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Pathobiology of cardiac dyssynchrony and resynchronization therapy

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Synchronous ventricular electrical activation is a prerequisite for adequate left ventricular (LV) systolic function. Conduction abnormalities such as left bundle branch block, and ventricular pacing lead to a dyssynchronous electrical activation sequence, which may have deleterious consequences. The present review attempts to connect the various processes involved in the development of 'dyssynchronopathy', and its correction by cardiac resynchronization therapy (CRT). Abnormal electrical impulse conduction leads to abnormal contraction, characterized by regional differences in timing as well as shortening patterns and amount of external work performed. Early activated regions may show 'wasted work', which leads to inefficient action of the entire left ventricle. Moreover, both the development of heart failure (HF) in general and the regional differences in mechanical load lead to structural, electrical, and contractile remodelling processes. These have been demonstrated at the level of the myocardium (asymmetric hypertrophy, fibrosis, prolongation of activation and reduction in repolarization forces, decrease in LV ejection fraction), cell (gap junctional remodelling, derangement of the T-tubular structure), and molecule (under or overexpression of ion channels and contractile proteins subtypes and abnormal calcium handling). The myocardial adaptations to dyssynchrony are 'maladaptive'. This also explains why CRT, unlike most pharmacological treatments, continues to increase its therapeutic effect over time. Finally, better understanding of all processes involved in dyssynchrony and CRT may also lead to new pharmacological agents for treating HF and to novel pacing strategies.

Keywords

Dyssynchrony • Left bundle branch block • Heart failure • Cardiac resynchronization therapy
• Remodelling • Pathophysiology

Introduction

Proper cardiac pump function is dependent on fairly synchronous and well distributed electrical activation. The intraventricular rapid conduction system plays a key role in this respect. The importance of this synchronous activation is illustrated by the deviations in structure and function that occur when impulse conduction becomes abnormally slow, as is the case during ventricular pacing and left bundle branch block (LBBB). Slow impulse conduction leads to large time differences in electrical activation and contraction within a ventricle and between the ventricles (intra- and interventricular dyssynchrony, respectively). The combination of all detrimental changes leading to dyssynchrony-induced cardiomyopathy can be termed 'dyssynchronopathy', a disease that can be treated by cardiac resynchronization therapy (CRT). The present overview aims to review and discuss current knowledge on the pathobiology of dyssynchrony

and CRT, i.e. the causes and consequences of dyssynchrony and resynchronization for structural and functional processes in the myocardium.

Electrical aspects

The pathobiology of conduction abnormalities and electrical dyssynchrony

Synchronous ventricular electrical activation is a prerequisite for adequate left ventricular (LV) function. In the healthy heart this is achieved by propagation of electrical impulses from the atrioventricular (AV) node through the fast-conducting His-Purkinje system. An additional role may be played by fast conducting endocardial fibres, which conduction velocity is in between that of working

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myocardium and Purkinje fibres.¹ Of note, functionality of such fibres has only been demonstrated in the dog heart, the conduction system of which seems to be closest to the human heart of all non-primate mammals.² 'True' Purkinje fibres are characterized by a larger size² and by overexpression of connexin 43 (Cx43)³ compared with endocardial fibres. In relatively simple histological images, the subendocardial fibres in the dog heart appear uniformly oriented but otherwise similar to working myocardium.¹ Such fibres have not been identified in the human heart, but high resolution micro computed tomography (CT) images show dense networks of Purkinje-like fibres, which may be comparable to the fast conducting endocardial fibres in the dog heart. In the dog heart several studies showed fast impulse conduction along the LV endocardium^{4,5} apparently explaining the benefit of endocardial CRT.^{4,6,7} Although the existence of fast-conducting subendocardial fibres in the human heart is not clear, clinical studies support the evidence that endocardial CRT is at least as beneficial as epicardial CRT.⁸

While the ventricular endocardium is normally electrically activated within ~20 ms, the remaining transmural propagation from endocardium to epicardium requires another ~50 ms.⁹ The Purkinje system may be damaged or bypassed during conduction abnormalities such as LBBB and ventricular pacing. Under these conditions, conduction propagates primarily through working myocardium in which the conduction velocity is almost four times slower compared with the specialized His-Purkinje system.⁹ Additionally, the wavefront of activation changes. Propagation perpendicular to the fibre orientation, is half of that of propagation parallel to the fibres,¹⁰ contributing to the prolongation of total ventricular activation.

While the cause of abnormal conduction during ventricular pacing is obvious, this is much less the case during bundle branch block. Especially during LBBB, the conduction block may occur at any level in the His-Purkinje system. The wide variation in left bundle branch anatomies further complicates the diagnosis of LBBB.¹¹ Left bundle branch block may develop suddenly when its primary blood supply is obstructed or under iatrogenic circumstances, for instance after aortic valve replacement. In the latter case, the block is obviously proximal in the left bundle branch. However, more often, LBBB is a result of slow degeneration of the conduction system due to chronic conditions affecting the myocardium.¹²

There is interesting and growing evidence that, in the latter case, a considerable part of LBBB patients has a proximal block. This evidence comes from the fact that His-bundle pacing creates significant narrowing of the QRS complex in many patients with LBBB. Because this effect can only be explained if pacing occurred distal to the block, this LBBB should be located very proximal in the His bundle or even in the lower part of the AV node. Forty-year old studies already pointed this out,^{13,14} and results were explained by the theory of longitudinal dissociation of the His bundle. This theory assumes that the conducting fibres to the right and left bundle branch are histologically isolated inside the trunk. Injuring the trunk may lead to a complete AV-block or a bundle branch block.¹⁵ Stimulation of the fibres distal to the bundle branch block can normalize the QRS complex in case of pure His bundle capture and absence of pre-excitation of adjacent myocardium. More recent studies demonstrating ventricular resynchronization through His bundle pacing in CRT candidates reinforced this idea.¹⁶

Electro-anatomic insights in the pathobiology of electrical dyssynchrony

After the first crude mapping studies in LBBB and right ventricular (RV)-paced patients by Vassallo *et al.*¹⁷ in the 1970s, detailed mapping studies were performed by Auricchio *et al.*^{18,19} These studies showed that LBBB was characterized by a slow impulse conduction originating from the RV free wall gradually propagating to the LV lateral wall.¹⁹ Interestingly, a large variation in trans-septal conduction time (TST) was present in patients referred for CRT. While a few patients almost had simultaneous activation at the right and left ventricle side of the septum (TST near 0), most of the patients with LBBB showed TSTs of >30 ms, even up to 80 ms.²⁰ Long TSTs were also found in canine LBBB hearts, especially in canines with LBBB and tachypacing-induced heart failure (HF).²¹ Slow trans-septal conduction is also evident from epicardial contact maps in ventricular paced canine hearts⁷ and from non-invasive ECG imaging (ECGI) maps in LBBB patients (Figure 1).²² The slow conduction across the septum may be explained by its transverse conduction perpendicular to the fibre orientation. However, this is also the case in conduction from endocardium to epicardium of the LV free wall (LVFW), and this conduction is still faster than across the septum.¹⁰ Apparently, the septum has specific structural abnormalities that slow down conduction, especially after remodelling due to HF. The slow septal conduction reflects an electrical separation between activation of the right and left ventricle (RV and LV), which is proposedly responsible for QRS notching on the electrocardiogram (ECG) characteristic for LBBB.²³

Non-invasive assessment of electrical dyssynchrony

Much information about ventricular conduction abnormalities has been obtained using the 12-lead ECG. QRS duration ≥ 150 ms and a LBBB morphology on the ECG indicate a class 1A recommendation for CRT implantation.²⁴ However, QRS duration cannot distinguish between right or left sided conduction abnormalities and between inter- and intraventricular dyssynchrony. While QRS morphology provides more information, it is prone to subjective interpretation and there are multiple definitions for specific conduction disturbances such as LBBB. For example, in a small retrospective study of different LBBB criteria in patients receiving CRT, a 23% disagreement in LBBB classification was found between the European and American guidelines.²⁵

During recent years, multiple non-invasive techniques have been developed that allow more precise analysis of electrical dyssynchrony by incorporation of spatial or temporal information. First of all, there are techniques closely related to the conventional 12-lead ECG, such as vectorcardiography and ultra-high frequency ECG that can be easily implemented in clinical practice.^{26,27} A more complicated technology, ECGI, reconstructs the electro-anatomic activation of the epicardium based on body surface potential measurements using ~200 electrodes around the chest and a patient-specific heart-torso geometry.²⁸ Electrocardiogram imaging allows assessment of both inter- and intraventricular dyssynchrony.²² Interestingly, it was shown that a parameter describing interventricular dyssynchrony correlates better with CRT response than parameters of intraventricular dyssynchrony; an observation that was subsequently supported by computer simulations.^{22,29}

Figure 1 Overview of electrical dyssynchrony metric approaches. In the ECG imaging and contact mapping panels colour differences within the ventricles represent intraventricular dyssynchrony, whereas the mean difference in colour between the ventricles reflects interventricular dyssynchrony. ECG, electrocardiogram; VCG, vectorcardiography; UHF, ultra-high frequency.

An intermediate approach between the conventional 12-lead ECG and the extensive ECGI is the ECG-belt, where 53 chest electrodes are used. The standard deviation of all ECG-belt derived activation times (SDAT) has been proposed as a novel electrical dyssynchrony metric reflecting electrical heterogeneity. In 66 CRT recipients SDAT, but not QRS duration or morphology, was associated with LV end-systolic reduction and increase of LV function upon starting CRT.³⁰ An overview of the aforementioned electrical dyssynchrony assessment techniques is provided in Figure 1.

Mechanics of the dyssynchronous ventricle

A close relationship exists between excitation and contraction in both the normal^{31,32} and failing heart.^{33,34} The latter was most clearly demonstrated by the use of 3D electromechanical mapping, which allows measuring strains and electrical activation at exactly the same position.³³

This coupling between excitation and contraction makes it understandable that dyssynchronous electrical activation leads to dyssynchronous ventricular contraction. These contraction abnormalities are complex, as illustrated in Figure 2. Early shortening in early-activated regions is followed by a systolic rebound stretch, sometimes showing a bi- or triphasic pattern. In contrast, late-activated regions are subjected to early-systolic prestretch, followed by augmented systolic shortening that continues into diastole. The most likely physiological explanation for these patterns is that early contraction stretches the not-yet depolarized late-activated regions and that this prestretch activates the local Frank–Starling mechanism, and subsequently, creates a supranormal contraction in late-activated regions. Possibly the best support for this idea are results from simulations in the CircAdapt computer program. In this model, the ventricles are represented by three wall segments (right ventricle, septum, and LVFW), which contain the property of length-dependent activation. Simply delaying LVFW contraction results in

strain patterns in septum and LVFW, which are close to those observed in LBBB patients (Figure 2A).³⁵

Assessment of mechanical dyssynchrony

The analysis of mechanical dyssynchrony has developed rapidly over the last two decades. Initially tissue Doppler imaging was used,³⁸ while more recently, techniques to measure strains (length changes) emerged, such as speckle tracking echocardiography,^{36,39} cardiac magnetic resonance (CMR) imaging tagging^{31,40} and more recently feature tracking CMR⁴¹ and CT-SQUEEZE.⁴² However, still none of the guidelines recommend these techniques for selection of CRT patients. This is explained by the results of randomized clinical studies investigating the use of mechanical dyssynchrony for improving the selection of patients for CRT. Mechanical dyssynchrony had no additional predictive power on top of ECG parameters in cohorts of patients with a wide QRS complex,^{43,44} whereas neutral or even negative results were found when mechanical dyssynchrony was used as the only selection criterion in patients with a narrow QRS complex.^{45,46}

In part, these poor results can be explained by limitations of tissue Doppler imaging⁴⁷ and the strong operator dependency of acquisition and analysis of echocardiographic images. On the other hand, considerable differences in time to peak shortening may not only be caused by electrical dyssynchrony but also by regions with low contractility and scar.⁴⁸ Furthermore, peak shortening delay has at best a semi-quantitative relation with true dyssynchrony (Figure 2A). On the other hand, several studies showed the strength of relatively simple measures of dyssynchrony, such as apical rocking and septal flash do improve prediction of CRT response.^{49–51} Further improvements were made by using the analysis of strain patterns,⁵² resulting in parameters such as CURE,⁵³ septal systolic rebound stretch,^{36,54} and systolic stretch index.⁴⁸

Functional consequences of mechanical dyssynchrony

A direct consequence of ventricular dyssynchrony is the reduction in LV function. The gold-standard way to assess LV function is to

Figure 2 (A) Effect of dyssynchronous ventricular activation on mechanical dyssynchrony indices in the CircAdapt model. Computer simulations were performed to predict LV septal and lateral wall strain curves after inducing LVFW delays in increasing severity. (B) Strain patterns measured in a patient before (left) and during CRT (right). Red lines indicate systolic shortening, green early systolic prestretch, and blue septal rebound stretch. The bar graphs indicate that CRT reduces septal rebound stretch and increases systolic shortening of the septum (thick lines) and LVFW (thin lines) combined. Adapted with permission from Leenders *et al.*³⁷ (A) and De Boeck *et al.*³⁶ (B). AVC, aortic valve closing; AVO, aortic valve opening; CRT, cardiac resynchronization therapy; IntraVDA, intraventricular delayed activation; LV, left ventricle; LVFW, left ventricular free wall; MVC, mitral valve closing; MVO, mitral valve opening; RV, right ventricle; SEPT, septal.

determine pressure-volume (PV) loops. Immediately after the onset of dyssynchrony, the PV-loop shows a rightward shift, indicating that the LV needs to operate at a larger volume in order to generate the same pressure; furthermore, stroke volume decreases.⁵⁵ The reverse process has been observed upon starting CRT in patients.⁵⁶ This poorer pump function is largely caused by the reduced systolic shortening in early-activated regions, which is hardly compensated by an increase in shortening in late-activated regions, at least during the ejection phase. As a consequence, in LBBB hearts septal rebound stretch is a good predictor of CRT response.³⁶

Such septal stretch during systole implies that this region dissipates energy that was generated in opposing regions.^{57,58} In this respect Russell *et al.*^{58,59} introduced the term 'wasted work'. Using an elegant method, these investigators were able to show that the ratio of wasted and positive work predicts CRT response.⁵⁸ Importantly, the same research group recently showed that increasing afterload increases the amount of wasted work and disproportionately reduces global longitudinal strain and LV ejection fraction (LVEF).⁶⁰ This finding suggests that the dyssynchronous heart is more sensitive to

additional increases in cardiac work load than synchronous hearts and that the afterload should be taken into account when quantifying mechanical dyssynchrony.

The acute haemodynamic benefit of CRT can be understood from its correction of electromechanical dyssynchrony. Certainly in the heart with LBBB, CRT achieves a great deal of normalization of strain patterns and almost vanishing of septal rebound stretch³⁶ and wasted work.⁵⁸

A further consequence of the wasted work in the dyssynchronous heart is that the efficiency of conversion of metabolic energy (myocardial O₂ consumption) to mechanical energy (stroke work) at the level of the entire left ventricle can be up to 30% lower during LBBB or RV pacing when compared with normal activation.⁶¹ Conversely, CRT increases ventricular efficiency, which translates into a lower myocardial perfusion requirement for the same amount of pump work performed^{62–64} and into a larger perfusion reserve.⁶⁵ Because many CRT patients may also have compromised coronary perfusion, CRT may also lower the risk or amount of underperfusion. This all may explain why wasted work⁶⁶ and the work ratio between the septum and LVFW⁶⁷ are good predictors of CRT response.

Figure 3 Schematic representation of maladaptive processes following the onset of dyssynchronous activation (see text for details).

A third consequence of dyssynchrony is the considerable redistribution of myocardial work within the ventricles. Because systolic shortening (so shortening against a pressure) in the septum is approximately zero, external work is also zero. In contrast, systolic shortening and external work are supranormal in the LV lateral wall (Figure 2). Accordingly, also myocardial blood flow is redistributed, both in experimental LBBB models^{68,69} and in patients.⁶³ The fact that this redistribution is reversed by CRT, concurrent with the homogenization of local strains and work⁶⁹ indicates that workload drives flow and not the other way around. Earlier work of Amitzur supports this view by showing that administration of adenosine in RV paced hearts changes local blood flow but not contraction patterns.⁷⁰

Figure 3 summarizes how the various acute consequences of dyssynchronous electrical activation, mentioned above, lead to worsening cardiac function and ventricular dilatation. In clinical terms, the diminishment of systolic function is evidenced by a lower LVEF and lower strains, worse diastolic function by reduced diastolic filling times and the dilation is shown by a larger LV end-diastolic volume and a rightward shift of the PV-loop in conductance catheter measurements.⁵⁶

Remodelling: from myocardium to molecule

Figure 3 also depicts that 'dyssynchronous HF' leads to unique and extensive gene and protein expression patterns that can be linked to structural as well as electrophysiological and contractile changes.^{71–73} These 'remodelling processes' are driven by neurohumoral factors, like adrenergic stimulation and activation of the

renin-angiotensin-aldosterone system (RAAS), and by the mechanical load on the heart itself.⁷⁴ Although the exact mechanisms for transmitting mechanical load to the myocardial cells are not clear,⁷⁵ stretch is a well-known trigger for changing cellular and organ function, both *in vitro* and *in vivo*.^{55,76–78} Typically, in LBBB, the early systolic prestretch and augmented external work in late-activated regions seem logical explanations for the frequently more pronounced remodelling processes in these regions.

Because in-depth understanding of (reverse) remodelling processes requires invasive procedures, like biopsies, most knowledge in the field of dyssynchrony and resynchronization is derived from various animal models of dyssynchrony.⁷⁹ The most straightforward way is to induce dyssynchrony by RV pacing or by LBBB, induced using radio frequency ablation while maintaining a normal heart rate. However, since such dyssynchrony reduces pump function but does not lead to HF within a period of half a year,⁶⁸ several groups have added an increase in heart rate, ranging from 120 to 220 b.p.m. for a period of 3–4 weeks to 24 months.^{80,81} In all these models, resynchronization has been employed using biventricular pacing. Importantly, studies with tachypacing dyssynchronous HF use also tachy-biventricular pacing to resynchronize, which will be referred to as tachy-CRT. Tachy-CRT hardly improves functional parameters like LVEF, but reveals many changes at the cellular and molecular level presumably as a consequence of the better co-ordination of contraction.^{82,83}

Structural remodelling

In patients with dyssynchronous HF, CRT induces reverse remodelling with a reduction in LV end-systolic volume (LVESV)^{84,85} and reduced fibrosis.^{86,87} CRT responders (defined by LVESV reduction)

were also shown to have a decreased LV mass and regional wall thickness, with improved LV geometry, as determined by the sphericity index.^{88,89} An interesting observation is that polymorphisms in the mineralocorticoid receptor gene proved an important determinant for reverse remodelling in CRT patients.^{90,91} This supports the view that the RAAS is strongly involved in the remodelling process in dyssynchronous failing hearts. These clinical studies suggest that the capability to reverse the remodelling is an important determinant of long-term CRT response. It seems reasonable to suggest that the overall decrease in LV wall mass and the reduced fibrosis upon CRT are mediated by the improved LV systolic function. A reduction in LV cavity volume decreases wall stress and, together with the increased LV function, potentially lowers neurohumoral activation. The reduction in workload in the late-activated LVFW may be responsible for the excess reduction in LVFW mass.

Animal models of LBBB with natural heart rate show ventricular dilatation in combination with asymmetric hypertrophy, the most pronounced hypertrophy occurring at sites of late activation.^{55,69} The presence of this asymmetric hypertrophy (measured both by echocardiography and post-mortem histology^{55,92}) is accompanied by local molecular changes such as decreased miR133a expression and overexpression of connective tissue growth factor (CTGF) selectively in the LV lateral wall.⁹² These local changes and their reversal upon applying CRT^{69,92} are a strong indication of the importance of local mechanics for remodelling, because all regions of the dyssynchronous heart are subjected to the same neurohumoral stimulation. While the increase in LV cavity volume after onset of LBBB may directly follow the loss in LV systolic function (Figure 3), further LV dilatation may be mediated by changes in the extracellular matrix (ECM) properties and matrix metalloproteases (MMPs). This fits with the finding of ECM-remodelling and increased MMP activity in the LVFW of RV-paced dogs⁹³ and in dogs with tachypacing-induced dyssynchronous HF.^{81,94} The RV-pacing study also showed ECM accumulation (fibrosis) in the late-activated LVFW.⁹³ By contrast, in dog-models of dyssynchrony without significant cardiac dysfunction (LBBB or LV pacing), myocardial collagen content was not affected,^{55,92,95} although this did occur in a study of tachypacing-induced dyssynchronous HF.⁸¹ In patients, a modest reduction in fibrosis was observed after CRT,^{86,87} which may be explained by a lower neurohumoral activation. Also, expression of paracrine factors contributing to fibrosis or hypertrophy, including osteopontin, transforming growth factor beta, CTGF, and B-type natriuretic peptide, is increased during dyssynchrony and (partly) normalized by CRT.^{92,94,96}

Besides cardiomyocyte hypertrophy and ECM accumulation, apoptosis contributes to the cardiac remodelling process in dyssynchronous HF. An overall increase in various pro-apoptotic factors (such as caspases) has been shown in dyssynchronous HF.^{97,98} This pro-apoptotic state is ameliorated by CRT and the regional variance in the expression of several stress-kinases is reduced.⁹⁷ The pro-apoptotic factor tumour necrosis factor alpha (TNF α) is increased in animal models of dyssynchrony^{97,99} and in patients eligible for CRT.⁸⁷ In the animal model, the most pronounced increase in TNF α levels occurs in the LVFW, with tachy-CRT partially normalizing TNF α expression.⁹⁷ In accordance with this, also patients show reduced TNF α levels following CRT.^{86,87} Moreover, DNA-fragmentation, a marker of apoptosis, is increased in dyssynchronous HF and reduced

by CRT.^{86,97,98} Interestingly, increased DNA fragmentation occurs in both the septum and the LVFW and tachy-CRT is capable of reducing the occurrence of this process in both locations.⁹⁷

Electrical remodelling

Electrical remodelling in dyssynchronous and resynchronized hearts may affect both the sequence of depolarization and repolarization.

Changes in the depolarization sequence have been observed from the broadening of the QRS complex during longer lasting dyssynchrony in animal models.^{55,68} Similarly, longer lasting CRT has been reported to decrease QRS duration (both the paced and the non-paced QRS complex) in patients.¹⁰⁰ Besides changes in the gross anatomy (changes in LV mass and diameter and degree of fibrosis) discussed above, also changes in ion channels may play a role. Figure 4A schematically illustrates the contribution of the various ion channels to the ventricular action potential.

Connexin 43 is the main gap junction protein responsible for sodium influx during phase 0 of the action potential and subsequently conduction velocity. Increased lateralization of Cx43 in the left ventricle is associated with remodelling processes after tachypacing-induced HF and after myocardial infarction (Figure 5).^{101,102} Interestingly, electrical dyssynchrony by itself already influences Cx43 localization. In the lateral segments of the canine LBBB heart, a reduced endocardial conduction velocity was observed in combination with lateralization of Cx43.⁹⁵ Lateralization of Cx43 may lead to a more zig-zag conduction pattern,¹⁰³ and consequently slower conduction, heterogeneity of refractoriness, and increased risk of reentry circuits. In addition, in canine hearts with tachypacing-induced HF both lateralization and decreased expression of Cx43 were associated with slowing of His-Purkinje conduction duration (Figure 4B),¹⁰⁴ indicating that remodelling processes secondary to HF solely already prolong QRS duration.

Another factor contributing to conduction and cardiac excitation is the fast-inward voltage-dependent sodium channel (I_{Na}), but its role in dyssynchrony is unequivocal. I_{Na} density was decreased in explanted human hearts with HF,¹⁰⁵ but contradictory results have been reported for canine hearts with tachypacing-induced HF.^{105,106}

While changes in the QRS complex reflect changes in depolarization, T-wave changes reflect altered repolarization. In this respect, 'cardiac memory' is of interest. Cardiac memory refers to persistent T-wave changes on the ECG during restoration of normal ventricular activation sequence after a period of abnormal ventricular activation. These persistent T-wave abnormalities indicate that the sequence of repolarization adapts to a new activation sequence.¹⁰⁷ This phenomenon has been studied in animals and humans.^{108,109} In patients with RV pacing, changes in T-wave amplitude and duration were already present within one day of pacing and became persistent after 1 week.¹¹⁰ Similar cardiac memory phenomena developed between 1 day and 2 weeks of CRT.¹¹¹ Interestingly, animal studies showed that cardiac memory could be suppressed by mechanical unloading of the heart.¹⁰⁸ At the molecular level, involvement of the L-type calcium channel¹¹² and the cyclic adenosine monophosphate response element binding protein, a factor heavily involved in regulation of gene expression, was shown.¹¹³ These results strongly argue that the ventricular repolarization changes underlying cardiac memory are related to the mechanical consequences of the activation sequence ('mechano-electrical feedback').

Figure 4 (A) Schematic overview of the five phases of the action potential, ECG, and ion channels involved. The action potential consists of: phase 0 (upstroke), phase 1 (fast early repolarization), phase 2 (plateau), phase 3 (repolarization), and phase 4 (resting membrane potential). (B) ECG and His electrograms demonstrating increase in HV-interval and QRS duration after tachypacing-induced heart failure in canine hearts (adapted with permission from Maguy et al.¹⁰⁴). ECG, electrocardiogram.

Figure 5 Processes contributing to the structural, electrical, and contractile remodelling in the dyssynchronous heart as seen on functional measurements (left) and on a cellular and molecular level (right). Red colour indicates the situation during dyssynchrony. Dyssynchrony causes asymmetric, eccentric hypertrophy, and (in the failing heart) fibrosis as well as apoptosis. Some of the molecular factors are mentioned. Similarly, some of the processes involved in altered excitation-contraction coupling are displayed in the inset, illustrating a part of the plasmalemma, T-tubule and SR (see text for further details). BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CTGF, connective tissue growth factor; Cx43, connexin 43; LBBB, left bundle branch block; LVfw, LV free wall; MHCα, myosin heavy chain α; MMP, matrix metalloproteases; OPN, osteopontin; PLN, phospholamban; SR, sarcoplasmic reticulum; SERCA, SR Ca²⁺ ATP-ase; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

While the T-wave changes in the setting of cardiac memory are indicative of changes in action potential duration (APD), such APD changes have indeed been observed in normal animal hearts during longer lasting periods of ventricular pacing.^{114,115} These studies showed APD lengthening in early-activated regions and gradual APD lengthening towards later activated regions. However, in the very latest activated regions the APD lengthened in the dog heart,¹¹⁵ whereas it was shortened in rabbit hearts.¹¹⁴

Commonly, the upright 'concordant' T-wave in the normal ECG is explained by late-activated regions having a shorter APD than early-activated regions.¹¹⁶ While cardiac memory indicates some potential of the ventricles to adapt APD to activation sequence, the usually discordant T-wave in hearts with RV pacing and LBBB suggests that this potential to adjust APD is insufficient in case of severe dyssynchrony. However, studies in patients without HF show that during longer lasting dyssynchrony (RV pacing and LBBB), the amplitude of the T-wave decreases over time,^{109,117,118} suggesting some adaptation to the abnormal conduction. However, a recent electrical mapping study in HF patients showed that, regardless of QRS duration and morphology, the sequence of repolarization largely follows the sequence of activation, pointing towards reduced 'capacity' of failing myocardium to adjust APD to abnormal activation sequence.¹¹⁹

Concordant with the experimentally observed role of the L-type calcium channel in cardiac memory, data from tachypaced dyssynchronous dog hearts show differential expression and current flow of this calcium channel, with lower values in the LV lateral than in the anterior wall.⁸² However, while larger L-type calcium currents are expected to prolong APD, in the same study APD was shorter in myocytes from earlier-activated LV anterior wall regions.⁸² The investigators explain this paradox by referring to the slower decay in the current in the LV lateral wall. In addition, the severe, but uniform reduction in various potassium channels (important during phase 3 and 4 of the action potential, Figure 4A), may change the influence of the various ion channels during the repolarization phase.⁸²

Computer model studies investigated how to reconcile the aforementioned mechano-electrical feedback, observed in cardiac memory studies, and the electrical and contractile remodelling in dyssynchronous hearts. It was assumed that mechano-sensing aims to maintain a constant mechanical function (like strain), and that adjustments occur through varying activity of the L-type calcium current.⁸² According to the computer simulation, a reduction in local mechanics in early activated regions was followed by increased activity of the L-type calcium channel.¹²⁰ During small time differences in activation (e.g. sinus rhythm), this adaptation process was able to lead to the well-known concordant T-wave.¹²⁰ In the dyssynchronous ventricle, T-waves only became less discordant over time,¹²¹ much like what has been observed in patients (see above).

Clearly, our understanding of electrical remodelling processes influencing ventricular repolarization in the dyssynchronous heart is incomplete. Beside factors discussed above, also the poor understanding of electrotonic influences on repolarization *in vivo* and of the relation between APD heterogeneity and T-wave morphology should be recognized.^{116,119}

Contractile remodelling

Dyssynchrony results in acute negative effects on LV contractile function in animals⁶⁹ and patients.¹²² Moreover, a study in patients with

normal LVEF showed that RV pacing immediately reduces LVEF by ~6%, followed by a further ~8% during the subsequent week of RV pacing. Full recovery of LVEF after termination of pacing took 2 days, further indicating some kind of contractile remodelling.¹²³ Similarly, CRT reverses some of the contractile defects beat-to-beat^{124,125} and continues to do so over years.^{69,126}

While the acute hemodynamic effects can be explained by changes in mechanical coordination, as explained above, the chronic effects seem mediated by subcellular and molecular changes.⁴ In this regard calcium probably plays a dual role, also being involved in electrical remodelling. As mentioned above, in the tachypacing model LBBB lead to a significant and regionally different reduction in the L-type calcium current and this disparity was resolved by tachypacing CRT.⁸² L-type calcium current densities were also reduced in ventricular myocytes from a minipig model of RV pacing, compared with controls.¹²⁷

Also, other proteins involved in calcium handling may play a role in contractile remodelling. Patients with ischaemic or idiopathic dilated cardiomyopathy show reduced sarcoplasmic reticulum (SR) Ca²⁺-ATP-ase (SERCA) activity compared with controls.¹²⁸ Lower SERCA expression was found in patients who are eligible for CRT⁹⁶ and CRT increases SERCA expression.^{129,130} Vanderheyden *et al.*⁹⁶ showed that the increase in SERCA only occurs in CRT responders. Several,^{129,130} albeit not all studies report an increase in phospholamban (PLN) levels after CRT.⁹⁶

These clinical data fit with observations of reduced SR calcium uptake in a porcine model of RV pacing⁹⁹ and down-regulation of SERCA in tachypaced⁸² and non-tachypaced¹³¹ dog hearts. In one study, the change occurred in the LVFW but not in the interventricular septum.¹³¹ In the LVFW of tachypaced dyssynchronous HF a reduction in SERCA expression was selectively found in the endocardium, leading to a steep transmural expression gradient.⁸⁰ After tachy-CRT, SERCA was no longer significantly down-regulated in either early or late activated myocardium.⁸² Slightly smaller, but still significant reductions were observed for PLN in both tachypaced and non-tachypaced canine models of dyssynchrony,^{82,131} but not in a porcine model.⁹⁹

An upregulation of the sodium-calcium exchanger was found in animal models of (tachy) dyssynchrony^{82,99} and a similar trend could be observed after CRT in patients.¹³⁰

These molecular changes may relate to subcellular changes. In patients, abnormalities in T tubular structure have been linked to impaired contractility.¹³² In the LV lateral wall of the tachypacing LBBB model, regression of the T-tubular system has been reported, which was partially reversible upon tachy-CRT.^{133,134}

An important role in the contractile remodelling processes may also be reserved for the autonomic nervous system. The response to β -adrenergic stimulation is diminished in patients with HF.¹³⁵ Cardiac resynchronization therapy treatment recovers the β -adrenergic response.¹³⁶

On the cellular level, the contractile response to β -adrenergic stimulation (increase in calcium transient, cellular shortening) is reduced in HF,¹³⁷ which may be (partially) explained by down-regulation of the β 1 and β 2 adrenergic receptors.^{138,139} In tachypaced dyssynchronous HF, tachy-CRT normalizes the response in cells from both anterior and lateral LV wall.^{138,139} Interestingly, most studies, in both patients¹³⁰ and animals,^{138,139} demonstrate that CRT

upregulates the β_1 -, but not the β_2 -receptor. In addition, a unique feature of β_2 -receptor signalling is observed during dyssynchrony being an increased G-protein α -I (G_{α_i}) coupling, leading to reduced adenylyl cyclase activity and thus lowering cyclic AMP production. This contributes to decreased contractile function. Upon resynchronization, the β_2 receptor becomes uncoupled from these G_{α_i} proteins and restores G_{α_s} signalling.¹³⁸ This mechanism may also be active in CRT responders.¹³⁸

Also at the level of the myofibrils, some remodelling may be present, for instance in myosin heavy chain α (MHC α). In patients, dyssynchronous HF is associated with reduced expression of MHC α and this reduction seems reversed by CRT.^{96,129} The CRT-induced MHC α -increase correlated with the reduction in cavity dimensions.¹²⁹

Studies in skinned muscle fibres from animals with tachypacing-induced HF showed yet another mechanism of contractile modulation: calcium sensitivity of the myofilaments. This sensitivity was shown to be reduced in dyssynchronous HF due to glycogen synthase kinase (GSK)-3 β -dependent phosphorylation of contractile proteins. Tachy-CRT restored calcium sensitivity through increased GSK3- β activity.¹⁴⁰

Summarizing, a large range of processes seem responsible for the contractile remodelling processes in dyssynchrony and its reversal upon CRT, which are depicted in Figure 5.

Conclusion

This review illustrates that conduction abnormalities (such as LBBB) lead to extensive immediate and long-term changes in the heart and reversal of functions by CRT. The long-term adaptations of the myocardium can be characterized as 'maladaptive' because many functions continue to decrease over time. This also explains why CRT, unlike most pharmacological treatments, continues to increase its therapeutic effect over time.

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