverse remodeling na annuloplastie. Preoperatieve bepaling van deze parameter voegt belangrijke informatie toe aan de gebruikelijke indexes van globale en regionale functie, en vormen een eenvoudige en kosteneffectieve manier om nauwkeurig die patiënten te herkennen die werkelijk baat kunnen hebben bij een annuloplastie.

Als conclusie kan worden gesteld, dat undersized mitraal annuloplastie veilig kan worden uitgevoerd in een beperkt aantal patiënten met CIMR. Deze patiënten kunnen preoperatief worden herkend op basis van echocardiografisch verkregen gegevens. Bij patiënten die geen baat zullen hebben van een undersized annuloplastie, wordt het meest frequent symmetrische tethering gezien, met voornamelijk anterior klepblad tethering en/of een vergroot en meer bolvormige linker ventrikel, en/of vergevorderde diastolische disfunctie.

Publications

1. Lorusso R, Corradi D, Maestri R, Bosio S, Curulli A, Beghi C, Gerometta P, Russo C, Gelsomino S, Moreo A, De Cicco G, Rosano G, Volterrani M. Atorvastatin attenuates post-implant tissue degeneration of cardiac prosthetic valve bovine pericardial tissue in a subcutaneous animal model. *Int J Cardiol*. 2009 Jan 21. [Epub ahead of print]
2. Gelsomino S, Lorusso R, De Cicco G, Billè G, Caciolli S, Rostagno C, Capecci I, Chioccioli M, Stefano P, Gensini GF. Does preoperative tethering symmetry affect left ventricular reverse remodeling after restrictive annuloplasty? *Int J Cardiol*. 2009 Jan 19. [Epub ahead of print]
3. Bevilacqua S, Romagnoli S, Ciappi F, Lazzeri C, Gelsomino S, Pulli R, Pratesi C, Gensini GF. Patient Cooperation During General Anesthesia for Combined Carotid and Coronary Artery Surgery. *J Cardiothorac Vasc Anesth*. 2008 Oct 2. [Epub ahead of print]
4. Bevilacqua S, Lazzeri C, Romagnoli S, Gelsomino S, Lorusso R, De Cicco G, Gensini GF. Unexpected Severe Tricuspid Regurgitation After Successful Mitral Valve Repair. *J Cardiothorac Vasc Anesth*. 2008 Apr 15. [Epub ahead of print]
5. Bonacchi M, Nistri S, Nanni C, Gelsomino S, Pini A, Cinci L, Maiani M, Zecchi Orlandini S, Lorusso R, Fanti L, Silvertown J, Bani D. Functional and histopathological improvement of the post-infarcted rat heart upon myoblast cell grafting and relaxin therapy. *Journal of Cellular and Molecular Medicine* 288 (Epub Ahead of Print).
6. Caciolli S, Gelsomino S, Fradella G, Bevilacqua S, Favilli S, Gensini GF. Severe Hypoplasia of the Posterior Mitral Leaflet. *Ann Thorac Surg* 2008; 86 (6): 1978-9.
7. Lorusso R, De Cicco G, Tironi A, Gelsomino S, De Geest R. Giant Primary Paraganglioma of The Left Ventricle. *J Thorac Cardiovasc Surg*. 2009; 137 (2): 499-500.
8. Lorusso R, Gelsomino S. El Corazon Espinado. *The Lancet* "in press".
9. Lorusso R, De Cicco G, Etti F, Curello S, Gelsomino S, Fucci C. Emergency surgery after saphenous vein graft perforation complicated by catheter balloon entrapment and hemorrhagic shock. *Ann Thorac Surg* 2008; 86 (3): 2002-4.

10. Lorusso R, De Cicco G, Gelsomino S. Reply to Foroughi et al. *Eur J Cardiothorac Surg*. 2008 Aug 11. [Epub ahead of print].
11. Gelsomino S, Lorusso R, Caciolli S, Capecchi I, Rostagno C, Chioccioli M, De Cicco G, Billè G, Stefàno P, Gensini GF. Insights on left ventricular and valvular mechanisms of recurrent ischemic mitral regurgitation after restrictive annuloplasty and coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2008;136(2):507-18.
12. Lorusso R, De Cicco G, Totaro P, Gelsomino S. Effects of phosphorylcholine coating on extracorporeal circulation management and postoperative outcome: a double-blind randomized study. *Interact Cardiovasc Thorac Surg*. 2009; 8(1):7-11.
13. Gelsomino S, Lorusso R, Rostagno C, Caciolli S, Billè G, De Cicco G, Romagnoli S, Porciani C, Stefàno P, Gensini GF. Prognostic value of Doppler-derived mitral deceleration time on left ventricular reverse remodelling after undersized mitral annuloplasty. *Eur J Echocardiogr*. 2008 Mar 11.
14. Gelsomino S, Lorusso R, Billè G, Rostagno C, De Cicco G, Romagnoli S, Porciani C, Tetta C, Stefàno P, Gensini GF. Left ventricular diastolic function after restrictive mitral ring annuloplasty in chronic ischemic mitral regurgitation and its predictive value on outcome and recurrence of regurgitation. *Int J Cardiol*. 2008 Mar 26.
15. Gelsomino S, Lorusso R, Capecchi I, Rostagno C, Romagnoli S, Billè G, De Cicco G, Tetta C, Stefàno P, Gensini GF. Left ventricular reverse remodeling after undersized mitral ring annuloplasty in patients with ischemic regurgitation. *Ann Thorac Surg*. 2008 Apr;85(4):1319-30.
16. Lorusso R, Gelsomino S, De Cicco G, Beghi C, Russo C, De Bonis M, Colli A, Sala A. Mitral valve surgery in emergency for severe acute regurgitation: analysis of postoperative results from a multicentre study. *Eur J Cardiothorac Surg*. 2008 Apr;33(4):573-82.
17. Gelsomino S, Lorusso R, Billè G, De Cicco G, Da Broi U, Rostagno C, Stefàno P, Gensini GF. Cardiac surgery in type-1-myotonic muscular dystrophy (Steinert syndrome) associated to Barlow disease. *Interact Cardiovasc Thorac Surg*. 2008 Apr;7(2):222-6.

18. Gelsomino S, Lorusso R, Romagnoli S, Bevilacqua S, De Cicco G, Billè G, Stefano P, Gensini GF. Treatment of refractory bleeding after cardiac operations with low-dose recombinant activated factor VII (NovoSeven): a propensity score analysis. *Eur J Cardiothorac Surg*. 2008 Jan;33(1):64-71.
19. Gelsomino S, Lorusso R, De Cicco G, Capecechi I, Rostagno C, Caciolli S, Romagnoli S, Da Broi U, Stefano P, Gensini GF. Five-year echocardiographic results of combined undersized mitral ring annuloplasty and coronary artery bypass grafting for chronic ischaemic mitral regurgitation. *Eur Heart J*. 2008 Jan;29(2):231-40.
20. Lorusso R, De Cicco G, Gelsomino S, Fucci C. Dissection of the posterior mitral leaflet. *Eur J Cardiothorac Surg*. 2007 Dec;32(6):936.
21. Lorusso R, Gelsomino S, De Cicco G. Acute pulmonary embolism after removal of central venous catheter. *Int J Cardiol*. 2007 Sep 18.
22. Pavoni D, Badano LP, Ius F, Mazzaro E, Frassani R, Gelsomino S, Livi U. Limited long-term durability of the Cryolife O'Brien stentless porcine xenograft valve. *Circulation*. 2007 Sep 11;116(11 Suppl):I307-13.
23. Braconi L, Pretelli P, Calamai G, Montesi G, Romagnoli S, Gelsomino S, Bevilacqua S, Stefano P, Gensini GF. An unusual case of cardiac tamponade. *J Cardiovasc Med (Hagerstown)*. 2006 Mar;7(3):219-21.
24. Romagnoli S, Bevilacqua S, Gelsomino S, Pradella S, Ghilli L, Rostagno C, Gensini GF, Sorbara C. Small-dose recombinant activated factor VII (NovoSeven) in cardiac surgery. *Anesth Analg*. 2006 May;102(5):1320-6.
25. Bevilacqua S, Gelsomino S, Romagnoli S. Difficult intubation in pediatric cardiac surgery. *J Cardiothorac Vasc Anesth*. 2006 Apr;20(2):290-1.
26. Gelsomino S, Romagnoli S, Gori F, Nesi G, Anichini C, Sorbara C, Stefano P, Gensini GF. Annuloaortic ectasia and giant cell arteritis. *Ann Thorac Surg*. 2005 Jul;80(1):101-5.
27. Gelsomino S, Romagnoli S, Dragotto A, Cassai M, Fiorani B, Sorbara C, Stefano P. Multistep endobronchial-endovascular approach in recurrent acute respiratory failure caused by thoracic aneurysm. *J Thorac Cardiovasc Surg*. 2005 Jun;129(6):1436-8.

28. Gelsomino S, Romagnoli S, Stefano P. Right coronary perforation due to a toothpick ingested at a barbecue. *N Engl J Med*. 2005 May 26;352(21):2249-50.
29. Gelsomino S, Morocutti G, Masullo G, Da Col P, Frassani R, Spedicato L, Livi U. Patient-prosthesis mismatch after small-size stentless aortic valve replacement. *J Card Surg*. 2004 Mar-Apr;19(2):91-7.
30. Gelsomino S, Rostagno C, Bevilacqua S, Caciolli S, Capecchi I, Casolo G, Gensini GF, Stefano P. A complex triple valve repair in a young rheumatic patient. *Ital Heart J*. 2003 Dec;4(12):884-7.
31. Gelsomino S, Masullo G, Morocutti G, Frassani R, Da Col P, Parise O, Spedicato L, Livi U. Sixteen-year results of composite aortic root replacement for non-dissecting chronic aortic aneurysms. *Ital Heart J*. 2003 Jul;4(7):454-9.
32. Gelsomino S, Morocutti G, Frassani R, Masullo G, Da Col P, Spedicato L, Livi U. Long-term results of Bentall composite aortic root replacement for ascending aortic aneurysms and dissections. *Chest*. 2003 Sep;124(3):984-8.
33. Gelsomino S, Rubattu G, Terrosu PF, Cossu L, Orrù F, Barbosa G. Successful repair of a coronary artery to pulmonary artery fistula with saccular artery aneurysm and critical stenosis of the left anterior descending coronary artery. *Ital Heart J*. 2003 May;4(5):350-3.
34. Gelsomino S, Morocutti G, Da Col P, Masullo G, Carella R, Guzzi G, Spedicato L, Livi U. Early in vivo hemodynamic results after aortic valve replacement with the St Jude Medical Regent mechanical heart valve in patients with pure aortic stenosis. *J Card Surg*. 2003 Mar-Apr;18(2):125-32.
35. Morocutti G, Gelsomino S, Spedicato L, Shiety Toh H, Pitzorno C, Masullo G, Bernardi G, Da Col P, Frassani R. Transesophageal echocardiography follow-up of patients undergoing replacement of the ascending aorta and aortic valve with a Cabrol procedure for chronic aneurysm and dissection. *J Am Soc Echocardiogr*. 2003 Apr;16(4):360-6.
36. Gelsomino S, Frassani R, Morocutti G, Masullo G, Da Col P, Spedicato L, Porreca L, Livi U. A short-term experience with the Tirone David I valve sparing operation for the treatment of aneurysms of the ascending aorta and aortic root. *Cardiovasc Surg*. 2003 Jun;11(3):189-94.

37. Gelsomino S, Frassani R, Da Col P, Morocutti G, Masullo G, Spedicato L, Livi U. A long-term experience with the Cabrol root replacement technique for the management of ascending aortic aneurysms and dissections. *Ann Thorac Surg.* 2003 Jan;75(1):126-31.
38. Morocutti G, Spedicato L, Gelsomino S, Toh HS, Bernardi G, Fioretti P. Use of barcodes of biomedical products in a catheterization laboratory. A required step to improve quality and reduce costs. *Ital Heart J Suppl.* 2002 Aug;3(8):851-7.
39. Morocutti G, Gelsomino S, Spedicato L, Frassani R, Bernardi G, Da Col P, Paparella G, Fioretti P, Livi U. Intraoperative transesophageal echo-Doppler evaluation of stentless aortic xenografts. Incidence and significance of moderate gradients. *Cardiovasc Surg.* 2002 Aug;10(4):328-32.
40. Morocutti G, Gasparini D, Spedicato L, Gelsomino S, Paparella G, Bernardi G, Fioretti P. Functional evaluation of steal by unligated first intercostal branch before transcatheter embolization in recurrent angina after a LIMA-LAD graft. *Catheter Cardiovasc Interv.* 2002 Jul;56(3):373-6.
41. Gelsomino S, Morocutti G, Da Col P, Frassani R, Carella R, Minen G, Livi U. Preliminary experience with the St. Jude Medical Regent mechanical heart valve in the aortic position: early in vivo hemodynamic results. *Ann Thorac Surg.* 2002 Jun;73(6):1830-6;
42. Morocutti G, Bernardi G, Gelsomino S. Prosthetic valve dysfunction presenting as intermittent acute aortic regurgitation. *Heart.* 2002 Jul;88(1):3.
43. Gelsomino S, Morelli A, Porreca L, Morocutti G, Da Col P, Livi U. Video-assisted thoracoscopic surgery for primary chylopericardium after orthotopic heart transplantation. *J Heart Lung Transplant.* 2002 Jun;21(6):701-5.
44. Gelsomino S, Da Col P, Morocutti G, Frassani R, Porreca L, Minen G, Livi U. Stentless aortic valve replacement in elderly patients. *Cardiovasc Surg.* 2002 Jun;10(3):233-7.
45. Gelsomino S, Morocutti G, Frassani R, Da Col P, Carella R, Livi U. Usefulness of the Cryolife O'Brien stentless suprannular aortic valve to prevent prosthesis-patient mismatch in the small aortic root. *J Am Coll Cardiol.* 2002 Jun 5;39(11):1845-51.

46. Morocutti G, Gelsomino S, Bernardi G. Covered stent for iatrogenic coronary arteriovenous fistula in heart transplant recipient. *Heart*. 2002 Apr;87(4):339.
47. Gelsomino S, Morocutti G, Masullo G, Cheli G, Poldini F, Da Broi U, Livi U. Open heart surgery in patients with dialysis-dependent renal insufficiency. *J Card Surg*. 2001 Sep-Oct;16(5):400-7.
48. Gelsomino S, Morocutti G, Frassani R, Da Col P, Morelli A, Spedicato L, Minen G, Livi U. Early recovery of left ventricular function after stentless versus stented aortic valve replacement for pure aortic stenosis and severe cardiac dysfunction. *Semin Thorac Cardiovasc Surg*. 2001 Oct;13(4 Suppl 1):120-8.
49. Gelsomino S, Frassani R, Morocutti G, Porreca L, Tursi V, Masullo G, Lumini R, Livi U. Left ventricular mass regression after aortic valve replacement with CryoLife-O'Brien stentless aortic bioprosthesis. *J Heart Valve Dis*. 2001 Sep;10(5):603-10.
50. Spedicato L, Bonin M, Bernardi G, Gelsomino S, Fioretti PM, Morocutti G. "Side balloon stenting": a novel technique for bifurcation lesions. *J Invasive Cardiol*. 2001 Oct;13(10):684-8.
51. Gelsomino S, Frassani R, Morocutti G, Nucifora R, Da Col P, Minen G, Morelli A, Livi U. Time course of left ventricular remodeling after stentless aortic valve replacement. *Am Heart J*. 2001 Sep;142(3):556-62. PMID: 11526373 [PubMed - indexed for MEDLINE]
52. Livi U, Gelsomino S, Da Col P, Poldini F, Masullo G, Cheli G, Nucifora R, Muzzi R, Da Broi U. The A-Med right heart support for off-pump coronary artery bypass grafting. *Ital Heart J*. 2001 Jul;2(7):502-6.
53. Gelsomino S, Da Col P, Frassani R, Morocutti G, Muzzi R, Bassi F, Cappelletto G, Livi U. Coronary artery bypass grafting in patients with dialysis-dependent renal failure: ten-year results. *Ital Heart J*. 2001 May;2(5):379-83.
54. Gelsomino S, Frassani R, Porreca L, Morocutti G, Morelli A, Livi U. Early and midterm results of model 300 CryoLife O'Brien stentless porcine aortic bioprosthesis. *Ann Thorac Surg*. 2001 May;71(5 Suppl):S297-301.
55. Gelsomino S, Frassani R, Porreca L, Livi U. Aortic repair in Marfan's syndrome: prevention of mechanical leaflets damage. *Cardiovasc Surg*. 2001 Jun;9(3):299-301.

56. Gelsomino S, Frassani R, DaCol P, Porreca L, Masullo G, Morocutti G, Livi U. The CryoLife O'Brien stentless porcine aortic bioprosthesis: 5-year follow-up. *Ann Thorac Surg.* 2001 Jan;71(1):86-91.
57. Gelsomino S, Frassani R, Porreca L, Morocutti G, Livi U. Clinical and hemodynamic evaluation of 21 mm and 23 mm Cryolife-O'Brien stentless bioprostheses implanted in the aortic position. *Ital Heart J.* 2000 Sep;1(9):613-20.
58. Frassani R, Gelsomino S. A right atrial approach in redo postinfarction ventricular septal defect. *Cardiovasc Surg.* 1999 Oct;7(6):656-8.
59. Frassani R, Gelsomino S, Puricelli C. The recurrence of a postinfarct interventricular defect. An alternative approach *G Ital Cardiol.* 1998 Dec;28(12):1409-12.
60. Frassani R, Gelsomino S, Puricelli C. The Tirone David operation in a young patient with Marfan syndrome. Description of a clinical case. *G Ital Cardiol.* 1998 Sep;28(9):1017-20.

Curriculum Vitae

CURRICULUM VITAE

- ✚ Born in Cosenza, Italy, on the 24/07/1962.
- ✚ Graduated at The University of Bologna (magna cum laude), Italy.
- ✚ Cardiac Surgery Degree at The University of Bologna (magna cum laude), Italy.
- ✚ Recipient of Award of University of Bologna, Bologna, Italy, 1990.
- ✚ Senior House Officer (SHO), Bristol Royal Infirmary, Bristol, UK.
- ✚ Senior House Officer, County Hospital, Hereford, UK.
- ✚ Clinical Fellow, Cardiac Surgery, Brescia, Italy.
- ✚ Surgical Assistant, Cardiac Surgery, Torino, Italy.
- ✚ Senior Cardiac Surgeon, Cardiac Surgery, Udine, Italy.
- ✚ Senior Cardiac Surgeon, Cardiac Surgery, Sassari, Italy.
- ✚ Senior Cardiac Surgeon, Cardiac Surgery, Florence, Italy.
- ✚ Chief Experimental Cardiac Surgery, Florence, Italy.

MEMBERSHIPS

- ✚ Society of Cardiovascular Research
- ✚ Italian Society of Cardiac Surgery
- ✚ Society of Heart Valve Disease