The Effects of Chronic Atrial Dilatation on Atrial Electrophysiology and Contractility

Hans-Ruprecht Neuberger

The Effects of Chronic Atrial Dilatation on Atrial Electrophysiology and Contractility

PROEFSCHRIFT

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Promotor:

Prof.dr. M.A. Allessie

Copromotor:

Dr. U. Schotten

Beoordelingscommissie:

Prof.dr. H.J.G.M. Crijns (voorzitter)

Prof.dr. M. Böhm (Universität des Saarlandes, Germany)

Prof.dr. D.J. Duncker (Erasmus Universiteit Rotterdam)

Prof.dr. J. Smits

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CHAPTER 1

Introduction

The Relevance of Atrial Fibrillation

Atrial fibrillation (AF) is a cardiac rhythm disturbance characterized by rapid and uncoordinated atrial activation. On the electrocardiogram P waves are missing, but rapid oscillations or F waves can be recognized (Figure 1).[1] The ventricular response is irregular and causes a "Pulsus irregularis perpetuus".[2]

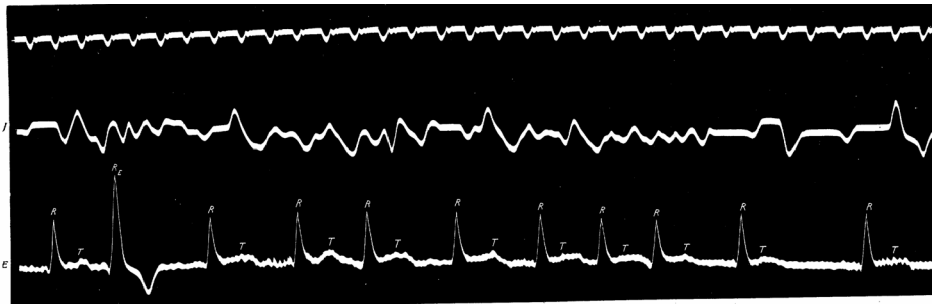

Figure 1
Electrocardiographic recording of probably F waves in a 62-year-old locksmith with "Pulsus irregularis perpetuus" by Hering in 1908. Upper trace: marks of 0.2 seconds. Mid trace: jugular vein pulse. Lower trace: ECG lead I according to Einthoven. Hering himself interpreted the oscillations in the ECG as artifacts due to skeletal muscle activity.[1]

Besides a persistent (not self-terminating) form of the arrhythmia, paroxysmal (self-terminating) AF can occur.[3] Atrial fibrillation doubles overall mortality.[4-6] When atrioventricular conduction is intact, the heart beats rapidly (100-160 beats per minute), which can cause a tachycardiomyopathy.[7;8] In the presence of an accessory atrioventricular pathway, very high ventricular rates can occur (>200 bpm) and ventricular fibrillation may be induced. Patients with AF often have symptoms like palpitations, dyspnea, chest pain, reduced exercise tolerance, dizziness, and syncope due to the irregular heartbeat and/or the reduced cardiac output. However, a significant proportion of patients remains asymptomatic.[9]
The largest clinical and socio-economic problem with AF is that it increases the risk of stroke (about five-fold), particularly at advanced age.[10;11] Conversely, almost 90% of all strokes are ischemic and cardiac thromboembolism is the most important mechanism.[12] AF induces impaired atrial contractility that recovers slowly after cardioversion.[13-15] This tachycardia-induced atrial contractile dysfunction is one of the major mechanisms for thrombus formation in the left atrial appendage and subsequent thromboembolic complications.

Epidemiology

Atrial fibrillation is the most frequent sustained cardiac arrhythmia. Its prevalence is estimated to be 0.5-1.0% in the general population.[16]

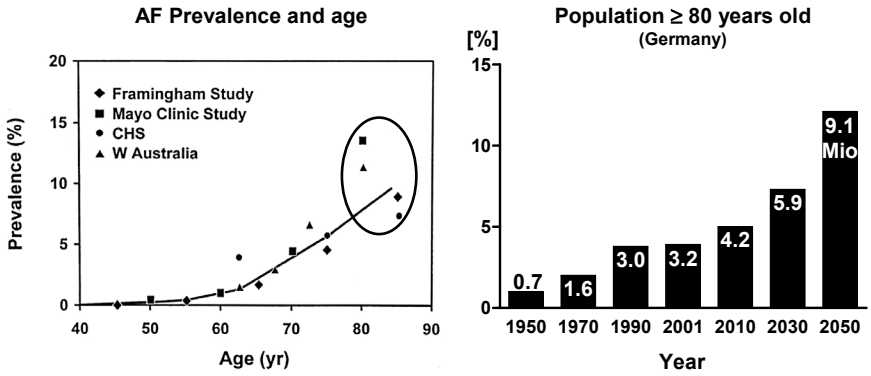

Figure 2
Left: Prevalence of AF according to four natural history studies. In persons 80 years old or older, the AF prevalence is about 10% (circle).[68] *Right:* Relative proportion and absolute number of persons 80 years old or older in Germany from 1950 to 2050 (10th coordinated population projection[18]).

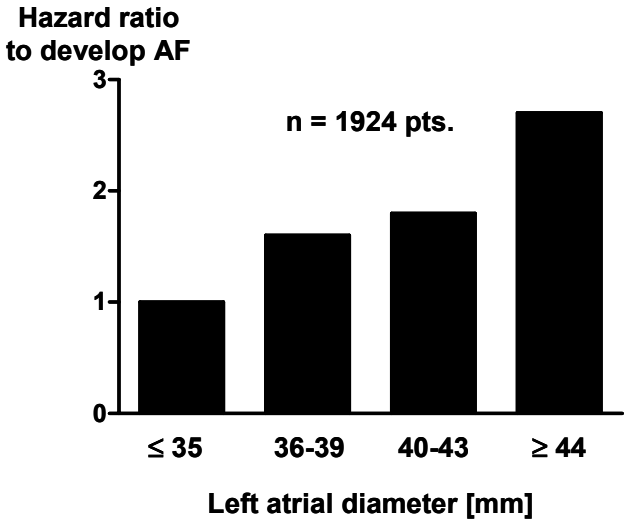

Figure 3
Relative risk to develop AF depending on atrial size.[22]

The arrhythmia rarely occurs in persons below 60 years of age, but about 10% of the 80-year old are affected (Figure 2, left). Because AF occurs mainly in diseased hearts, an increase in cardiac morbidity due to advances in medicine may even raise this fraction in the future.[17] Furthermore, in an aging society AF will become more and more "epidemic". Data from the Federal Statistical Office in Germany can serve as an example. In 1950 only 1% of the population or 690 000 individuals were 80 years or older. In 2001, this group had already increased to 3.8% or 3.2 millions, whereas in 2050 about 9 millions or 12% of the population are expected to be 80 years or older (Figure 2, right).[18] Besides age, other epidemiological risk factors for AF have been identified: male sex,

smoking, diabetes, heart failure, left ventricular hypertrophy, left ventricular dysfunction, diuretic use, myocardial infarction, cardiac/thoracic surgery, hypertension, cerebrovascular accident.[19] Large prospective clinical trials showed, that atrial dilatation is an independent risk factor for the development of the arrhythmia (Figure 3).[20-22] Atrial enlargement occurs in mitral or tricuspid valve disease, left ventricular hypertrophy, chronic obstructive lung disease, pulmonary embolism, ventricular failure (e.g. in acute myocardial infarction) or paroxysmal supraventricular tachycardias (atrioventricular nodal reentrant tachycardia or reentry via an accessory atrioventricular pathway). In addition, idiopathic atrial dilatation has been reported.[23] Remarkably, also atrial fibrillation by itself can induce atrial dilatation.[24] Atrial dilatation per se increases the risk of ischemic stroke independent of the presence of AF.[25-31]

Arrhythmia Mechanisms

The initial theories to explain the rapid irregular atrial activation during AF proposed one or more rapidly depolarizing atrial foci.[32-34] Indeed, particularly in patients with paroxysmal AF this mechanism may underlie the arrhythmia. Foci seem to be mainly located in the pulmonary veins and ablation can be curative.[35;36] They may not only initiate but also perpetuate AF.[37;38] A self-sustaining circuit mechanism (reentry) is the basis of the other main theory, first described by Mayer in 1906 and further developed by Mines, Garrey and Lewis.[39-42] In 1959 Moe introduced the multiple wavelet hypothesis which was experimentally evaluated by Allessie 25 years later.[43]

Traditionally, the patterns underlying the irregular atrial activation in AF have been described as random. However, mapping studies in humans during AF led to a description of different "degrees of disorganization", which were grouped in 3 types, ranging from repetitive, broad and rapidly conducting wavefronts to multiple, irregular and frequently blocking wavelets below the mapping electrode.[44]

Potential Mechanisms of Atrial Fibrillation in Dilated Atria

In 1783, de Senac already emphasized that in mitral valve disease the irregularity of the heart originates from the distended atrium.[45] One possible mechanism underling the increased tendency of dilated atria to fibrillate would be an enhanced automaticity in one or several rapidly firing *foci*. They could serve either as initiator or as perpetuator of the arrhythmia. Another explanation for an AF substrate in dilated atria would be that the physical length of a circuit can be larger and thereby facilitates *reentry*. Such a link has been suggested already in the 19th century by Bouilland (1835), Marey (1863), and Riegel (1882).[46] Reentry will also be facilitated by a decrease in the wavelength (i.e. the product of conduction velocity and refractory period, or in other words: the distance the excitation wave travels during the refractory period). A shorter wavelength shortens the physical path length necessary for a functional reentry.

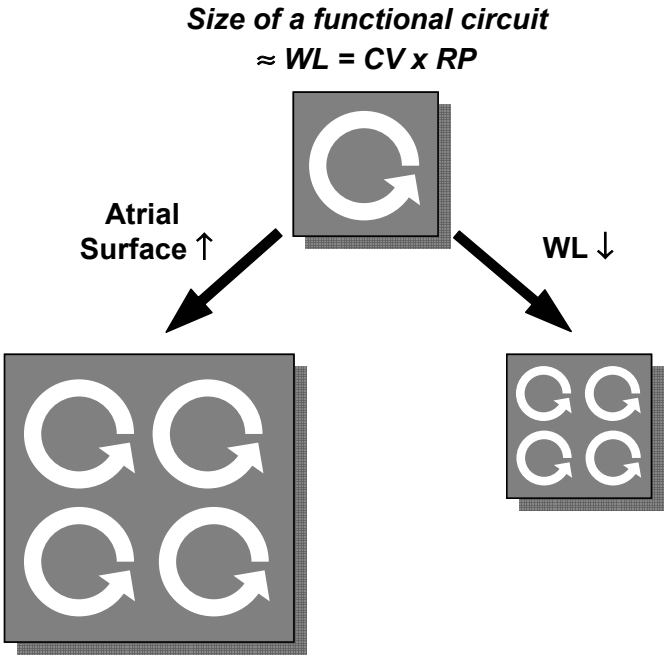

Figure 4
Schematic of the effect of an increase in atrial surface or a decrease in wavelength on the maximal number of simultaneously re-entering wavelets during AF. WL: wavelength, CV: conduction velocity, RP: refractory period.

According to the multiple wavelet hypothesis, this will stabilize atrial fibrillation due to an increased number of simultaneously occurring wavelets (Figure 4). AF itself shortens the wavelength by shortening the refractory period (atrial electrical remodeling) and thus initiates a vicious circle: AF begets AF.[47] Consequently, in atrial dilatation the substrate for AF could be formed by (1) a shortening of the atrial refractory period, (2) a reduced conduction velocity and/or (3) the increased atrial mass or surface. Figure 5 shows this in a simplified way. Both atria are schematically depicted as two hemispheres with a disc in between as the inter-atrial septum. The maximal number of reentrant circuits is calculated as the "atrial" surface area ($4\pi r^2 + \pi r^2$) divided by the area of a circle with a circumference equal to the wavelength ($WL^2/4\pi$). An increase in atrial diameter or a decrease in atrial wavelength results in an exponential increase in the potential number of wavelets and is therefore supposed to stabilize the arrhythmia. The dashed line indicates the number of wavelets (n=6) critical for perpetuation of AF, as observed by Allessie et al.[43]
Additionally, heterogeneity of electrophysiological properties is a prerequisite for the initiation and perpetuation of reentrant arrhythmias and may be increased in dilated atria. Dispersion in atrial refractoriness will favor local functional conduction block necessary for the initiation of a reentry.[48]

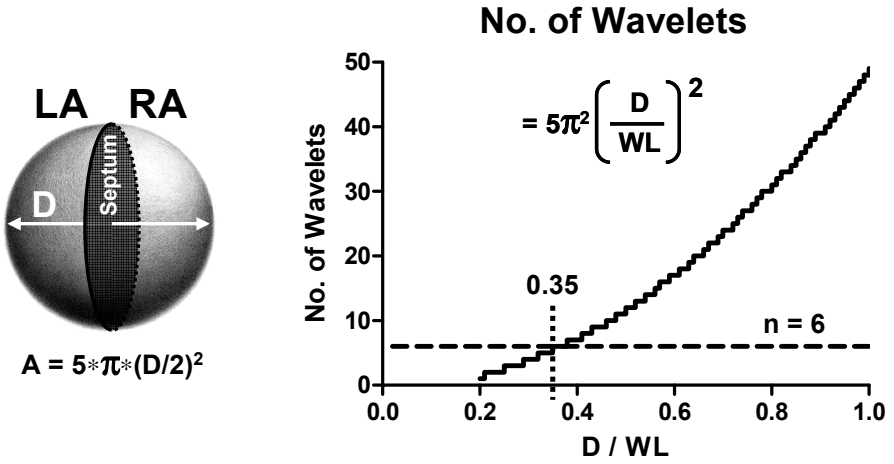

Figure 5
Relationship between the quotient D/WL (atrial diameter / wavelength) and the maximal number of wavelets. Right (RA) and left atrium (LA) are regarded as two hemispheres with a disc in between representing the interatrial septum. When the quotient D/WL equals 0.35, the critical number of wavelets for perpetuation of AF is reached (n=6, dashed lines).[43] There is an exponential increase in the number of wavelets as the diameter increases or the wavelength decreases. A: surface area.

Spatial heterogeneity in conduction also can play a crucial role in the initiation of reentrant arrhythmias and may lead to local differences in refractory periods.[49] Areas of conduction block will fractionate propagating wavefronts and thereby further increase the number of reentering wavelets.

Experimental Data

Atrial Dilatation and Refractoriness

To evaluate the effect of atrial dilatation on atrial refractoriness different animal models have been used. Most of them addressed *acute* dilatation. However, the results are inconsistent. Whereas most models showed a prolongation of atrial refractoriness or action potential duration,[50-53] in others atrial dilatation was associated with a shortening[54;55] or no change of the AERP.[56] Boyden et al. studied *chronic* atrial dilatation both in dogs with surgically induced tricuspid insufficiency (TI) plus pulmonary stenosis and in dogs with mitral valve fibrosis.[57;58] Histology showed hypertrophied cardiomyocytes and increased interstitial fibrosis. TI dogs were more susceptible to induced atrial arrhythmias. Dogs with mitral valve fibrosis had spontaneous atrial arrhythmias. In both studies, action potential duration was not different from control. On the other hand, in dogs with induced chronic mitral regurgitation AERP was prolonged at most sites.[59] In heart failure models, the atria are supposed to be enlarged, too. The action potential duration in cats with cardiomyopathy was prolonged

whereas in the dog model of tachycardiomyopathy AERP did not differ from control.[60;61]

Atrial Dilatation and Conduction Disturbances

Acute atrial dilatation in isolated Langendorff-perfused rabbit hearts induced a slowing of conduction at high rates and an increased heterogeneity in conduction.[62] In cats with cardiomyopathy the maximum rate of phase 0 depolarization (Vmax), the resting potential and the action potential amplitude were reduced.[60] This may cause slow conduction and block, but these parameters were not determined. In dogs with tachycardiomyopathy conduction velocity was normal but heterogeneity of atrial conduction was increased during atrial pacing.[61] Both chronic heart failure models were characterized by extensive interstitial fibrosis, which may account for conduction disturbances.[63]

Aim of the Thesis

Probably, there are different electrophysiological mechanisms that cause the one arrhythmia named atrial fibrillation. Focal and reentrant tachycardias may influence each other, and the particular mechanisms may depend on the underlying disease or condition. *Chapter 2* illustrates this with the case of a 50-year old patient suffering from different atrial arrhythmias. Besides, the case report mentions atrial enlargement due to AF-induced tachycardiomyopathy, which may further stabilize the arrhythmia. This introduces atrial dilatation as the focus of this thesis. Epidemiological end experimental data addressing the possible role of atrial dilatation in the domestication of AF are discussed in *Chapter 3*.

It was the aim of this thesis to examine the role of slowly progressive atrial dilatation in the development of a substrate for AF. Chronic complete AV block was used to enlarge the atria. Its effect on the stability of AF, neurohormones, atrial refractoriness, conduction velocity and microscopic structure is reported in *Chapter 4*. *Chapter 5* describes the differential effect of AF-induced electrical remodeling on dilated versus non-dilated atria. It illustrates that depending on the substrate different types of AF can exist.

Interestingly, chronic complete AV block as a model of chronic atrial dilatation appeared to impair atrial contractility. Therefore, the model was further used to investigate this “dilated atrial cardiomyopathy”. *Chapter 6* addresses the underlying mechanisms by reporting *in vivo* and *in vitro* measurements.

Finally, clinical implications of load-induced atrial remodeling are discussed in *Chapter 7*, including new antiarrhythmic strategies derived from basic mechanistic insights.

The Model

It seems impossible to study the effect of chronic atrial dilatation on the substrate for AF separate from other factors. Atrial enlargement has to be induced by any intervention and thus may simply be an epiphenomenon.

Nevertheless, we tried to develop a model of progressive atrial dilatation that is relatively "pure". We aimed to preserve ventricular pump function and to leave the heart structurally as intact as possible. Furthermore, atrial size, atrial electrophysiology, and neurohumoral parameters should be measured in awake animals. Starting with normal atria, we determined these parameters repetitively during progressive dilatation. Finally, epicardial mapping of the atria was performed.

Chronic complete AV block seemed a suitable dilatation model. From previous studies in the dog it had been known, that the low rate of an idioventricular rhythm stimulates an increase in stroke volume to maintain cardiac output. This represents a volume-overload per beat. The ventricles hypertrophy, and their contractility is increased or at least preserved.[64-66] We expected the same to occur in the atria. AV block can be induced reproducibly by radiofrequency ablation of the His-bundle. Except the first goat (in which ablation directly induced fatal ventricular fibrillation) we could achieve complete AV block in all cases.[*)]

For follow-up measurements, an endocardial instrumentation was developed (Chapter 3, Figure 1), because the caprine anatomy does not allow reliable transthoracic echocardiography. Piezoelectric crystals were mounted with silicone on the tip of pacemaker leads. One of these modified leads was implanted in the interatrial septum, another in the lateral wall of the right atrium. The crystals were used as ultrasound transmitters and receivers to calculate the distance between both lead tips (traces in Figure 1, Chapter 3). The implantation was technically challenging and the particular implantation site varied considerably from goat to goat. However, because of the fixed positions of the crystals and the high spatio-temporal resolution, the intra-individual measurements were highly reproducible. Relative changes in the distance of the lead tips were assumed to be proportional to changes in "the" atrial diameter. To obtain additional atrial electrograms, lateral electrodes were made from silver wire and placed between the crystals at the lead tip.

[*)] As expected, during slow idioventricular rhythm QT time increased. This facilitates ventricular arrhythmias (Torsades de pointes).[67] In the sacrifice experiments, we lost some goats due to ventricular tachycardia and subsequent ventricular fibrillation (VF) during induction or the first 15 minutes of anesthesia. Interestingly, defibrillation was mostly not successful, neither transthoracically nor epicardially. Rarely, a regular rhythm could be restored for a few beats, but in all cases, VF was spontaneously reinitiated.

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CHAPTER 2

Atrial Tachycardia, Atrial Flutter, Atrial Fibrillation: Curative Therapy by Focal Ablation in a Pulmonary Vein

Hans-Ruprecht Neuberger, Christian Mewis, Ralph F. Bosch, Matthias Gass, Volker Kühlkamp

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Summary

We describe the case of a 50-year-old woman with the clinical diagnosis of cardiomyopathy associated with supraventricular tachycardia refractory to pharmacological treatment. The totally irregular rhythm was the result of different episodes of atrial tachycardia, atrial flutter and atrial fibrillation that could be identified in the surface-ECG. These findings and the patient's symptoms were all caused by a single focal tachycardia originating from the left upper pulmonary vein. Ablation of this focus represented a curative antiarrhythmic therapy and restored normal ventricular function. Thus, an ablation of the AV node with consecutive pacemaker implantation could be prevented.

Zusammenfassung

Wir beschreiben den Fall einer 50-jährigen Patientin mit der klinischen Diagnose einer Kardiomyopathie bei medikamentös therapierefraktärer Tachyarrhythmia absoluta. Deren elektrokardiographisches Korrelat bestand aus Episoden mit atrialer Tachykardie, Vorhofflattern und Vorhofflimmern. Die Symptome und Befunde ließen sich allesamt ursächlich auf eine fokale Tachykardie mit Ursprung in der linken oberen Pulmonalvene zurückführen. Ihre erfolgreiche Ablation stellte eine kurative antiarrhythmische Therapie dar, die auch zur Normalisierung der Ventrikel-Funktion führte. Eine AV-Knoten-Ablation mit Schrittmacher-Implantation konnte so vermieden werden.

Einleitung

Nachdem in der kurativen Therapie des Vorhofflimmerns Medikamente bislang die in sie gesetzten Erwartungen nicht erfüllen konnten, sind interventionelle Ansätze in den Mittelpunkt des Interesses gerückt. Dazu werden zwei Konzepte verfolgt: Zum einen soll die Aufrechterhaltung von Vorhofflimmern verhindert, zum anderen sollen die Auslöser der Arrhythmie ausgeschaltet werden. Um erstgenanntes zu erreichen, wird durch relativ aufwändige Maze-Prozeduren im weiteren Sinne (lineare Läsionen durch Operation oder perkutane Katheterablation) die Größe elektrisch zusammenhängenden Vorhofmyokards reduziert, um so die Zahl gleichzeitig möglicher funktioneller Kreiserregungen zu verringern. Das zweite Therapiekonzept versucht dagegen, Auslöser von Vorhofflimmern (wie einzelne atriale Extrasystolen, atriale Tachykardien oder Vorhofflattern) durch perkutane Katheterablation minimal-invasiv auszuschalten. In diesem Zusammenhang sind insbesondere die Pulmonalvenen in letzter Zeit als häufige Lokalisation ektoper Foci genannt worden.[2,3]

Wir beschreiben im folgenden den Fall einer Patientin mit medikamentös therapierefraktärer Tachyarrhythmie und Tachykardiomyopathie bei verschiedenen Vorhofrhythmusstörungen, deren Zusammenhänge und gemeinsame kurativ-interventionelle Therapie wir exemplarisch erläutern.

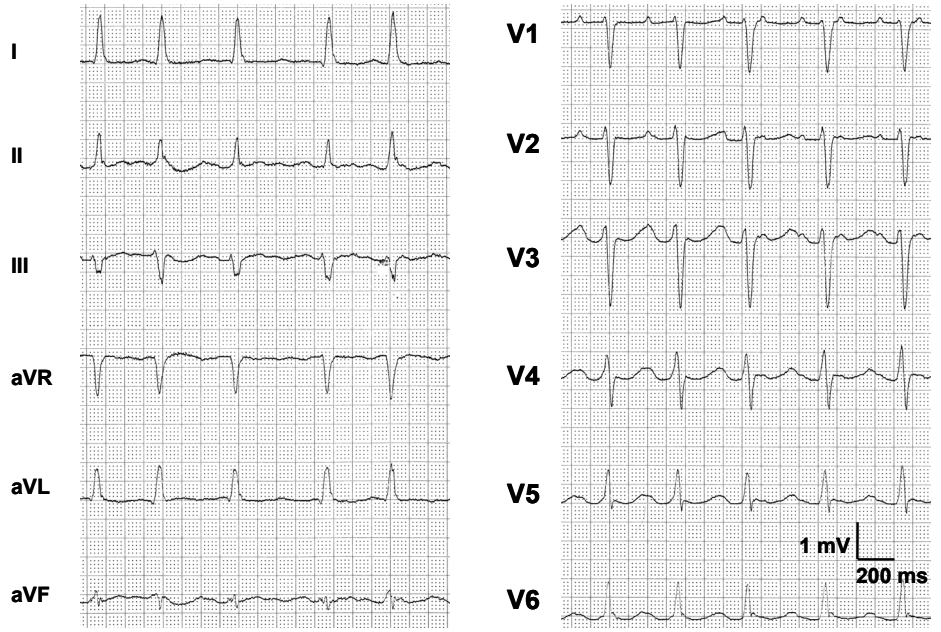

Abbildung 1
12-Kanal-Oberflächen-EKG bei Aufnahme. P-P-Intervall um 200 ms (s. V1) mit wechselnder Überleitung auf die Kammern.

Kasuistik

Bei einer 50-jährigen Patientin war anlässlich des Hausarztbesuchs aufgrund eines akuten Infekts der oberen Atemwege eine Tachyarrhythmia absoluta aufgefallen, die intermittierend und jeweils nur kurz anhaltend bereits seit 3 Jahren bestanden hatte. Nach Aufnahme in ein regionales Krankenhaus war Vorhofflimmern diagnostiziert und bei Vergrößerung des linken Herzens, eingeschränkter Globalfunktion und arterieller Hypertonie eine orale Antikoagulation begonnen worden. Unter einer hoch dosierten Therapie mit Metoprolol, versuchsweise in Kombination mit Verapamil, traten jedoch Kammerfrequenzen bis 200/min im Wechsel mit symptomatischen Bradykardien auf. Die Verlegung in unsere Klinik erfolgte zur AV-Knoten-Ablation und Herzschrittmacher-Implantation wegen therapierefraktärer Tachyarrhythmie bei Vorhofflimmern.

Aufnahmebefund

Die 50-jährige Patientin ist 162 cm groß und wiegt 101 kg. Die Lungen sind auskultatorisch unauffällig. Die Herzaktion ist unregelmäßig bei einer Frequenz um 160/min; es besteht ein Pulsdefizit der A. radialis. Herzgeräusche sind nicht auskultierbar; der Blutdruck beträgt 150/90 mmHg.
Im EKG (Abb. 1) besteht unter 200 mg Metoprolol pro Tag eine Tachyarrhythmia absoluta mit Kammerfrequenzen um 160/min bei wechselnd

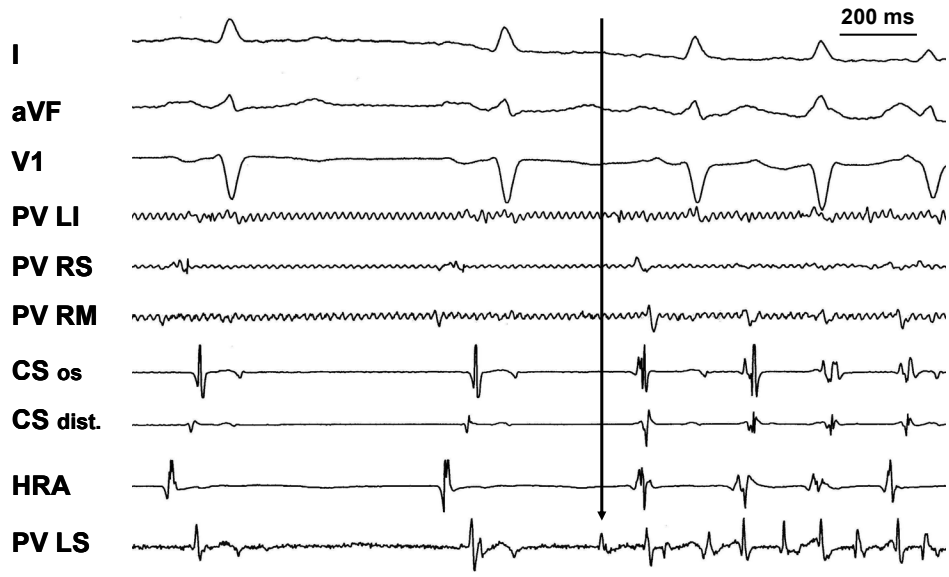

Abbildung 2
Früheste lokale Aktivität zu Beginn einer atrialen Salve in der linken oberen Pulmonalvene (PV LS). PV LI, RS und RM: Bipolare Elektrogramme aus der Pulmonalvene links unten, rechts oben und Mitte. CS os./dist.: proximaler und distaler Sinus coronarius. HRA: hoher rechter Vorhof.

übergeleiteten P-Wellen (s. Ableitung V1, P-P-Intervall 200 ms, in anderen Aufzeichnungen bis 340 ms [nicht dargestellt]). Es findet sich ein horizontaler QRS-Vektor.
Im Verlauf wiederholte EKG-Registrierungen dokumentieren zudem (neben Phasen mit normofrequentem bis bradykardem Sinusrhythmus) eine Tachyarrhythmia absoluta mit Kammerfrequenzen um 120/min bei oszillierender Grundlinie und ohne erkennbare P-Wellen. Bei kurzen R-R-Intervallen tritt eine intermittierende Leitungsaberration mit Linksschenkelblock-, teilweise auch Rechtsschenkelblock-Morphologie auf.
Die Röntgen-Thorax-Aufnahme zeigt einen dilatierten Herzschatten (Herz-Thorax-Relation 17/32 cm) bei im übrigen unauffälligem Befund.
Echokardiographisch findet sich eine grenzwertig reduzierte linksventrikuläre Globalfunktion (FS 20%) mit geringer symmetrischer Hypertrophie (Septum 14 mm) und leichtgradiger Dilatation des linken Ventrikels (LVEDD 57 mm). Es besteht eine geringe Dilatation des linken Vorhofs (43 mm) bei Mitralklappeninsuffizienz I°.
Die Laborwerte liegen einschließlich der Schilddrüsen-Hormone im Normbereich (Ausnahmen: CRP 1,3 mg/dl, INR 3,6).
Während der elektrophysiologischen Untersuchung tritt spontan eine selbstlimitierte Vorhoftachykardie mit Zykluslängen zwischen 240 und 330 ms sowie wechselnder Überleitung auf die Kammern auf. Die früheste Erregung

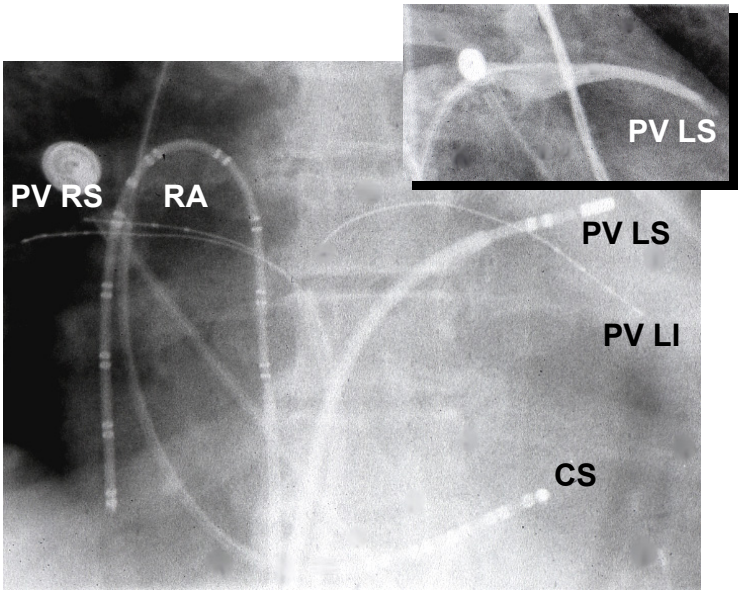

Abbildung 3
Durchleuchtungsbild (p.a.) der Katheterpositionen bei Ablation des Fokus in der linken oberen Pulmonalvene. Kleines Bild: Angiographiebefund der schmallumigen Pulmonalvene nach

während dieser atrialen Tachykardie ist gleichzeitig im hohen rechten Vorhof und im inferioren linken Vorhof (CS-Katheter) abzuleiten. Unterbrochen von nur kurzen Episoden mit Sinusrhythmus münden diese Tachykardiephasen teilweise in Vorhofflattern (A-A 200 ms, 2:1-Überleitung), meist jedoch in Vorhofflimmern, so dass unaufhörlich Vorhof-Rhythmusstörungen vorliegen. Daraufhin erfolgt nach transseptaler Punktion ein Mapping des linken Vorhofs und der Pulmonalvenen. In der linken oberen Pulmonalvene lässt sich konstant bei allen atrialen Extraschlägen, bei atrialer Tachykardie und zu Beginn von Vorhofflimmer-Episoden die früheste Erregung nachweisen (76 ms Vorzeitigkeit zum hohen rechten Vorhof bzw. zum Beginn der P-Welle, s. Abb. 2). Nach 8 Hochfrequenzstrom-Applikationen bei max. 35 W über bis zu 40 s an der Wand des Gefäßes und an dessen Ostium ist kein lokales Signal mehr ableitbar; eine Stenosierung der primär bereits schmallumigen Lungenvene wird angiographisch ausgeschlossen (Abb. 3). Während der Nachbeobachtung von 90 min tritt auch unter Orciprenalin (bis 2,5 mg/h) keine einzige atriale Extrasystole mehr auf; es besteht durchgehend Sinusrhythmus.

Verlauf

Bei der ambulanten Vorstellung sowohl 6 Wochen als auch 6 Monate nach erfolgreicher Ablation ist die Patientin beschwerdefrei; Herzrasen sei nie wieder aufgetreten. Das Langzeit-EKG dokumentiert über 24 h durchgehenden Sinusrhythmus. Echokardiographisch ist eine Normalisierung der

linksventrikulären Funktion (FS 34%) und des linksventrikulären Diameters (LVEDD 55 mm) festzustellen. Die adipöse Patientin ist bis 150 W (Erreichen der Zielfrequenz von 171/min) ohne Beschwerden oder signifikante EKG-Veränderungen belastbar.

Diskussion

Schlüssel zum Verständnis der unterschiedlichen Arrhythmien und des Krankheitsverlaufs der Patientin ist eine rezidivierende fokale atriale Tachykardie mit Ursprung in einer Pulmonalvene. Darin findet sich in interindividuell unterschiedlichem Ausmaß Vorhofmyokard,[6] das das Substrat solcher Foci darstellen kann. Berichte aus jüngster Zeit weisen zunehmend häufig darauf hin, dass in Pulmonalvenen für die Induktion aber auch den Unterhalt von Vorhofflimmern wichtige Arrhythmien entstehen können.[2-4] Die atriale Tachykardie hielt im genannten Fall über längere Zeiträume an, rezidivierte häufig und induzierte klinisch wie auch während der elektrophysiologischen Untersuchung Vorhofflattern. Diese im allgemeinen aus einer einzigen Erregungswelle bestehende Makro-Reentrytachykardie hielt über die Terminierung der fokalen Tachykardie hinaus an, um schließlich spontan zu sistieren. Letztere bedingte allerdings noch häufiger Vorhofflimmern, das ebenfalls unabhängig vom Auslöser für eine gewisse Zeit sich selbst unterhielt und mit multiplen gleichzeitigen funktionellen Erregungskreisen vereinbar ist.[5,1] Anamnestisch hielt dies im zeitlichen Verlauf immer länger an, was als Folge des atrialen „remodeling“ anzusehen ist („Atrial fibrillation begets atrial fibrillation“).[8] Schließlich bestand eine unaufhörliche Tachyarrhythmie bei einem Wechsel zwischen atrialer Tachykardie, Vorhofflattern und Vorhofflimmern, die zu einer Tachykardiomyopathie mit eingeschränkter Pumpfunktion und geringer Dilatation der Herzhöhlen führte.[7] Medikamentöse Versuche, die AV-nodale Überleitung zu bremsen, blieben erfolglos, so dass bei Verlegung der Patientin zu uns eine AV-Knoten-Ablation vorgeschlagen wurde. Die Interpretation der (schließlich invasiv diagnostizierten) fokalen atrialen Triggerarrhythmie als Ursache der übrigen Befunde ließ im weiteren Verlauf jedoch den Schluss zu, dass sich in einem solchen Fall mittels Katheterablation des potenziellen Fokus eine kurative Therapieoption ergibt. Tatsächlich gelang es, durch Ablation eines Pulmonalvenen-Fokus sowohl die atriale Tachykardie als auch Vorhofflattern und Vorhofflimmern, die jeweils klinisch als Tachyarrhythmie und Tachykardiomyopathie in Erscheinung getreten waren, kausal zu behandeln. Der Verlauf bei der elektrophysiologischen Untersuchung wie auch Nachbeobachtungen über 6 Monate zeigten, dass der Erfolg (einschließlich einer Normalisierung der ventrikulären Pumpfunktion) von Dauer war. Zwar liegen bislang keine ausreichenden Daten zu Langzeitergebnissen der fokalen Ablation in Pulmonalvenen vor, so dass die Nutzen-Risiko-Relation dieser relativ neuen Behandlungsmethode derzeit nicht abschließend zu beurteilen ist; dennoch erscheint es als vorteilhaft, bei einer solchen Patientin eine Palliation mittels AV-Knoten-Ablation und

Herzschrittmacher-Therapie durch die perkutane fokale Radiofrequenz-Ablation vermeiden zu können.
Damit unterstreicht der Fall die Bedeutung einer sorgfältigen Interpretation des wiederholt bzw. über einen längeren Zeitraum anzufertigenden Oberflächen-EKGs bei der klinischen Diagnose einer absoluten Arrhythmie.

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CHAPTER 3

The Role of Atrial Dilatation in the Domestication of Atrial Fibrillation

Ulrich Schotten, Hans-Ruprecht Neuberger, Maurits Allessie

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Abstract

Numerous clinical investigations as well as recent experimental studies have demonstrated that atrial fibrillation (AF) is a progressive arrhythmia. With time paroxysmal AF becomes persistent and the success rate of cardioversion of persistent AF declines. Electrical remodeling (shortening of atrial refractoriness) develops within the first days of AF and contributes to the increase in stability of the arrhythmia. However, 'domestication of AF' must also depend on other mechanisms since the persistence of AF continues to increase after electrical remodeling has been completed. During the first days of AF in the goat, electrical and contractile remodeling (loss of atrial contractility) followed exactly the same time course suggesting that they are due to the same underlying mechanism. Contractile remodeling not only enhances the risk of atrial thrombus formation, it also enhances atrial dilatation by increasing the compliance of the fibrillating atrium. In goats with chronic AV-block atrial dilatation increased the duration of artificially induced AF-episodes but did not change atrial refractoriness or the AF cycle length. When AF was maintained a couple of days in these animals, a shortening of the atrial refractory period did occur. However, the AF cycle length did not decrease. Long lasting episodes of AF with a long AF cycle length and a wide excitable gap suggest that in this model AF is mainly promoted by conduction disturbances. Chronic atrial stretch induces activation of numerous signaling pathways leading to cellular hypertrophy, fibroblast proliferation and tissue fibrosis. The resulting electroanatomical substrate in dilated atria is characterized by increased non-uniform anisotropy and macroscopic slowing of conduction, promoting reentrant circuits in the atria. Prevention of electroanatomical remodeling by blockade of pathways activated by chronic atrial stretch therefore provides a promising strategy for future treatment of AF.

Atrial Dilatation as a Risk Factor for Atrial Fibrillation

A relationship between atrial size and atrial fibrillation (AF) has been established already 50 years ago. In 1955 Fraser and Turner showed that left and right atrial enlargement correlated with the incidence of AF in patients with mitral valve disease.[1] Two decades later Henry et al. reported that in patients with valve disease or asymmetric septal hypertrophy AF was rare (3 %) when the left atrial diameter was less than 40 mm, but common (54 %) when it exceeded 40 mm. Furthermore, they found that a left atrial diameter of more than 45 mm predicts a high likelihood of AF recurrence within 6 months after cardioversion. They hypothesized that in these patients a chronic haemodynamic burden resulted in atrial dilatation which in turn increased the propensity to AF.[2] Two further decades later, large prospective trials established left atrial enlargement as an independent risk factor for the development of AF.[3;4] In the Cardiovascular Health Study Psaty et al. included about 5000 participants who were all in sinus rhythm.[5] Left atrial size at baseline was

strongly and independently associated with the incidence of AF during the follow-up of 3 years. In a very recent study left atrial size was (apart from age) even the only predictive parameter for the occurrence of AF in patients with mitral regurgitation. Left ventricular ejection fraction and severity of the regurgitation were not independently associated with AF.[6] According to these data atrial dilatation may be a *cause* of AF, and it was suggested that "interventions that maintain left atrial size may be important in the prevention of AF".[5]

On the other hand, several studies imply that atrial enlargement is also a *consequence* of AF. In 1949 Phillips and Levine reported a series of patients with AF as a cause of reversible heart failure and cardiac dilatation.[7] Probst et al. proposed in 1973 that "gross atriomegaly is an effect rather than a cause of AF in most patients" with mitral stenosis, because a high incidence of left atrial enlargement was seen only in patients with *chronic* AF but not in patients with intermittent AF or sinus rhythm.[8] Keren et al. showed in 1987 that patients with mitral stenosis and sinus rhythm had *normal right* atrial dimensions but an increased left atrial size.[9] In contrast, patients with mitral stenosis and AF as well as patients with lone AF showed significantly enlarged right *and* left atria. Sanfilippo et al. performed in 1990 a small but prospective echocardiographic study in patients with AF, a normal atrial size at baseline and no evidence of other cardiac abnormalities. After an average time of 20.6 months left and right atrial volume was significantly increased.[10] Recently the investigators of the Stroke Prevention in Atrial Fibrillation (SPAF) trials estimated that the independent contribution of AF (> 1 year) to the increase in left atrial diameter is about 2.5 mm.[11]

It should be noted, that none of the above-mentioned studies established a *causal* relationship between atrial dilatation and AF. Both could be surrogates for one and the same underlying condition. Nevertheless, these studies suggest that atrial dilatation and AF are mutually dependent.

Positive Feedback Loops during Atrial Fibrillation

In the 90s several experimental investigations addressed the self-perpetuating and progressive nature of AF. In a dog model of prolonged rapid atrial pacing Morillo et al. found that the atrial refractory period was reduced by about 15%.[12] In the goat, Wijffels et al. maintained AF by a fibrillation pacemaker automatically delivering bursts of stimuli (1 second, 50Hz) as soon as sinus rhythm occurred.[13] This resulted in a marked shortening of atrial refractoriness from ~150 to ~80ms (-45%). More importantly, these studies showed that long-term rapid atrial pacing or maintenance of AF led to a progressive increase in the stability of AF. After 6 weeks of rapid atrial pacing, in 82% of the dogs episodes of AF lasting >15 minutes could be induced.[12] In the goat, initially only short paroxysms of AF were induced by burst pacing (mean 6±3 seconds) but after 2 days of AF the paroxysms lasted more than 4 hours and by that time in 2 of 12 animals AF had become sustained (>24hours). After 2-3 weeks in

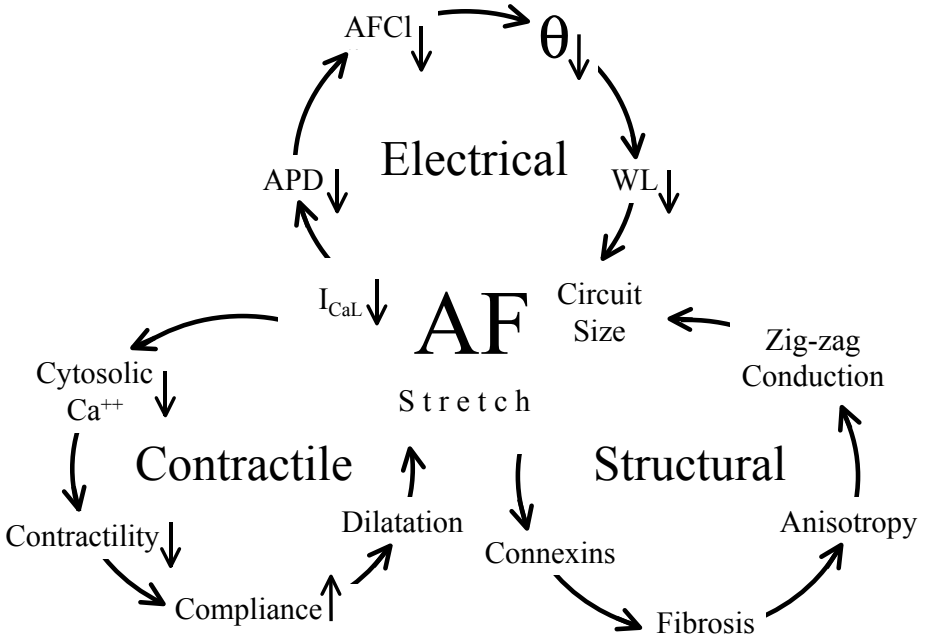

Figure 1
Three proposed positive feedback-loops of atrial remodeling on AF. Reduction of the L-type Ca^{2+} inward current is considered to be the primary cause for electrical and contractile remodeling. The loss of atrial contractility leads to an increase in compliance of the fibrillating atria which in turn facilitates atrial dilatation. The resulting stretch acts as a stimulus for structural remodeling of the enlarged atria. The combination of electrical and structural remodeling allows intra-atrial reentrant circuits of a smaller size, due to a reduction in wavelength (shortening of refractoriness and slowing of conduction) and increased non-uniform tissue anisotropy (zig-zag conduction). Modified from Allessie, 2002.

90% of the goats AF was persistent. This observation of tachycardia-induced electrical remodeling creating a substrate for persistent AF, led to the concept that '*Atrial Fibrillation Begets Atrial Fibrillation*'.[13] The longer duration of the AF episodes was explained by a shortening of the wavelength of the atrial impulse.[14;15] When the wavelength is short, small regions of intra-atrial conduction block may already serve as a site for initiation of reentry, thus increasing the vulnerability for AF. A short wavelength is also expected to increase the stability of AF because it allows more reentering wavelets to coexist on the available surface area of the atria.
However, there are reasons to believe that besides the shortening of refractoriness also other factors play a role in the development of chronic AF. Already in the initial study in the goat model of AF it was noted that the time course of the changes in atrial refractoriness did not run parallel with the increase in persistence of AF. Whereas the AF cycle length reached a new

steady state within 3-5 days, it took an additional 1-2 weeks before AF became persistent.[13] This led to the hypothesis that a so-called 'second factor' was involved in the development of persistent AF.

Therefore, we recently suggested the existence of additional positive feedback loops in AF (Figure 1).[16] While the positive feedback between electrical remodeling and AF is well established, the proposed cascades of contractile and structural remodeling are still partly hypothetical. Structural remodeling has been demonstrated to occur as a consequence of AF but is also believed to promote the arrhythmia. Also, changes of the mechanical properties of the atria might contribute to the domestication of AF. AF induces a pronounced contractile dysfunction of the atria[17;18] which might increase atrial compliance and size. As explained above clinical observations suggest that increased atrial size might in turn promote AF. Recently, we tried to verify this hypothetical contractile feedback loop in the goat model of AF. The following two paragraphs will describe time course and extent of the AF-induced atrial contractile dysfunction in these animals, the subsequent changes in atrial compliance and size, and the effect of chronic atrial dilatation on the electrophysiological properties of the atria and the stability of AF.

Atrial Dilatation as a Consequence of Atrial Fibrillation

We recently evaluated the effects of AF on atrial contractility, compliance, and size in the goat model of AF.[19] The animals were instrumented with epicardial electrodes and ultrasonic piezoelectric crystals to measure the medio-lateral diameter of the atrium. A tip pressure transducer was implanted in the right atrium via the right jugular vein. AF was induced by burst pacing as soon as sinus rhythm (SR) was detected.[13] During 5 days of artificially maintained AF changes in atrial pressure, contractility, compliance and size were followed. After spontaneous cardioversion the recovery of atrial contractility and dimensions was studied for 5 days in SR.

Right atrial pressure diameter loops were obtained by plotting right atrial pressure against its medio-lateral diameter. The area enclosed by these surrogate PV-loops reflects the work performed by the atrium and is referenced to as the atrial work index (AWI). Figure 2 shows right atrial PV-loops recorded during slow atrial pacing at a cycle length of 400ms. During the 5 days of AF the area enclosed by the loop (=AWI) progressively declined. After 2 days of AF, AWI was reduced by ~75%, and after 5 days the loop was almost closed indicating that the atrial contractile function was nearly completely abolished. After resumption of SR, atrial contractile function completely recovered within 5 days. As expected, AF also shortened the atrial effective refractory period (AERP). The AERP declined from ~140ms before the induction of AF to ~85ms after 5 days of AF. Interestingly, contractile remodeling (reduction of the atrial work index) and electrical remodeling (shortening of AERP) followed exactly the same time course. Since the main cellular mechanism responsible for electrical remodeling is the reduction of the L-type Ca^{2+} inward current

(I_{CaL})[20] it is likely that atrial contractile dysfunction during the first 5 days of AF is also due the reduction of I_{CaL}.

To quantify atrial contractility during AF the amplitude of the right atrial pressure waves during AF was measured. After 5 days of AF the amplitude of the pressure waves and the atrial wall excursions during AF were reduced to less than 15%. This clearly indicates that the loss of atrial contractility is not only present when assessed during SR or slow atrial pacing. Also, the contractility of the *fibrillating* atrium is markedly reduced after a couple of days in AF. After resumption of SR, also the atrial contractility during brief episodes of AF also recovered completely within 3 days of SR.

To study the effect of the loss of atrial contractility on the compliance of the fibrillating atrium, pressure and diameter were measured after unloading the atria with a fast acting loop diuretic and after loading the atria with 1L saline infused within 10min.[21] In Figure 3 representative compliance curves during baseline (acute AF), after 3 days, and after 5 days of AF are given. The mean atrial pressure (P_{mean}) did not change throughout the experiment. During the first days of AF the compliance curve flattened indicating that the compliance of the atrium increased. This caused a rightward shift of the working point (gray) and the mean atrial diameter (D_{mean}) increased from 24.2 to 26.3 mm. The changes in atrial compliance and size followed the same time course as the loss of contractility of the fibrillating atria and were fully reversible within two days of SR. Administration of the Ca^{2+}-sensitizer EMD 57033 significantly increased the contractility of the fibrillating atria leading to a decrease in atrial compliance and size. This suggests that the increase in atrial size during the first days of AF is mainly due to a loss of contractility of the fibrillating atrium resulting in an increase in atrial compliance.

Echocardiographic studies have shown that atrial dilatation during AF is a progressive process which may continue for months to years.[10] In contrast, in our experimental studies atrial contractile function was almost completely abolished after a couple of days of AF. Obviously, apart from the loss of atrial contractility, additional mechanisms are operative which cause the atria to dilate during prolonged AF. The loss of atrial contractility will transfer the atrial stretch more to the passive elements of the atrial wall which might lead to elongation of collagen fibres. Synthesis of connective tissue fibres and cellular hypertrophy could also result in a slow increase in atrial dimensions.

Our results emphasize the role of atrial contractile dysfunction for dilatation of the atria. Prevention of the atrial contractile dysfunction during AF thus might be able to delay or even prevent atrial dilatation. Verapamil[22;23] and the Na^+/H^+-exchange inhibitor HOE 642[24] have been shown to prevent atrial hypocontractility following short-lasting AF. However, prevention of the atrial contractile dysfunction during prolonged AF has not been reported yet. Nevertheless, since atrial enlargement decreases the success rate of pharmacological and electrical cardioversion, treatment of contractile remodeling might be a worthwhile therapeutic goal in itself.

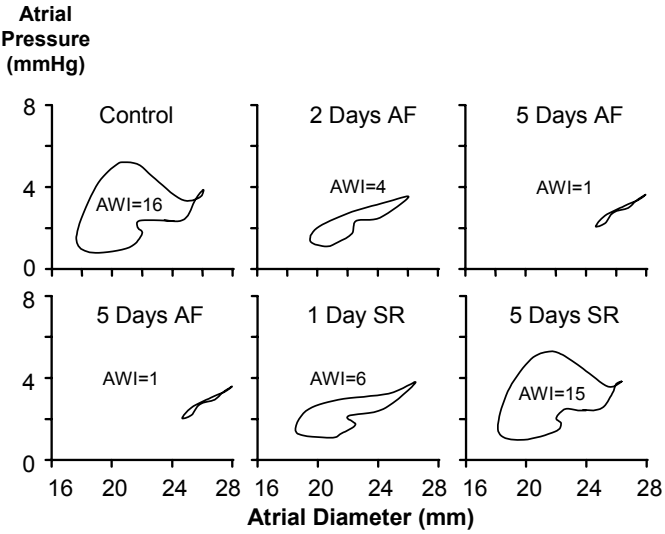

Figure 2
Contractile remodeling of the atria during the first 5 days of AF. Pressure-diameter loops and atrial electrograms of a goat during slow atrial pacing at a cycle length of 400 ms. The atrial work index (AWI) decreased from 16mm*mmHg to 1 mm*mmHg within 5 days of AF. The atrial contractile function was completely restored within 5 days after cardioversion. Modified from Schotten, 2001.

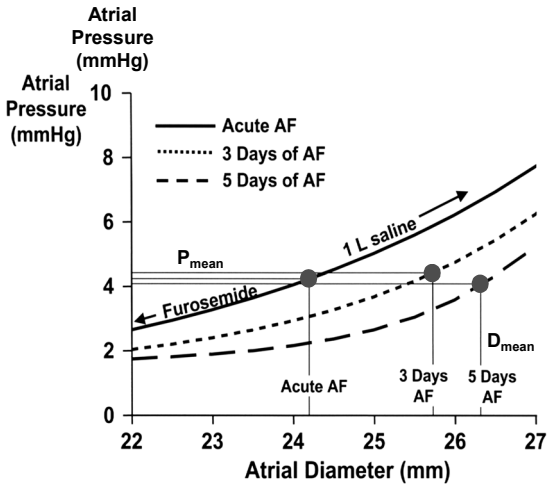

Figure 3
Representative right atrial compliance curves during acute AF and after 3 or 5 days of AF. The compliance was measured by unloading the atria with a rapidly acting loop-diuretic and loading by infusion of 1L saline in 10 min. Due to an increase in atrial compliance at low atrial diameters (flattening of the compliance curve) the working point during AF shifted to the right. P_{mean}=mean atrial pressure. D_{mean}=mean atrial diameter. Modified from Schotten, 2002.

Atrial Dilatation as a Cause of Atrial Fibrillation

The effect of atrial enlargement on atrial electrophysiology was repeatedly addressed during the past two decades. Mostly, the effect of *acute* atrial dilatation on atrial refractoriness and conduction was investigated. These studies, however, revealed conflicting results. Acute atrial dilatation in isolated rabbit hearts or in open-chest dogs resulted in a shortening of atrial refractoriness.[25;26] Others described no change[27] or even a prolongation of the refractory period during acute stretch.[28;29] The only common finding was an increase in the inducibility and persistence of AF.

The first experiments on *chronic* enlargement of the atria were performed in the early 1980s by Boyden et al. In 8 dogs with tricuspid regurgitation and stenosis of the pulmonary artery the right atrial volume increased by 40 % during ~100 days of follow-up. Atrial arrhythmias did not occur spontaneously. However, the inducibility and the duration of artificially induced atrial tachyarrhythmias significantly increased. Atrial refractoriness was not measured, but the duration of action potentials recorded in vitro were not different compared to control. Histological and ultrastructural analysis revealed cardiac hypertrophy and an increase in connective tissue content.[30] In another study in dogs with spontaneous mitral valve fibrosis (MVF) and left atrial enlargement also no change in transmembrane potentials was found.[31] In MVF dogs left atrial volume was six to eight times the left atrial volume of control dogs. In-between the greatly hypertrophied atrial myocytes (17 vs. 10 µm in diameter) a large amount of connective tissue was present. Most MVF animals had spontaneous atrial arrhythmias, but the underlying mechanism could not be defined. The authors speculated that atrial conduction could be impaired. An alternative explanation for the increased stability of AF in chronically dilated atria was provided by Le Grand et al. They demonstrated that in trabeculae from human dilated atria the action potential was shortened and the plateau was markedly depressed. In isolated cells of dilated atria the Ca^{2+} inward current was reduced.[32]

To describe the chronological sequence of progressive atrial dilatation and its correlation with alterations in atrial electrophysiology, we studied goats with chronic complete AV block.[33] Six goats were instrumented with modified screw-in leads with two sonomicrometer crystals attached to the tip. Two of these modified leads were placed in the right atrium, one in the anterolateral and one in the posteroseptal wall. With the ultrasound crystals the distance between the lead tips could be measured as an index of the atrial diameter. Two weeks after instrumentation the mean atrial diameter and the atrial effective refractory period (AERP) were measured. AF was induced by 50 Hz burst pacing and both, the duration of AF episodes (AFD) and the AF interval (AFCL) were determined. After these control measurements the His bundle was ablated and the goats were left in a slow idioventricular rhythm. The atrial diameter, AERP, AFD and AFCL were determined weekly during 4 weeks.

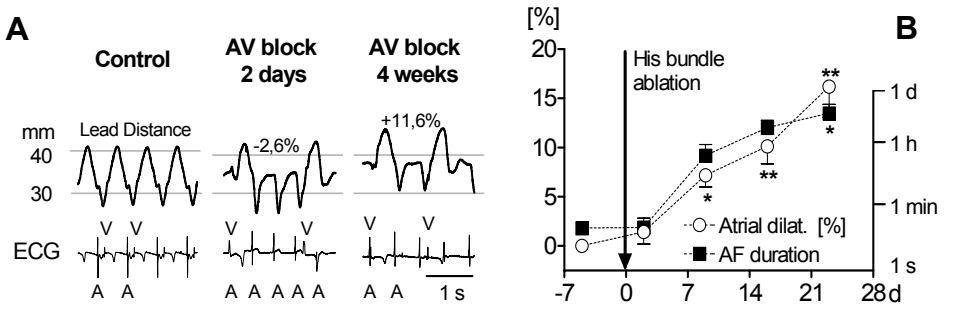

Figure 4

A: A representative example of traces obtained from goats endocardially instrumented with modified atrial leads. Upper trace: Distance between the antero-lateral and the posteroseptal lead in the right atrium measured by ultrasound crystals attached to the lead tip. Lower trace: Unipolar atrial electrogram. Both during control and AV-block the atrial diameter reaches a maximum at the end of the ventricular systole (T-wave) followed by passive and then active atrial emptying. During AV-block single isolated atrial contractions can be recognized during the long diastolic pause. Two days after His bundle ablation the mean diameter is not increased, whereas 4 weeks of AV-block result in a relative dilatation of about 12 % in one dimension.

B: Relative atrial dilatation and duration of induced AF episodes during control and 4 weeks of chronic complete AV block in 6 goats. From Neuberger, 2002.

Figure 4A (left panel) shows an atrial electrogram together with the changes in atrial diameter during normal sinus rhythm (Control). The atrial diameter is maximal at the end of the ventricular contraction, followed first by passive and then by active atrial emptying. After His bundle ablation the ventricular heart rate decreased from about 120 to 50 bpm. Mean atrial and end-diastolic ventricular pressures acutely increased by ~5mmHg but remained constant during 4 weeks of AV block. Within the first days in AV block the atrial diameter did not change (Figure 4A, mid panel). However, 4 weeks after the ablation, the atrial diameter was increased by ~12%. Together with atrial dilatation the duration of AF paroxysms increased from a few seconds during control to several hours (Figure 4B). Since the AERP and AFCL kept constant throughout 4 weeks of complete AV block, the increased persistence of AF could not be explained by a shortening of AERP. Studies in humans with bi-atrial dilatation even showed a longer AERP compared to control,[34;35] and animal models of rapid pacing induced heart failure and atrial dilatation demonstrated either a prolongation of the AERP[36;37] or no change.[38] Possibly, the enlarged atria simply allow more re-entrant circuits to coexist, which increases the stability of AF.

An interesting finding in the goats with chronic AV block was that AF-induced electrical remodeling (shortening of AERP) was not associated with a shortening of the mean AFCL (Fig. 5, left panel). First, this demonstrates that electrical remodeling still occurs in dilated atria. Unlike recent reports in a dog model of heart failure,[39] the time course and the extent of tachycardia induced electrical remodeling in AV block goats were similar to control suggesting that

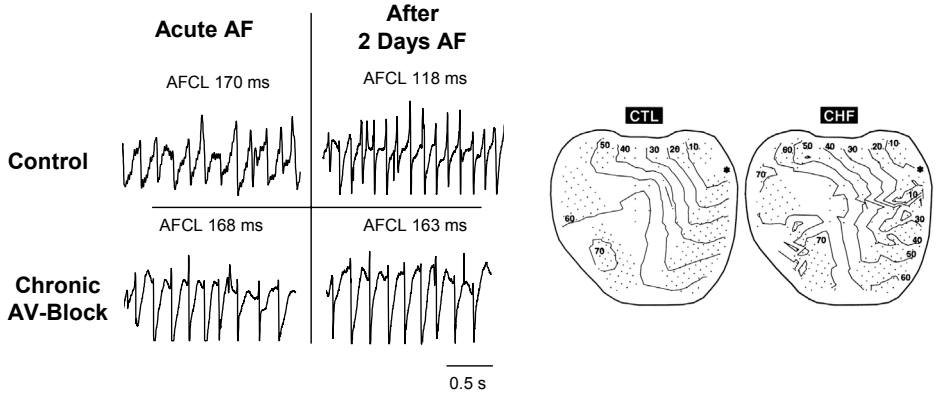

Figure 5
Left panel: A representative example of unipolar endocardial atrial electrograms obtained from a goat after induction of AF by burst pacing. Under control conditions (conducting AV node, upper panels) the median AF interval and the AERP shorten during 2 days of AF. During chronic complete AV block (lower panels) AF maintenance during 2 days still reduces AERP, but AFCL keeps constant. This indicates a widening of the excitable gap during electrical remodeling in the AV block goat.
Right panel: Activation map of the left and right atrium in a dog with tachycardiomyopathy. Left: Control. Right: Dog with heart failure (rapid ventricular pacing for 6 weeks). Crowding of isochrones indicates local slowing of conduction. Modified from Li, 1999.

the same mechanisms are also operating in dilated atria. Secondly, a shortening of the AERP without a concomitant shortening of AFCL means that the excitable gap during AF becomes wider. This observation may be explained by lines of conduction block resulting in macroreentrant circuits during AF as described in a dog model of mitral regurgitation.[40] In dogs with cardiomyopathy and pronounced atrial dilatation, a prolonged AFD and discrete regions of slow atrial conduction were found (Figure 5, right panel). Atrial myofibres were separated by thick layers of connective tissue which may cause local conduction block during AF.[38]
Although the causal relationship has not been established yet, all these experimental results indicate that impairment of atrial wavefront propagation can be a consequence of atrial dilatation and thereby stabilises AF.

The Role of Mechanoelectric Feedback in the Generation of the Substrate of AF

The original concept of mechanoelectrical feedback described electrophysiological changes induced by acute stretch. These alterations included changes of the action potential duration, a decrease in the resting diastolic potential, the occurrence of early afterdepolarisations and the generation of ectopic beats.[41] They are mediated by the activation of mechano-sensitive channels and might provoke stretch-induced arrhythmias by changes in excitability and refractoriness or the occurrence of ectopic activity.

A different kind of mechano-electric feedback may be induced by chronic stretch. Chronic stretch has been demonstrated to activate numerous intracellular signaling pathways including the mitogen-activated protein kinase pathway (MAPK), the janus kinase/signal transducers and activators of transcription pathway (JAK/STAT) as well as Ca^{2+}/calmodulin dependent pathways.[42] Stretch also stimulates local secretion of angiotensin II, which together with other growth factors, causes activation of various second messengers systems.[43] These signaling pathways are known to promote cellular hypertrophy, to stimulate fibroblast proliferation, and to activate matrix protein synthesis leading to tissue fibrosis.[44] In fibrotic myocardium conduction velocity is slowed by microscopic zigzagging circuits or depressed propagation in branching muscle bundles.[45] Such an electroanatomical substrate will allow multiple small reentrant circuits which will stabilize the arrhythmia.[46] Multiple entry and exit points and multiple sites at which unidirectional block occurs will shift the balance between generation and extinction of wavelets more to the favor of generation of new wavefronts. Also, tissue fibrosis will tend to increase electrophysiological dispersion.[47] While the scarred matrix will transfer stretch primarily to the adjacent atrial myocardium, other regions might even become shielded by surrounding strands of connective tissue. Unequal atrial stretch has been shown to affect the local refractory period differentially depending on the degree of elongation of the atrial muscle fibers.[28] Therefore, tissue fibrosis will not only increase anisotropy in conduction but also dispersion in refractoriness. Cellular hypertrophy increases the complexity of the substrate even more since in hypertrophied myocytes smaller mechanical stimuli are sufficient to activate stretch-activated channels.[48]

Finally, the development of such an electroanatomical substrate would also explain the loss of efficacy of drugs to cardiovert AF. In discontinuous tissue the safety-factor for conduction is higher than in normal tissue.[49] Thus, a higher degree of I_{Na}-blockade is required to terminate AF. Anatomical obstacles might widen the excitable gap during AF making drugs that prolong atrial refractoriness less effective.[50] Also, multiple sites at which unidirectional block occurs might facilitate reinduction of AF immediately after cardioversion by early premature beats.

Therefore, new experimental strategies more focus on the prevention of structural remodeling. Recently, the ACE-inhibitor enalapril has been shown to attenuate atrial fibrosis and conduction disturbances in dogs with rapid pacing-induced heart failure.[51] This observation supports the hypothesis that the activation of the renin-angiotensin system is involved in the signalling cascade leading to atrial cell growth, proliferation of fibroblasts and atrial fibrosis. Also, in clinical trials ACE-inhibitors proved to be effective against AF in patients with heart failure[52] or left ventricular dysfunction after myocardial infarction.[53] While this effect might be explained by an improvement of the patients hemodynamics a recent trial with the angiotensin receptor blocker irbesartan showed that blockade of the renin-angiotensin system can reduce the recurrence

rate of AF in a heterogeneous patient population with less diseased hearts.[54] However, since in structurally remodeled atria mechanical strain is heterogeneously transferred to the atrial myocytes, more detailed studies on the role of mechano-sensitive channels for the perpetuation of AF would certainly be worthwhile.

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CHAPTER 4

Development of a Substrate of Atrial Fibrillation during Chronic Atrioventricular Block in the Goat

Hans-Ruprecht Neuberger, Ulrich Schotten, Sander Verheule, Sabine Eijsbouts, Yuri Blaauw, Arne van Hunnik, Maurits Allessie

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Abstract

Atrial dilatation is an important risk factor for atrial fibrillation (AF). In the present study we monitored the electrophysiological changes during progressive atrial dilatation in chronically instrumented goats.

Methods: In 8 goats 2 screw-in leads with piezoelectric crystals were implanted transvenously in the right atrium (RA). After 2 weeks atrial diameter and effective refractory period (AERP) were measured. AF paroxysms were induced by burst pacing to determine the baseline AF cycle length (AFCL) and stability of AF. After His-bundle ablation the above measurements were repeated once a week. After 4 weeks of complete AV-block the free wall of the right atrium was mapped and the atrium was fixed in formalin for histological analysis.

Results: After His-bundle ablation the ventricular rate decreased from 113.8±4.8 to 44.6±2.5 beats/min. RA diameter increased gradually by 13.5±3.9% during 4 weeks of AV-block ($p<0.01$). The duration of induced AF paroxysms increased from 4.6s to 6.4min ($p<0.05$). AERP and AFCL remained constant. Spontaneous paroxysms of AF were not observed. Atrial mapping during rapid pacing revealed that slow conduction (<30cm/s) was present in 3.7±1.0% of the mapped area (control 0.9±0.5%, $p<0.05$). Histological analysis showed hypertrophy without atrial fibrosis. Connexin40 and 43 expression was unchanged.

Conclusions: Chronic AV-block in the goat leads to progressive atrial dilatation, prolongation of induced AF-paroxysms and local conduction delays. The increase in AF-stability was not due to a shortening of atrial refractoriness or atrial fibrosis.

Introduction

Large prospective clinical trials have shown that chronic atrial dilatation is an important and independent risk factor for the development of atrial fibrillation.[1] Furthermore, spontaneous conversion of AF to sinus rhythm is less likely to occur in enlarged atria.[2] However, the mechanisms by which atrial dilatation creates a substrate for AF are largely unknown. First, an increase in atrial surface per se may allow more reentrant circuits to coexist. Second, a shortening of the wavelength due to a shortening of the AERP and/or a reduced conduction velocity would augment the number of waves that can be present simultaneously. Third, inhomogeneities in atrial refractoriness or conduction could stabilize the arrhythmia. Finally, stretch-induced focal activity could induce or perpetuate AF in dilated atria.

In the present study we used a goat model of chronic complete AV-block to produce progressive dilatation of the atria. Chronic endocardial instrumentation allowed to follow the time course of atrial dilatation and the associated electrophysiological changes. The development of a substrate of AF was monitored by measuring the duration of electrically induced paroxysms of AF.

Methods

Animal Model

Twenty-two female goats weighing 53.6±2.7kg were used for this study. Six non-instrumented goats in sinus rhythm served as a control group. In 8 non-instrumented goats chronic AV-block was made for mapping studies and to measure RA and LA size. In 8 goats two bipolar screw-in leads with a pair of piezoelectric crystals mounted at their tips were implanted through the jugular vein in the anterolateral and posteroseptal wall of the RA (Figure 1). Two silver electrodes (1.2x4mm) between the crystals served to record a bipolar atrial electrogram. A third unmodified lead was screwed into the right ventricular apex. Two weeks after lead implantation atrial diameter and baseline electrophysiological and neurohumoral parameters were measured in the awake state. Two days later the animals were anaesthetized again and the His-bundle was ablated by radiofrequency energy. This resulted in a slow idioventricular rhythm between 38 and 66bpm. Hemodynamic parameters were determined immediately before and after His-bundle ablation. RA, LV, aortic and pulmonary wedge pressures were measured by a Swan-Ganz catheter. Cardiac output was measured by thermodilution. The mean atrial diameter was measured weekly during 5 consecutive ventricular cycles (Figure 1). Plasma samples were taken at 9 a.m. 30min after insertion of a cannula in a hind leg vein for determination of noradrenaline, atrial natriuretic factor (ANF), angiotensin II and aldosterone.

Electrophysiological Measurements

Atrial effective refractory period (AERP) was measured at pacing intervals of 400, 300 and 200ms at the anterolateral wall of the RA. Single premature stimuli (4x threshold) were interpolated after every fifth interval, starting at a coupling interval shorter than the AERP. The longest coupling interval (steps 2ms) not resulting in a propagated response was taken as the AERP. The first propagated response was used to test the inducibility of AF (>1s). AF stability was expressed as the mean duration of AF paroxysms repetitively induced by burst pacing (50Hz; 1s; 4 x threshold) during 1 hour. If a single episode lasted >1h the measurement was terminated. Median AF cycle length (AFCL) was determined from >100 consecutive AF intervals. After 4 weeks of AV-block the animals were anaesthetized again (thiopental 10-15mg/kg i.v.; halothane 1% and a 1:2 mixture of O_2 and N_2O) and the heart was exposed by a left thoracotomy. Spatial dispersion of atrial refractoriness was determined by measuring the AERP (pacing interval 350ms) at 9 different sites, both at the free wall of the right and left atrium and at Bachmann's bundle. To analyze atrial conduction, a spoon-shaped mapping electrode (diameter 4cm; 234 unipolar electrodes; interelectrode spacing 2.4mm) was placed on the RA free wall.[3] To measure atrial conduction during sinus rhythm and atrial pacing (400, 300 and

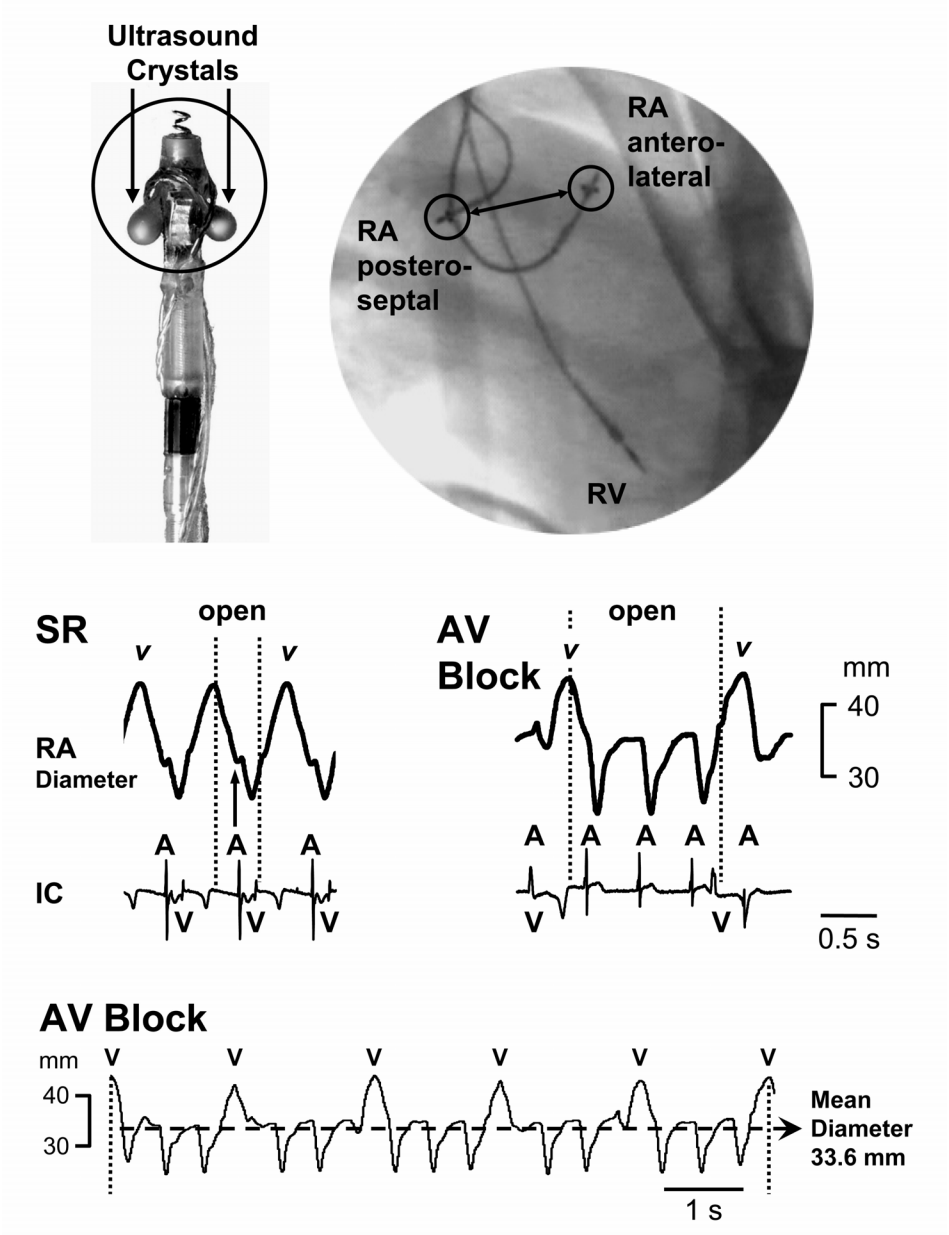

Figure 1
Top: A modified bipolar screw-in lead with a pair of ultrasound crystals mounted at the tip. *Middle:* Changes in RA diameter during sinus rhythm and AV-block together with a unipolar atrial electrogram. *Bottom:* Variations in RA diameter during 5 consecutive ventricular cycles (mean atrial diameter 33.6mm). SR: sinus rhythm; RA: right atrium; RV: right ventricle.

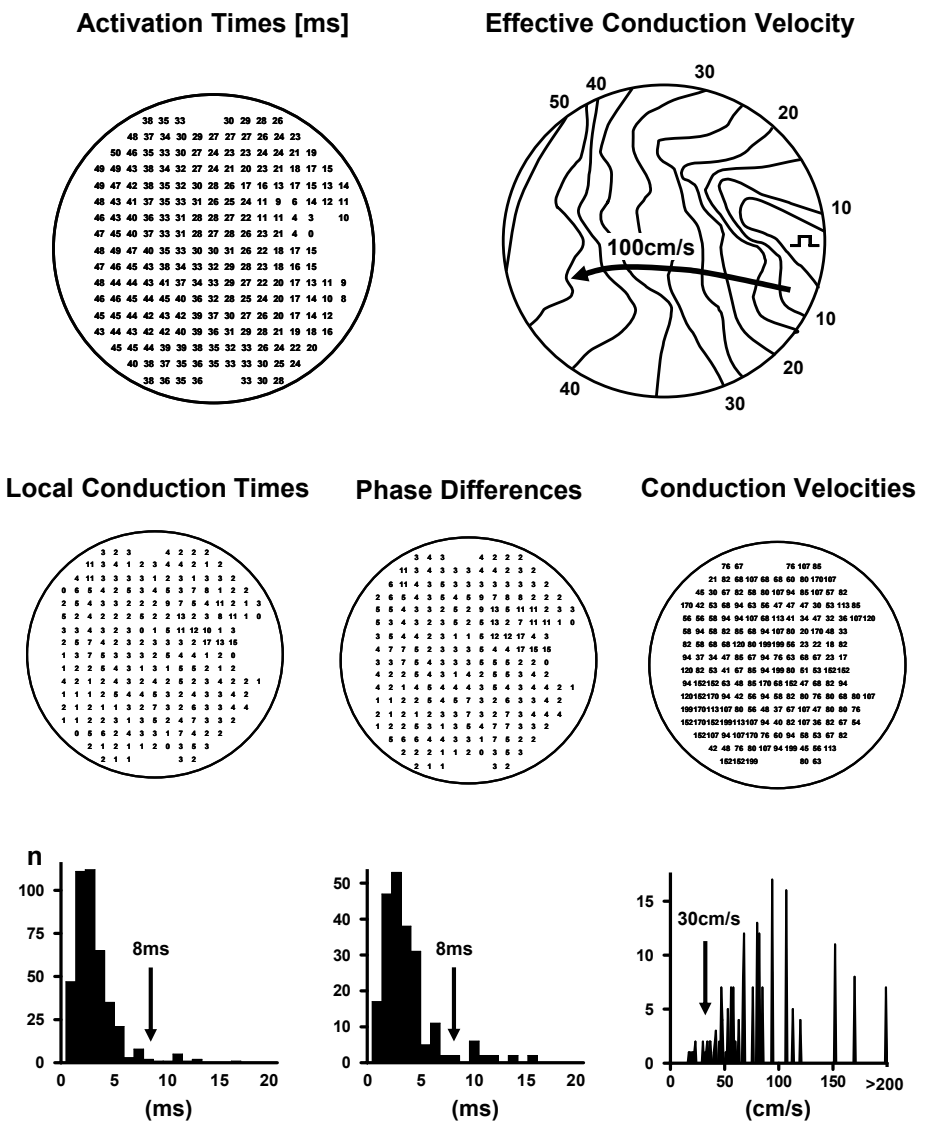

Figure 2
Different methods to quantify atrial conduction. The free wall of the right or left atrium was mapped by an array of 234 electrodes (interelectrode distance 2.4mm). The effective conduction velocity was determined by drawing an arrow normal to broad and uniformly spaced isochrones (effective CV=length arrow/conduction time). Conduction times (between neighboring electrodes) and the phase differences (largest difference in activation in a square of 4 electrodes) were plotted. [7] The local velocities of conduction were calculated from conduction vectors measured in surface areas of 2.4x2.4mm.[4-6] The amount of heterogeneity in conduction was determined by analysis of the distribution of the conduction times, phase differences and conduction velocities. A conduction time or phase difference >8ms and a conduction velocity of <30cm/s were taken as the lower limit of normal conduction.

200ms) maps from 5 consecutive beats were analyzed. A curved arrow was drawn manually normal to uniformly spaced isochrones across the mapping area. From the length of this arrow and the number of isochrones the effective uniform conduction velocity along that path was obtained (Figure 2). Regions of non-uniform or delayed conduction were excluded. With a second method, local conduction vectors were calculated in areas of 2x2 electrodes, as described by Holm et al.[4] This method *included* local conduction delays and was used to measure spatial heterogeneities in conduction.[5;6] Analysis of 5 consecutive beats resulted in a total of about 1000 local conduction vectors. Although the individual vectors showed considerable variation the histogram of the length of these vectors provided a reliable measurement of local conduction velocity. For comparison with previous studies also the distribution of local conduction times (difference in activation time between neighbouring electrodes) and phase differences (maximal time difference in areas of 2 x 2 electrodes) were measured. The heterogeneity index was calculated from the local phase differences as the p5-p95 divided by the p50.[7]

Histology

The hearts were fixed in buffered formalin and samples from the upper and lower free wall of RA and LA (trabeculated area) were embedded in paraffin. Sections of 4µm were stained with Sirius red (collagen) or a modified azan technique (myocytes). The relative collagen content was determined excluding pericardial, endocardial and perivascular fibrosis.[8] The size of atrial myocytes was measured in cells showing a nucleus in the center and intercalated discs on either side. Connexin40 and connexin43 were visualized in cryosections from the right and left atrial appendages as described elsewhere.[9]

Statistics

Results are given as mean±SEM. The group mean duration of AF episodes is expressed as the geometric mean±geometric SEM. An unpaired *t*-test was used to evaluate differences between groups. Multiple groups were compared by analysis of variance (ANOVA). To correlate atrial size and AF stability, multiple regression was applied treating the subject (goat) as categorical factor using dummy variables.[10] $P<0.05$ was considered statistically significant.

Results

Hemodynamic and Neurohumoral Changes due to AV-block

During 4 weeks of AV-block the body weight of the instrumented goats did not change (53.1±3.5 vs. 51.3±2.9kg). The heart/body weight ratio was higher in the AV-block group (6.9±0.5 vs. 5.5±0.2g/kg, $p<0.05$). The idioventricular rhythm (44.6±2.5bpm, Table 1) did not change significantly during the 4 weeks of AV-block. The atrial rate initially increased from 114±5 to 130±8bpm and returned to baseline values within 4 weeks (107±5bpm).

Table 1: Hemodynamic Characteristics and Atrial Size

	Sinus Rhythm	Acute AV-Block	4 Weeks AV-Block
Atrial Rate (bpm)	113.8±4.8	129.5±7.7	106.8±4.7 #
Ventricular Rate (bpm)	113.8±4.8	44.6±2.5**	53.5±2.7**
Cardiac Output (l/min)	4.05±0.24	2.34±0.54**	2.74±0.27*
Stroke Volume (ml)	35.8±2.5	50.4±10.0	52.2±6.1
Systolic Blood Pressure (mmHg)	147.4±6.1	120.0±11.7	136.8±13.3
Diastolic Blood Pressure	119.0±5.3	78.5±8.2**	93.4±9.4
RAP	4.3±0.6	10.1±2.1**	8.8±0.7*
PCW	5.7±1.3	9.3±1.8	11.1±0.8*
LVEDP	7.7±0.7	14.2±1.7**	12.5±1.2*
RA Diameter (mm)	27.8±4.6	26.6±4.4	31.6±5.5**
RA: Anteroposterior	49.7±2.9		62.3±2.9*
Craniocaudal	25.0±0.4		32.7±0.6**
LA: Anteroposterior	41.5±2.0		53.1±1.9**
Craniocaudal	32.1±1.6		39.6±2.4*
Myocyte Length RA (μm)	84±2		106±7*
LA	92±2		116±7*
Myocyte Width RA (μm)	13.0±0.9		16.4±1.1
LA	13.2±0.8		16.6±1.3

Mean values ± SEM (number of animals: see Methods); *p<0.05, **p<0.01 vs. control; #p<0.05 vs. acute AV-block. RAP: mean right atrial pressure, PCW: mean pulmonary capillary wedge pressure, LVEDP: left ventricular end-diastolic pressure.

Hemodynamic measurements showed an increase in stroke volume by about 40% (Table 1). Cardiac output acutely decreased from 4.1±0.2 to 2.3±0.5L/min and was slightly improved after 4 weeks of AV-block (2.7±0.3L/min). During idioventricular rhythm both systolic and diastolic blood pressure were lower than during sinus rhythm. Left ventricular end-diastolic pressure acutely increased by 6.5mmHg. Also the mean RA and pulmonary wedge pressure increased after His-bundle ablation. These pressures did not rise further during 4 weeks of AV-block, indicating that the animals did not develop progressive heart failure.

In Figure 3 heart rate and plasma-levels of neurohormones are shown. Within the first week of AV block noradrenaline, ANF, angiotensin II, and aldosterone increased about 3-fold. During 4 weeks follow-up none of these neurohormones further increased. The plasma-level of noradrenaline and aldosterone tended to decrease again.

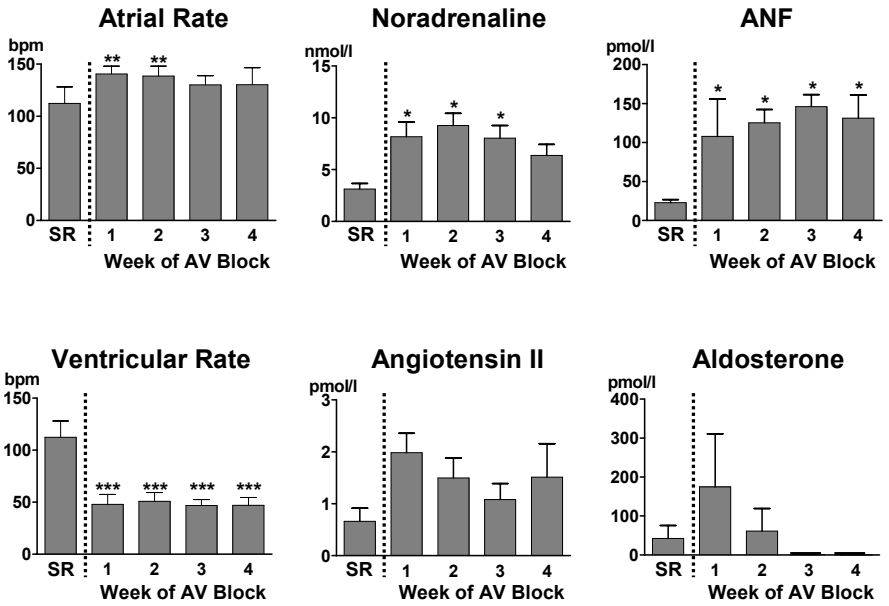

Figure 3
Heart rate and plasma-levels of noradrenaline, ANF, Angiotensin II and Aldosterone before and during the first 4 weeks of AV-block. * P<0.05.

Atrial Dilatation and Duration of AF

In Figure 4 the changes in RA diameter and duration of electrically induced AF paroxysms during the first 4 weeks of AV-block are plotted for all goats. In the first week after His-bundle ablation RA diameter decreased slightly. Thereafter, atrial size progressively increased from 27.8±4.6 to 31.6±5.5mm after 4 weeks of AV-block (+13.5±3.9%; p<0.0001). In one goat (Δ) RA was still not dilated after 4 weeks of idioventricular rhythm. In two others (O and €) the atria only started to dilate in the third week after AV-block. In these goats (Δ-O-€) the duration of AF paroxysms remained short. In animals with marked dilatation AF duration became prolonged to more than one hour. In general, the increase in atrial size was accompanied by an increase in duration of AF (correlation coefficient r=0.53; p<0.001). The low correlation coefficient was mainly due to the high inter-individual variation (lower panels). The inducibility of AF did not change significantly during 4 weeks of AV-block (10.7±7.4% vs. 4.6±2.4%, p=0.32).

To determine whether the left atrium dilated to the same extent as the right atrium, in a separate series of 6 control and 5 AV-block goats the dimensions of the right and left atrial free wall were measured directly after excision of the heart. After 4 weeks of AV-block the anteroposterior dimension of RA and LA had increased by 24 and 29% (p<0.01) and the craniocaudal dimension by 32 and 25% (p<0.001 and p<0.05; absolute values see Table 1). The surface of the right and left atrial wall was enlarged by 64 and 58% (p<0.001 and p<0.01).

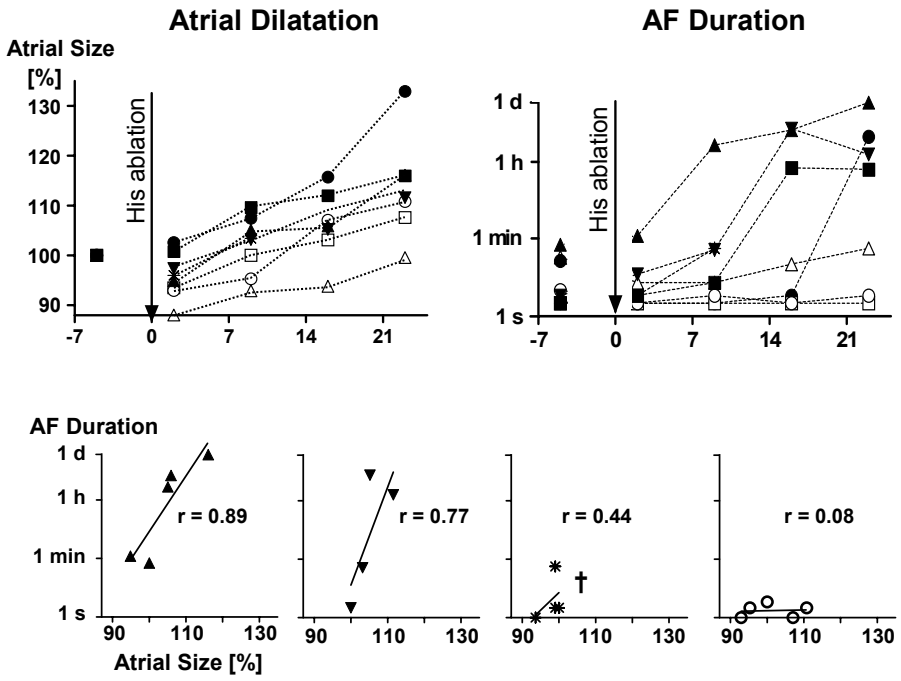

Figure 4
Top: Time course of relative changes in atrial size and duration of induced AF paroxysms during 4 weeks of AV-block (8 goats). One goat (⁕) was euthanized at day 15 due to sepsis. *Below:* Individual correlation between atrial size and AF duration for some goats. Overall, the correlation coefficient within subjects is 0.53, $p<0.001$.

There was no difference between the degree of RA and LA enlargement ($p=0.75$).

Atrial Refractoriness

Figure 5 shows the AERP (pacing intervals 400, 300 and 200ms, RA) and AFCL before and after His-bundle ablation. During 4 weeks of slow idioventricular rhythm, the AERP remained constant. Also the differences between $AERP_{400}$, $AERP_{300}$ and $AERP_{200}$, representing the physiological rate adaptation, remained the same. Before His-bundle ablation the median AFCL was 152±10ms, compared to 132±6ms after 1 week and 139±11ms after 4 weeks of AV-block ($p=0.51$). After 4 weeks of idioventricular rhythm the goats (n=7) were anesthetized and the AERP was measured at 9 epicardial sites. The coefficient of spatial variation and the maximal spatial difference in AERP were lower than in the control group (0.14±0.01 versus 0.27±0.04, $p<0.01$ and 49±6ms versus 78±5ms, $p<0.01$). This indicates that the increase in stability of AF after 4 weeks of AV-block was not due to a higher dispersion in refractory period.

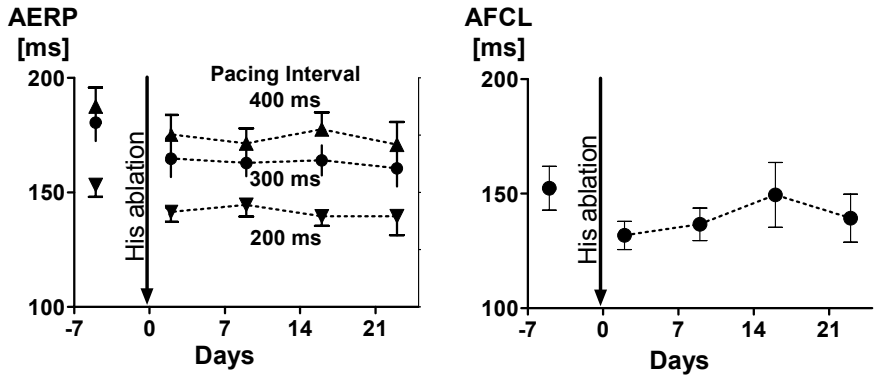

Figure 5
RA refractory period and median AF cycle length (AFCL) of 8 chronically instrumented goats during the first 4 weeks of complete AV-block. Neither AERP nor AFCL changed over time.

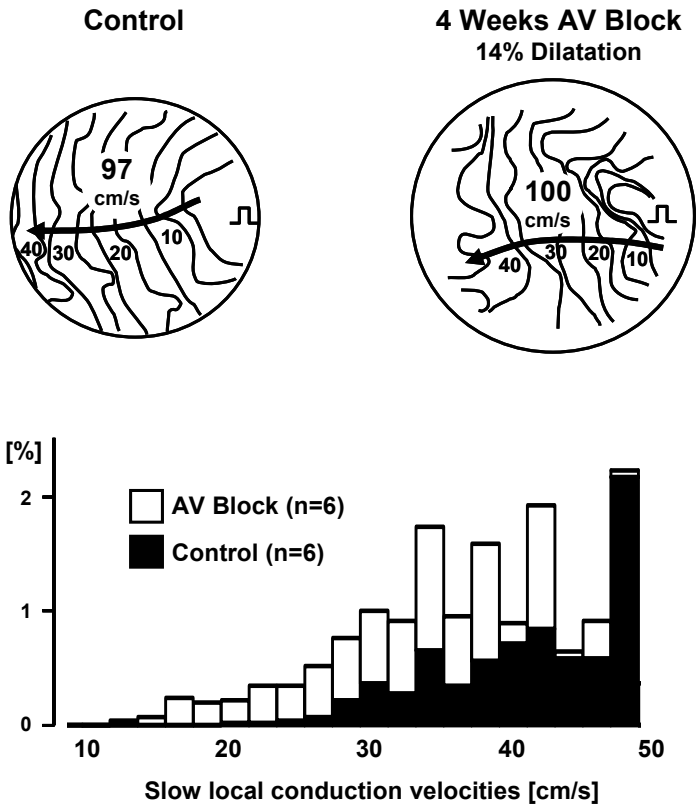

Figure 6
Isochrone maps of the RA free wall during rapid pacing (interval 200ms) in control and after 4 weeks of AV-block. The effective conduction velocity was similar in both cases (97 and 100cm/s). The histogram shows the increased frequency of apparently slow local CVs after 4 weeks of AV-block.

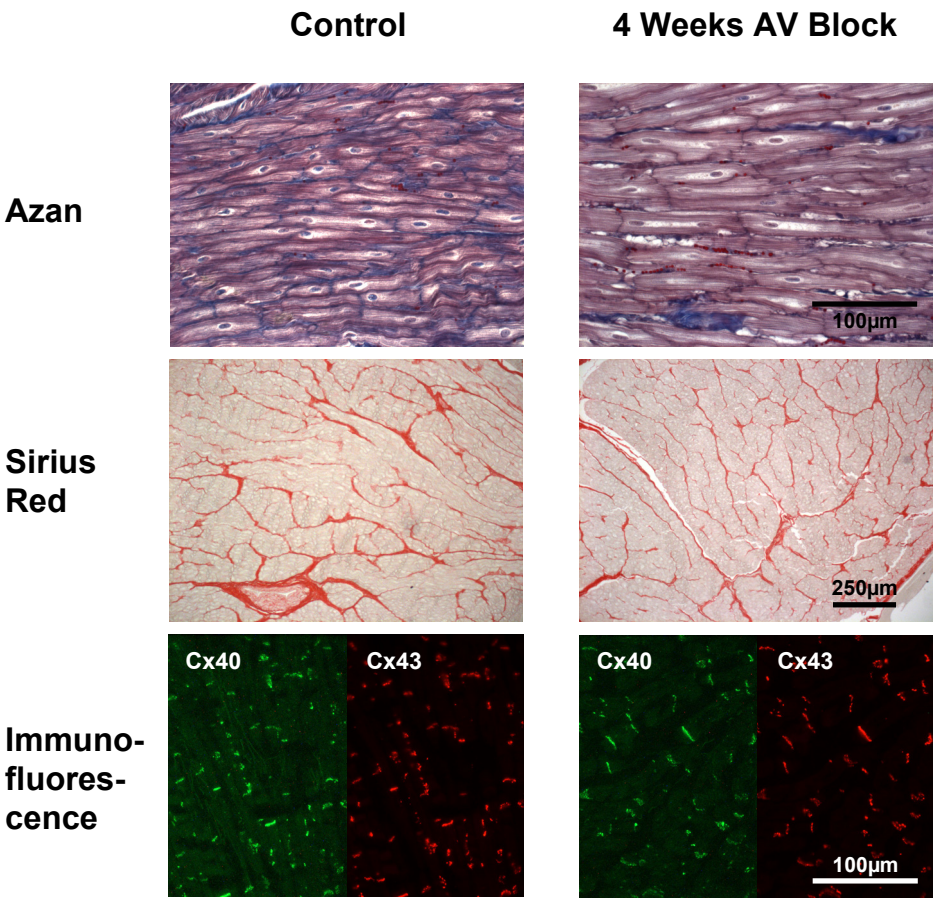

Figure 7
Photomicrographs from sections of the RA. A modified azan staining was used to determine cell size, Sirius red was used to visualize collagen. After 4 weeks of AV-block the atrial myocytes were clearly enlarged, whereas collagen was not increased. Immunohistochemistry with antibodies against connexin40 and 43 showed the expression of gap junction proteins.

Mapping of Atrial Conduction

The effective conduction velocity in the RA wall during sinus rhythm and slow atrial pacing (400ms) was slightly increased in AV-block-goats versus control animals (108±4 vs. 97±3cm/s, p=0.06 and 108±4 vs. 92±3cm/s, p<0.05). Also during rapid pacing (300-200ms) atrial conduction velocity was similar in both groups (97±2 vs. 93±4; p=0.41 and 96±3cm/s vs. 92±3cm/s; (p= 0.35; Figure 6, upper panel). The percentage of areas with slow conduction (CV<30cm/s) was not different in the 2 groups both during SR (0.50±0.26% vs. 0.50±0.30%; p=1.0) and pacing at 400ms (0.97±0.44% vs. 0.53±0.25%; p=0.41) and 300ms (1.54±0.63 vs. 0.67±0.39%; p=0.37). However, during rapid pacing (200ms)

Table 2: Atrial Conduction

	Sinus Rhythm	Acute AV-Block	4 weeks AV-Block
Effective CV (cm/s)			
SR	97±3		108±4
Pacing 400ms	92±3		108±4*
Pacing 300ms	93±4		97±2
Pacing 200ms	91±3		96±3
Local CV<30cm/s (%)			
SR	0.5±0.3		0.5±0.3
Pacing 400ms	0.5±0.2		1.0±0.4
Pacing 300ms	0.7±0.4		1.4±0.6
Pacing 200ms	0.9±0.5		3.7±1.0*
CT>8ms (%)	0.6±0.3		2.0±0.5*
Phase Differences>8ms (%)	3.0±0.8	(p=0.05)	8.0±2.2
P_5 (ms/mm)	0.67±0.21	(p=0.55)	0.83±0.17
P_{50} (ms/mm)	1.18±0.07	(p=0.60)	1.25±0.11
P_{95} (ms/mm)	6.50±0.56	(p=0.07)	8.67±0.88
P_{95-5} (ms/mm)	2.43±0.23	(p=0.06)	3.26±0.31
Heterogeneity index (P_{95-5}/P_{50})	2.1±0.2	(p=0.12)	2.7±0.3

more areas of slow conduction were seen after 4 weeks of AV-block (3.67±1.03% vs. 0.88±0.46%; $p<0.05$; Figure 6, lower panel). Similarly, the incidence of long local conduction times (>8ms) and phase differences (>8ms) was increased during rapid pacing in dilated atria (Table 2; $p\leq0.05$). Also the heterogeneity index calculated from the phase histograms tended to be higher.

Histological Changes

In AV-block-goats (n=9) a marked hypertrophy of cardiomyocytes was observed in the free wall of both atria (RA: cell length +26% ($p<0.05$); cell width +26% ($p=0.05$), LA: cell length +26% ($p<0.05$); width +26% ($p=0.06$); Figure 7, absolute values in Table 1). The relative tissue area positive for collagen was significantly lower after 4 weeks of AV-block (RA: 9.5±0.7% vs. 13.7±1 $p<0.01$; LA: 6.5±0.7% vs. 10.7±1%, $p<0.01$). This suggests that the absolute amount of collagen remained the same while the myocytes became

enlarged. No atrial fibrosis or signs of degeneration of myocytes were seen after 4 weeks of AV-block. Immunohistochemistry of RA and LA showed that connexin40 and 43 remained predominantly expressed at the end-to-end connections of the myocytes. Also the intensity of Cx40 and Cx43 staining was similar in control and AV-block animals. In general Cx40 was expressed more heterogeneously than Cx43, but this was true both in control and AV-block animals (Figure 7).

Discussion

Chronic complete AV-block and the resulting slow idioventricular rhythm cause volume overload and ventricular hypertrophy. In the present study we showed that it also leads to progressive atrial enlargement. Although the mean atrial pressures rose abruptly after His-bundle ablation, the atria became enlarged only after one week. This can be explained by the fact that during slow idioventricular rhythm the ventricular systole, during which atrial size is largest, comprises a shorter period of the cardiac cycle (Figure 1). The pericardium may also initially prevent atrial dilatation[11] During chronic volume overload the pericardial sac gradually enlarges thereby allowing the atria to dilate,[12] We could not follow the changes in left atrial size because, due to the anatomy of the caprine chest, this is not possible echocardiographically. However, after 4 weeks of AV-block the pressure was equally increased in both atria, as were the surface area of the free wall and the cell size. Like in the dog model of chronic AV-block,[13] LVEDP and cardiac output changed acutely but remained constant during the 4 weeks thereafter (no signs of heart failure). Atrial sinus rate showed a transient increase. The plasma-levels of several neurohormones increased and either reached a new steady state or gradually returned towards their original values. The atrial myocytes became markedly enlarged but no signs of atrial fibrosis were seen. Four weeks of AV-block and slow idioventricular rhythm thus create a different substrate of AF than heart failure or valvular dysfunction.[14-18]

How Does Atrial Dilatation Promote AF?

Atrial dilatation may cause atrial ectopy which triggers paroxysms of AF. In isolated Guinea pig hearts an acute increase in atrial volume induced premature beats and atrial arrhythmias.[19] Dogs with mitral valve fibrosis and LA enlargement also exhibited atrial arrhythmias.[18] In our present study spontaneous atrial premature beats or paroxysms of AF were never observed. All episodes of AF were induced by electrical stimulation.

Apart from providing a trigger, atrial dilatation may also create a substrate of AF. The underlying mechanisms could include rapid foci, an increase in atrial size together with a short wavelength and an increased in spatial heterogeneity in AERP or conduction. Studies addressing the *acute* mechanoelectrical feedback on AERP show contradictory results.[19-25] Few studies have been performed on the electrophysiological effects of *chronic* atrial dilatation. In

patients requiring permanent pacing Sparks et al. found that compared to DDD pacing, after 3 months of VVI pacing the atria were enlarged and the AERP was prolonged.[26] The first animal studies were performed in the early 1980's by Boyden and Hoffman.[16] In 8 dogs with tricuspid regurgitation and stenosis of the pulmonary artery RA volume increased by 40 %. Spontaneous atrial arrhythmias did not occur, but the inducibility and duration of atrial tachyarrhythmias were higher. The duration of the atrial action potential was not different from control. Histological analysis revealed hypertrophy of atrial myocytes and an increase in connective tissue.
In our present study there was a tendency for the atrial refractory period to shorten during the first week after His-bundle ablation. However, at this time the atria were not yet dilated and the paroxysms of AF were still of short duration. When the atria started to dilate and AF became more persistent atrial refractoriness remained constant and also the physiological rate adaptation was preserved. After 4 weeks of AV-block the spatial dispersion of AERP was *less* than during control. Therefore, changes in AERP did not seem to play a major role in the development of atrial fibrillation.
Experimental studies have shown that acute atrial stretch prolongs the conduction time between two anatomical landmarks and increases spatial heterogeneities in conduction.[6;22;24] In a canine model of progressive heart failure, interstitial fibrosis and heterogeneous conduction were considered important determinants of the substrate for AF.[14] Also in human studies atrial dilatation and impaired conduction were correlated with atrial arrhythmias.[27-29] A reduced conduction velocity shortens the wavelength and thereby could stabilize AF. In our present study the uniform conduction velocity in the dilated RA was slightly increased possibly due to an increase in atrial cell size.[30] During rapid pacing no effect on uniform CV was found, but the incidence of local conduction delays was clearly higher after 4 weeks of AV-block. This increased spatial heterogeneity in conduction may support the perpetuation of AF.[7] Interestingly, interstitial fibrosis was not seen in the present model. Also the expression of connexin40 and connexin43 was unchanged. A decrease in cell-to-cell coupling therefore does not seem to be involved in the observed conduction disturbances. According to Laplace's law an increase in atrial pressure and diameter will increase atrial wall stress. As a result, particularly the thinner parts of the atrial wall will be stretched.[21] In isolated cardiac muscle strips it has been demonstrated that at a certain critical level stretch depresses conduction.[6;21;31] In the isolated rabbit heart acute atrial dilatation slowed atrial conduction and caused spatial heterogeneities.[6] The atrial architecture leading to spatial differences in wall-stress may explain the heterogeneities in conduction observed during atrial enlargement.

Limitations and Clinical Implications

This study does not prove a causal relationship between chronic atrial dilatation and increased stability of AF. The correlation between dilatation and AF

duration was rather weak (r=0.53) indicating that also other factors are involved and that dilatation may be an epiphenomenon. The degree of atrial dilatation measured in-vivo was limited (13.5%), whereas post-mortem analysis revealed a more pronounced increase in atrial size (25-30%). Although it is difficult to judge which method is more reliable, the degree of atrial dilatation was moderate at most. Another limitation of our study is that atrial dilatation resulting from chronic AV-block does not have a clinical counterpart, because the slow idioventricular rhythm is prevented effectively by pacemaker therapy. The main goal of our study was to create an experimental model of progressive atrial dilatation without concomitant heart failure.

A chronically increased atrial pressure dilated the atria slowly though steadily. After 4 weeks the effects on atrial electrophysiology were still minor and did not lead to spontaneous or persistent AF. However, induced paroxysms of atrial fibrillation became longer in duration and in some cases lasted more than one hour. Studies in humans have shown that already a limited increase in atrial size (LA diameter 40-50mm) is associated with an increased risk of AF.[1] Our results suggest that this higher propensity of AF is due to increased heterogeneities in conduction. Considering our model as an early stage in the development of AF, a more prolonged rise in atrial pressure may lead to more extensive dilatation and more severe atrial conduction defects. The slow nature of the changes observed in our experiments is in agreement with the slow time course of the development of AF (often years) observed clinically. Measures to prevent the development of atrial dilatation in patients may help to delay the development of an electropathological substrate of AF.

Acknowledgements

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CHAPTER 5

Chronic Atrial Dilatation, Electrical Remodeling and Atrial Fibrillation in the Goat

Hans-Ruprecht Neuberger, Ulrich Schotten, Yuri Blaauw, Dirk Vollmann, Sabine Eijsbouts, Arne van Hunnik, Maurits Allessie

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Abstract

Both electrical remodeling and atrial dilatation promote the inducibility and perpetuation of atrial fibrillation (AF). This study was designed to investigate the mutual effects of chronic atrial dilatation and electrical remodeling on the characteristics of AF.

Methods: In 7 goats AF was induced during 48h by burst pacing, both at baseline and after 4 weeks of slow idioventricular rhythm (total AV-block). Atrial size and refractory period (AERP) were monitored together with the duration and cycle length of AF paroxysms (AFCL). After 4 weeks of total AV-block, the conduction in both atria was mapped during AF. Six non-instrumented goats served as control.

Results: At baseline, AF-induced electrical remodeling shortened AERP and AFCL to the same extent (from 185±9 to 149±14ms [$p<0.05$] and 154±11 to 121±5ms [$p<0.05$]). After 4 weeks of AV-block the right atrial diameter had increased by 13.2±3.0% ($p<0.01$). Surprisingly, in dilated atria electrical remodeling still shortened the AERP (from 165±9 to 132±15ms [$p<0.05$]), but failed to shorten the AFCL (140±19 vs. 139±11ms [$p=0.98$]). Mapping revealed a higher incidence of intra-atrial conduction delays during AF. Histological analysis showed no atrial fibrosis, but a positive correlation between the size of atrial myocytes and the incidence of intra-atrial conduction block ($r=0.60$, $p=0.03$).

Conclusions: In a goat model of chronic atrial dilatation, AF-induced electrical remodeling was unchanged. However, AFCL no longer shortened during electrical remodeling. Thus, in dilated atria a wider excitable gap exists during AF, probably caused by intra-atrial conduction defects and a higher contribution of anatomically defined reentrant circuits.

Introduction

Perpetuation of atrial fibrillation is promoted by an atrial substrate that favors initiation and continuation of reentering wavelets. Most patients with AF have structural heart disease often leading to more or less dilatation of the atria. Large clinical trials have identified atrial dilatation as an independent risk factor for the development of AF (hazard ratio: 1.4 per 5mm increment in left atrial size).[1;2] An increase in atrial size increases the possible number of multiple wavelets during AF. Furthermore, an elevated intra-atrial pressure will increase the atrial wall stress, which may result in local intra-atrial conduction disturbances.[3] In addition, atrial dilatation may promote focal arrhythmias that trigger self-perpetuating AF or maintain irregular atrial activation (fibrillatory conduction).[4;5] During the first months of atrial fibrillation, the atrial substrate becomes modified by electrical, contractile, and structural remodeling. This may further dilate the atria, impair conduction, and stabilize AF.

Recently we showed that in goats with chronic AV-block paroxysms of AF become progressively longer when the atria are slowly dilating.[6] Whereas atrial

dilation did not change the atrial refractory period, mapping during rapid pacing unmasked the presence of a higher degree of intra-atrial conduction disturbances. In the present study, we compared the time course and degree of electrical remodeling in dilated and non-dilated atria, and studied the interaction between electrical remodeling and dilatation on the cycle length and persistence of atrial fibrillation.

Methods

Animal Model

Sixteen female goats weighing 51.9±3.6kg were used for this study. Animal handling was performed according to the European directive on laboratory animals (86/609/EEC) and the study protocol was approved by the ethical committee of the University of Maastricht. Seven goats were chronically instrumented. Under general anesthesia (thiopental 10-15mg/kg i.v.; halothane 1% and a 1:2 mixture of O_2 and N_2O) two bipolar screw-in leads were implanted transvenously in the anterolateral and posteroseptal wall of the right atrium. At the tip of each lead a pair of piezoelectric crystals (diameter 2mm, Sonometrics) was mounted, together with two silver electrodes (1.2x4mm) to record atrial electrograms. A third unmodified lead was screwed into the right ventricular apex. Three silver plates (diameter 15mm) were implanted subcutaneously to serve as indifferent electrodes.

Electrophysiological Measurements

Two weeks after lead implantation, the size of the right atrium was measured together with the normal electrophysiological properties of the atrium. The atrial effective refractory period of the right atrium was determined at pacing intervals (S1-S1) between 400 and 200ms. The longest S1-S2 interval (4x threshold, steps 2ms) not resulting in a propagated response was taken as the AERP. The stability of AF was determined by measuring the duration of AF paroxysms induced by repetitive burst pacing during a period of 1 hour. The median AF cycle length and the 5^{th} percentile were determined from at least 100 consecutive AF intervals. After this baseline study, atrial fibrillation was induced for 48h by burst pacing, and the degree of electrophysiological atrial remodeling was measured.[7] The goats were then left in sinus rhythm, and after complete reversal of electrical remodeling (2 days), total AV-block was created by transcutaneous RF-ablation of the His bundle. The resulting slow idioventricular rhythm ranged between 33 and 67bpm. In case the ventricular rate was lower than 40bpm the ventricles were paced at 45bpm. Starting 2 days after His bundle ablation, the atrial diameter was measured once a week together with the average duration of AF paroxysms induced by burst pacing during 1 hour. After 4 weeks of total AV-block, when the atria were moderately dilated, the atria were electrically remodeled again by maintaining AF for 48 hours. Special attention was paid to the effects of electrical remodeling on atrial

refractory period, AF cycle length, and duration of AF-paroxysms. After complete reversal of electrical remodeling (>2 days of sinus rhythm), the animals were sacrificed and the right and left atria were mapped (see below).
In two goats the refractory period and temporal excitable gap during atrial fibrillation were measured by slow fixed-rate pacing (1Hz).[8] After 4 weeks of AV-block and 2 days of electrical remodeling, 600 consecutive stimuli (4x threshold) with a fixed interval of 1s were applied through one of the right atrial leads. A bipolar electrogram was recorded close to the pacing site. From this electrogram, the random coupling intervals (AF-S) between the fibrillation waves and the stimuli were measured together with the associated AF cycle length. The coupling interval that captured the fibrillating atria in 50% of cases was taken as the RP_{AF}. The temporal excitable gap was calculated by subtracting the RP_{AF} from the local median AF cycle length.
Atrial conduction during AF was mapped under general anesthesia after exposing the heart through a left thoracotomy. A spoon-shaped mapping electrode (diameter 4cm; 242 unipolar electrodes; interelectrode spacing 2.4mm) was placed on the free wall of the right and left atria. AF episodes, lasting longer than 30 seconds, were induced by burst pacing and the activation pattern during 4s of AF was mapped. Intra-atrial conduction block was defined as a local conduction time between neighboring electrodes of >24ms (apparent conduction velocity <10cm/s). A CT of >8ms (conduction velocity <30cm/s) was defined as slow conduction.[6] Since normal conduction velocity in caprine atria is about 100cm/s, using these criteria will rather under- than overestimate the amount of intra-atrial conduction disturbances.
Three non-instrumented goats with chronic AV-block were used for additional mapping studies. Six non-instrumented goats in sinus rhythm served as a control group. Hemodynamic measurements were made using a Swan-Ganz catheter with a pressure transducer at the tip (Sentron).

Histology

After mapping, the heart was excised from the chest, the remnants of the main vessels were cut and the blood was removed. The heart was then weighed and fixed in buffered formalin. Samples of the trabeculated parts of both atria were embedded in paraffin. Sections of 4µm were stained by a modified azan staining to determine myocyte dimensions or Sirius red for quantification of collagen.[9] The relative collagen content was defined as the area positive for Sirius red divided by the total tissue area. Of each section, an area of 2.4mm^2 was examined. Pericardial, endocardial and perivascular fibrosis was excluded from the measurements.

Statistics

Results are expressed as mean±SEM. The duration of AF episodes is expressed as the geometric mean±geometric SEM. An unpaired *t*-test was used to determine differences between two groups. Multiple groups were compared by

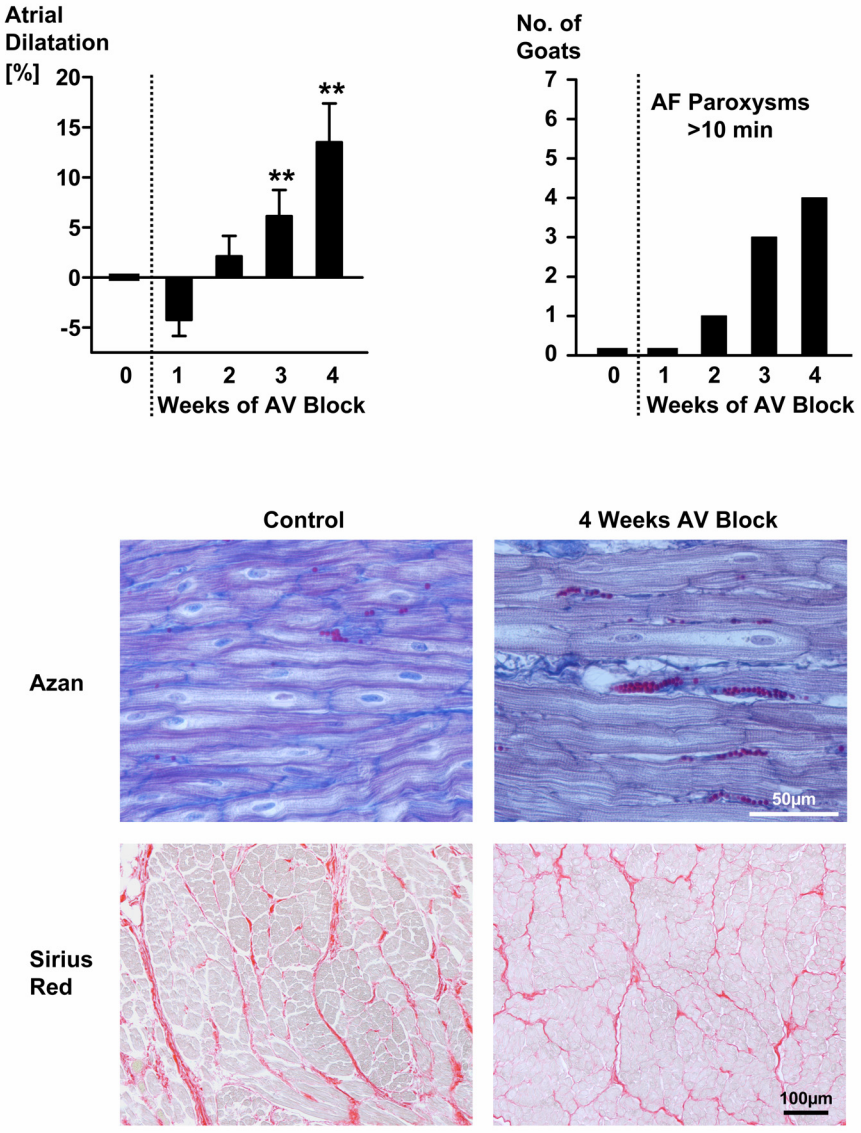

Figure 1
Top left: Relative changes in RA size measured during the first 4 weeks of total AV-block. The average RA diameter was measured during 5 consecutive ventricular cycles from the distance between the tips of two screw-in leads (ultrasound crystals). Immediately after His-bundle ablation (dotted line), the atrial diameter decreased because of the lower ventricular rate. The size of the atria then progressively increased, resulting in 13.2±3.0% dilatation after 4 weeks of AV-block. Top *right:* Time course of the increase in duration of AF paroxysms. In 4 of 7 animals, the AF episodes lasted longer than 10minutes after 4 weeks of idioventricular rhythm. **$p<0.01$
Lower panels: Photomicrographs from sections of the left atrium. A modified azan staining was used to determine cell size, Sirius red was used to visualize collagen. After 4 weeks of AV-block, the atrial myocytes were clearly enlarged while the amount of collagen was not increased.

Table 1: Effect of AF-Induced Electrical Remodeling in Normal and Dilated Atria

	Baseline (Normal Atria)								**4 Weeks AV Block** (Dilated Atria)								
	Sinus Rhythm				**After 48 h AF**					**Sinus Rhythm**				**After 48 h AF**			
Goat	AERP 200 (ms)	AERP 350 (ms)	AFCL p50 (ms)	AFD (s)	AERP 200 (ms)	AERP 350 (ms)	AFCL p50 (ms)	AFD (s)	**Atrial Dilat. (%)**	AERP 200 (ms)	AERP 350 (ms)	AFCL p50 (ms)	AFD (s)	AERP 200 (ms)	AERP 350 (ms)	AFCL p50 (ms)	AFD (s)
1	-	222	200	1	142	181	115	1	**16.0**	147	146	130	2472	118	-	123	>24 h
2	-	200	165	44	-	-	145	>24 h	**16.1**	170	208	143	>24 h	-	-	- ‖	-
3	168	180	129	2	144	122	121	1	**12.5**	136	150	120	5447	-	-	108	>24 h
4	160	194	170	3	-	-	118	8	**12.9**	166	184	194	2	156	158	233	402
5	152	184	132	1	152	180	120	1	**11.0**	134	160	105	1	114	124	113	1408
6	148	168	118	18	148	148	102	3	**25.1**	-	170	142	14099	-	152	132	>24 h
7	146	148	164	22	122	114	129	38	**-1.3**	120	140	141	36	94	92	131	2195
Mean	154.8	185.1	154	5	141.6	149 *	121.4 *	13	**13.2**	145.5	165.4	139.3	382 ‡	120.5 *	131.5 *	140	9638 †/§
SEM	4.1	8.9	10.9		5.2	14.0	5.0		3.0	7.9	9.1	10.5		13.0	15.1	19.0	

* $p<0.05$, † $p<0.01$ vs. sinus rhythm; ‡ $p<0.05$, § $p<0.01$ vs. baseline, ‖ AF was cardioverted after 24 h (AFCL 139 ms); AFCL p50: median AF cycle length; AFD: duration of induced AF episodes; mean AFD is given as geometric mean.

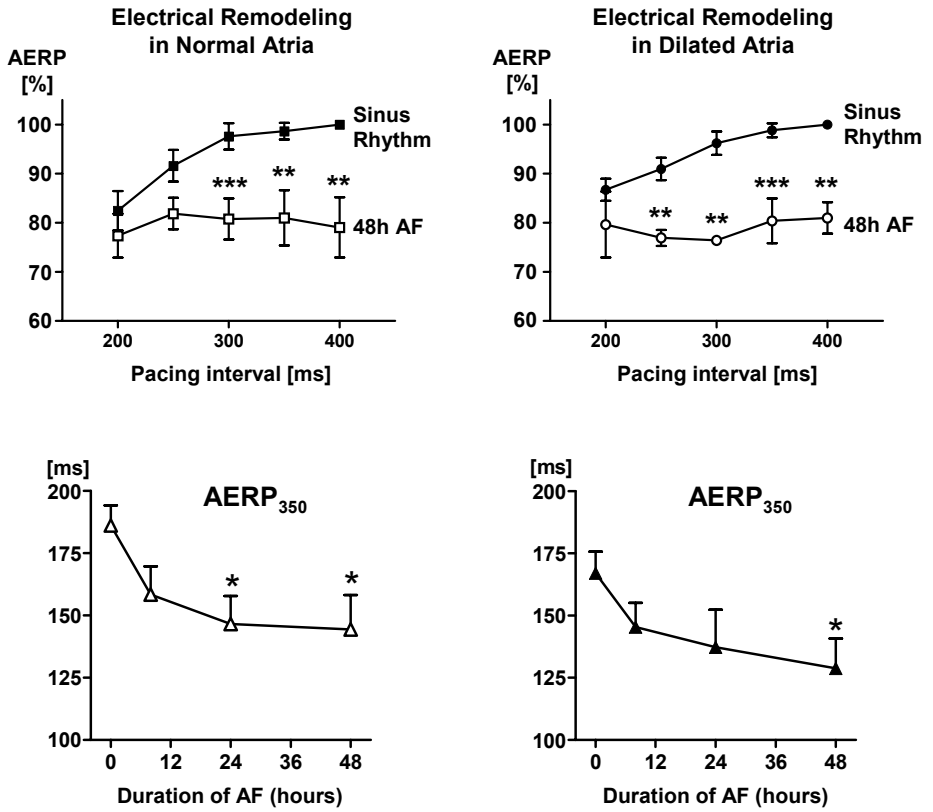

Figure 2
Upper panels: Effects of 48h of AF on AERP in normal and dilated atria at pacing intervals between 400 and 200ms (n=7). In dilated atria, electrical remodeling shortened the AERP to a similar extent as in normal atria. *Lower panels:* The time course of electrical remodeling (changes in $AERP_{350}$) during the first 48h of AF in normal and dilated atria. *p<0.05, **p<0.01, ***p<0.001.

analysis of variance (ANOVA). A p-value of <0.05 was considered as statistically significant.

Results

Atrial Dilatation due to Complete AV Block

After 4 weeks of idioventricular rhythm heart weight was increased compared to the control group (343±16 (n=7) vs. 266±31g (n=6);p<0.05). Body weight was the same in both groups. In the instrumented goats His bundle ablation slowed the ventricular rate from 113.7±4.5 to 53.5±2.7bpm (p<0.01). The atrial rate slightly increased, but normalized within 1-2 weeks. After 4 weeks of idioventricular rhythm, the atrial rate and left ventricular systolic pressure were unchanged (106.8±4.7 vs. 113.7±4.5bpm, p=0.32, and 135.0±12.2 vs.

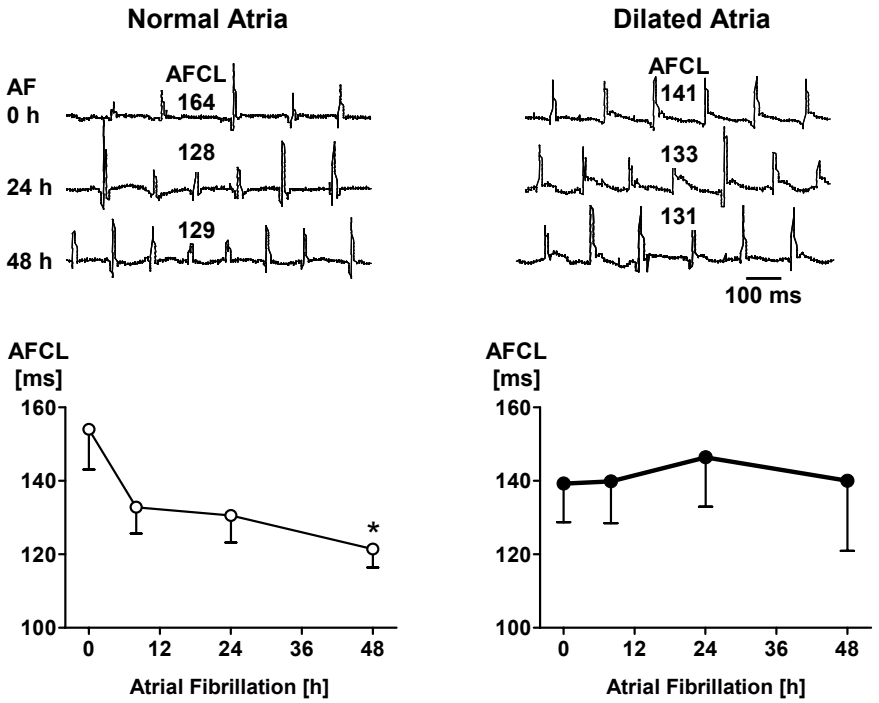

Figure 3
Top: Bipolar electrograms from the right atrial wall after 0, 24 and 48 hours of AF in dilated and non-dilated atria. The numbers indicate the median AFCL. *Bottom:* Effects of electrical remodeling on AFCL during the first 48h of AF (n=7; *p<0.05).

129.8±7.6mmHg, p=0.71). Right atrial pressure increased from 5.7±0.7 to 8.8±0.7mmHg (p<0.01), pulmonary wedge pressure from 7.4±1.1 to 11.1±0.8mmHg (p<0.05) and left-ventricular end-diastolic pressure from 8.6±1.2 to 12.5±1.2mmHg (p=0.06). The amount of atrial dilatation was 13.2±3.0% (absolute increase 3.7±1.1mm, p=0.02; Fig. 1). Histological analysis of the atrial wall showed that the right and left atrial myocytes were clearly enlarged. The average cell length and diameter were 110±7 and 16.5±1.2µm vs. 88±2 and 13.2±0.8µm in control animals (p<0.05 and p=0.06). The relative tissue area occupied by collagen was smaller after 4 weeks of AV-block (8.0±0.6% vs. 12.2±0.6%, p<0.01). However, because of the increased volume of the myocytes, the absolute collagen content of the atrial wall remained unchanged. During the first 4 weeks of slow idioventricular rhythm, the average duration of pacing-induced AF-paroxysms progressively prolonged from 5 to 382s (p<0.05) and in 4 of 7 animals persisted for more than 10 minutes (Fig.1 and Table 1). Spontaneous atrial ectopic beats or paroxysms of AF were never observed.

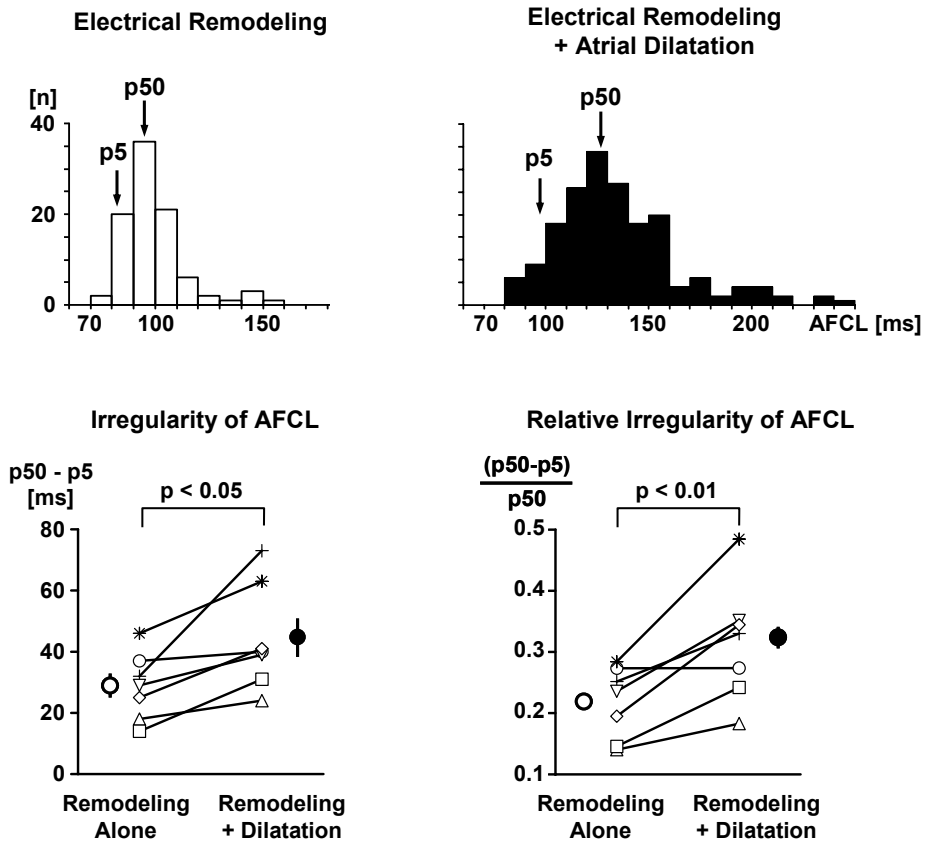

Figure 4
Top: Example of an AFCL histogram in electrically remodeled atria before and after 4 weeks of AV-block. In dilated atria the median AFCL was longer (shift to the right) and the temporal variation was higher (wider histogram). *Below:* The absolute and relative irregularity in AFCL in 7 goats. In 6 of 7 goats the absolute and relative beat-to-beat variation in AFCL was increased after 4 weeks of AV-block.

Electrical Remodeling in Dilated and Non-Dilated Atria

In Table I and Fig. 2, the effects of 48h of AF on right atrial refractoriness before and after 4 weeks of AV-block are compared. There was no difference in amount or time course of AF-induced electrical remodeling between normal and dilated atria. The shortening and loss of rate-adaptation of the AERP were the same. However, electrical remodeling had a greater effect on AF stability in dilated atria. Whereas 2 days of electrical remodeling increased the mean AF duration in normal atria about three-fold (from 5 to 13s; p=0.44), in dilated atria AF paroxysms were prolonged more than 20 times (from 6-7 minutes to almost 3 hours; p<0.01) (Table 1). Apart from this stronger effect on the stability of AF, there was yet another striking difference. Whereas shortening of atrial refractoriness normally leads to a proportional shortening in AF cycle length (in agreement with functional reentry), in dilated atria *electrical remodeling no*

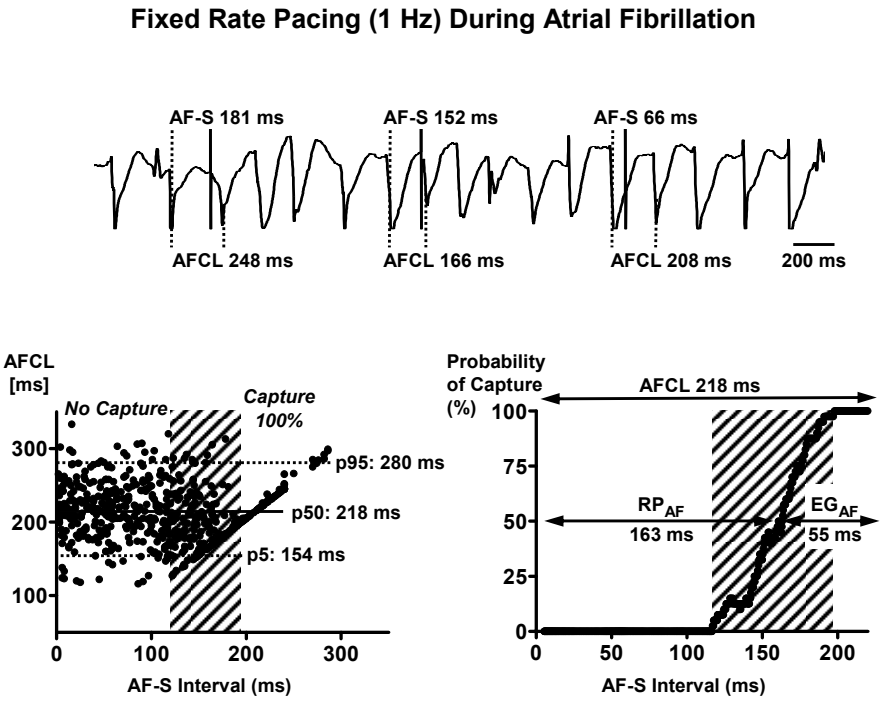

Figure 5
Measurement of the refractory period (RP_{AF}) and temporal excitable gap (EG_{AF}) during atrial fibrillation by slow fixed-rate pacing.[8] After 4 weeks of AV-block and 2 days of electrical remodeling 600 stimuli with an interval of 1 second were applied to the fibrillating atria. From a bipolar electrogram close to the pacing site, the random intervals between the fibrillation waves and the stimuli (AF-S intervals) were measured together with the associated AFCL. Capture was defined as atrial activation within 15ms after the stimulus. The probability of local capture of the fibrillating atria followed an S-shaped curve (lower right panel). At coupling intervals <117ms capture did not occur, whereas at AF-S intervals >197ms the atria were captured 100% of the time. The hatched column in the lower panels indicates the range of the measured refractory periods. The AF-S interval resulting in 50% capture was taken as the RP_{AF} (163ms). The average temporal excitable gap was calculated by subtracting the RP_{AF} from the median AF cycle length (218 – 163ms = 55ms).

longer resulted in shortening of the AF cycle length (Fig. 3). In non-dilated atria, the median AFCL shortened during the first 48h of AF from 154±11 to 121±5ms ($p<0.05$). In dilated atria, the AF-cycle length was not changed by electrical remodeling (140±19 vs. 139±11ms; $p=0.98$). The temporal variation in AF cycle length increased by atrial dilatation. Figure 4 shows the AFCL histogram of a goat before and after 4 weeks of AV-block (top) together with the variation in AFCL (difference between 5^{th} and 50^{th} percentile) in all animals (bottom). After 4 weeks of idioventricular rhythm the average p50-p5 was 44±7ms compared to 29±4ms during control ($p<0.05$). Also the relative irregularity in AFCL ((p50-p5)/p50) became significantly higher after atrial dilatation (0.32±0.04 vs. 0.22±0.02; $p<0.01$).

The longer median AFCL and higher temporal variation in AFCL implies a widening of the excitable gap in dilated atria. This was directly tested in two goats by fixed-rate pacing at 1Hz.(8) Fig. 5 shows an example with a median AFCL of 218ms. In the left plot, the random coupling intervals (AF-S) of 600 consecutive stimuli are plotted against the associated AF cycle lengths. At AF-S coupling intervals <120ms, AFCL was not affected by the stimuli and varied between 154 (p5) and 280ms (p95). However, at longer AF-S coupling intervals the normal distribution of AFCL became disturbed. Because of local capture of the fibrillating atria, long AF cycle lengths no longer occurred and the AFCL was determined by the AF-S interval. A stimulus with an AF-S interval of 163ms captured the atria in 50% of the cases (right panel). Taking this as the average refractory period during AF the mean excitable gap was calculated to be 55ms (median AFCL-RP_{AF}). This is considerably higher than the average EG_{AF} of 29±2ms determined by the same technique in non-dilated atria.[8]

Mapping of Atrial Fibrillation

To test the hypothesis that the higher stability of AF after 4 weeks of AV-block is due to the development of intra-atrial conduction disturbances, the free wall of the right and left atrium were mapped during electrically induced paroxysms of AF. The median AFCL was similar in normal and dilated atria (RA: 127±15 vs. 123±13ms, LA: 137±5 vs. 146±8ms, p=0.80). A total of 104 seconds of atrial fibrillation were analyzed, 48s in the control group (n=6) and 56s in the AV-block group (n=7). Fig. 6 shows a typical example for each group. In dilated atria, crowding of isochrones occurred more frequently with a higher incidence of local conduction delays. In Fig. 7 the percentage of slow conduction (conduction time between neighboring electrodes >8ms) and block (conduction delay >24ms) are plotted. The amount of conduction delay and conduction block was higher in dilated than in non-dilated atria (RA: 19.4±4.3 and 12.3±3.1% versus 12.0±4.2 and 7.0±2.7%; LA: 18.0±3.7 and 12.6±3.0% vs. 9.4±2.9% and 4.6±1.9%; p=0.05 and p<0.05). There was no difference between the right and left atrium (p=0.62 and p=0.71). In the lower panels of Fig. 7 the amount of conduction disturbances is correlated with the atrial cell length in normal (filled circles) and dilated atria (open circles). A moderate but statistically significant correlation was found between atrial cell size and the amount of conduction block (r=0.60, p<0.05).

Discussion

Electrical Remodeling in Dilated Atria

In the present study, complete AV-block was created to induce slowly progressive dilatation of the atria without concomitant heart failure. Atrial fibrillation was maintained during 48h to compare its electrophysiological effects in normal and dilated atria. AF-induced electrical remodeling occurred to the same extent and with the same time course in dilated and non-dilated

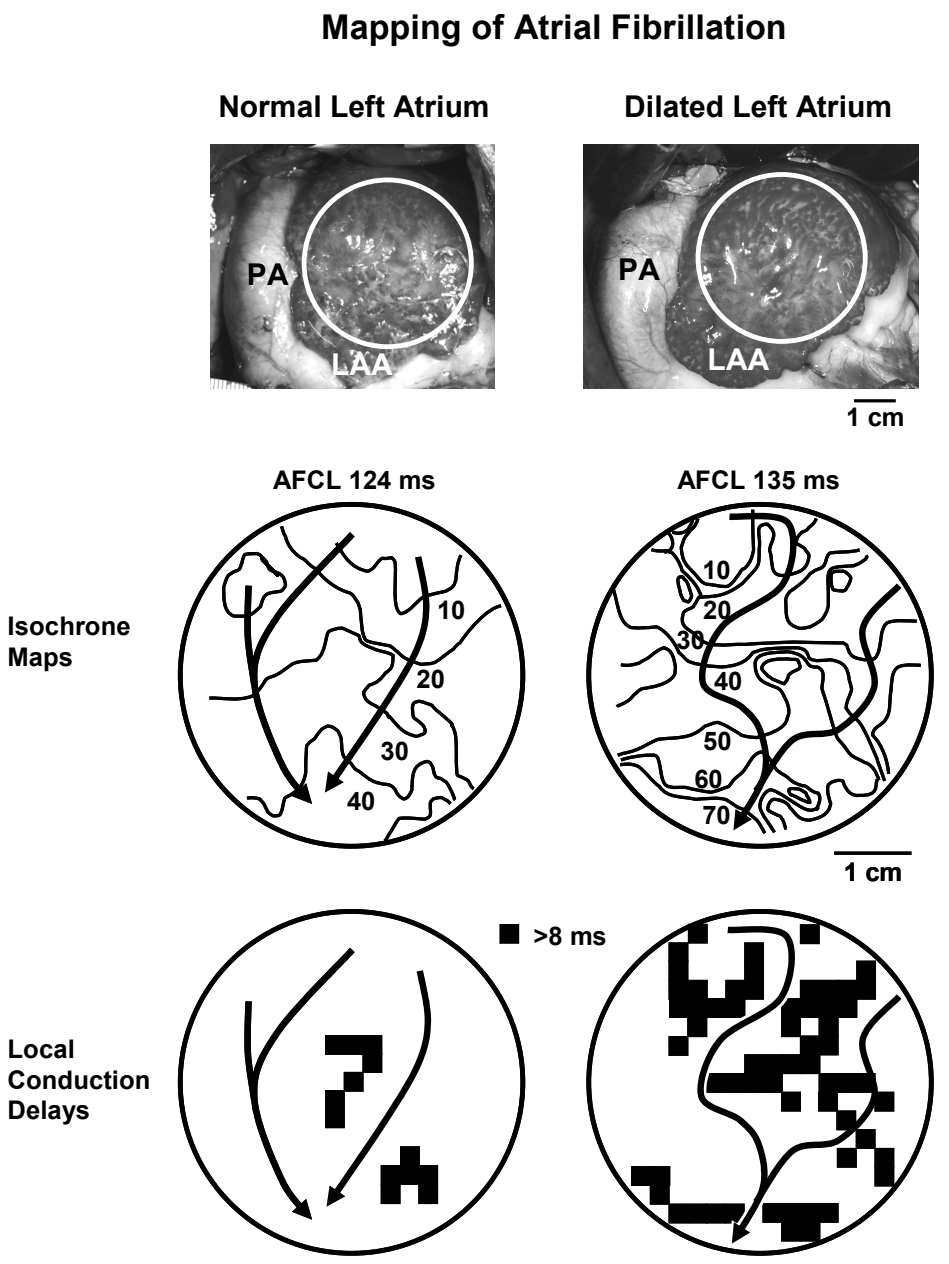

Figure 6
Fibrillation maps recorded from the free wall of the left atrium during control (left) and in a goat after 4 weeks of AV-block (right). In dilated atria, fibrillation waves were less uniform and local crowding of isochrones occurred more frequently. Local conduction delays of >8ms between neighboring electrodes are mapped in the lower panels. A higher degree of dissociation of fibrillation waves by lines of conduction delays was observed in dilated atria.

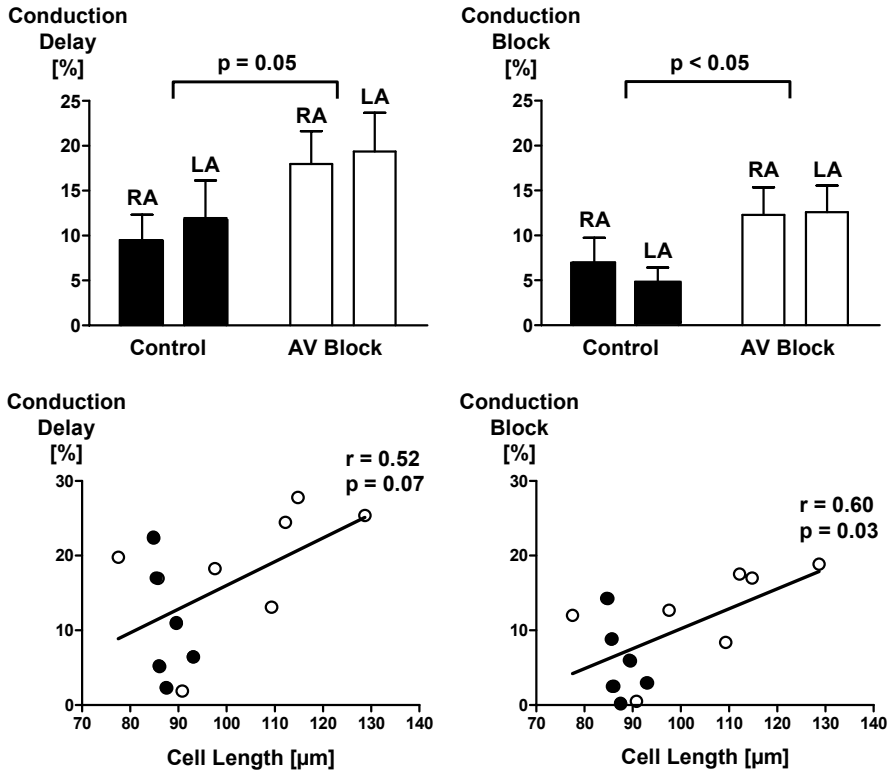

Figure 7
Top: Percentage of local conduction delays (>8ms/2.4mm) and conduction block (>24ms/2.4mm) in the right and left atrial wall of 6 control and 7 AV-block goats. In dilated atria, conduction disturbances during AF were about twice as frequent as in non-dilated atria. *Bottom:* The amount of intra-atrial conduction delay and block plotted against the mean atrial cell length in the control group (n=6; filled circles) and in 7 goats with chronic AV-block (open circles). A moderate but statistically significant correlation was found between atrial cell size and intra-atrial conduction block (r=0.60, p=0.03).

atria. This contrasts with observations in a dog model of heart failure where atrial tachycardia shortened the AERP less in dogs with atrial enlargement.[10] Thus, heart failure seems to reduce atrial electrical remodeling by other reasons than an increase in atrial size.

The Effects of Electrical Remodeling on AFCL

Whereas in normal atria the shortening of atrial refractoriness during the first days of atrial fibrillation is paralleled by a shortening in AF cycle length, in dilated atria the AFCL was not affected by electrical remodeling. This implies a wider temporal excitable gap during AF, and explains the broader AFCL histograms in dilated atria (Fig. 4). In one goat with chronic AV-block, in which the atrial refractory period could be directly measured, the excitable gap during AF was about twice as long as previously reported in non-dilated atria (Fig. 5).[8]

One possible explanation for a widening of the excitable gap is a shift from functional to anatomically determined circuits. In an ovine model of atrial flutter around a Y-shaped lesion, electrical remodeling caused only a minor shortening in flutter cycle length (from 194 to 183ms), but a clear widening (+46%) of the excitable gap.[11] The cycle length of conduction around rings of rabbit atrial myocardium was also not affected by shortening of the AERP. In contrast, functionally determined circuits became smaller (and their cycle length shorter) when the refractory period was shortened.[12] Ikeda et al. described the effects of anatomic obstacles on the meandering of reentrant wave fronts.[13] When atrial refractoriness was abbreviated by acetylcholine, the excitable gap of a reentrant impulse around an anatomic obstacle increased, whereas in isolated canine atria acetylcholine accelerated the rate of reentrant wave fronts. Also in ventricular tissue, shortening of the ERP reduced the core of functional circuits, thereby shortening the reentrant cycle length.[14] Gray et al. induced atrial arrhythmias in isolated right atria of sheep by burst pacing. Functionally determined reentrant waves became anchored to anatomical structures like the crista terminalis or pectinate muscles. Addition of acetylcholine shortened the lines of functional conduction block as well as the reentrant cycle length.[15]
These observations support the notion that a shortening in AFCL by electrical remodeling should be taken as evidence that AF is predominantly maintained by functional reentrant circuits.[7] In contrast, the lack of response of the median AFCL to a shortening in refractory period, suggests that other mechanisms (like anatomical circuits) are operative.
Instead of self-perpetuating multiple reentry, a single rapidly firing focus can also 'drive' the atria in an irregular way (fibrillatory conduction). Although the absence of spontaneous atrial ectopy in the goat makes this mechanism rather unlikely, the possibility that a micro-reentrant circuit outside the mapping area may have served as a 'driver' of AF cannot be excluded.

Intra-Atrial Conduction Disturbances in Dilated Atria

Mapping of AF showed spatial heterogeneities in conduction and a higher incidence of conduction disturbances in dilated atria. Because atrial conduction during slow pacing was normal, these conduction disturbances were functional in nature and rate-dependent.[6] Disturbances in conduction are usually attributed to increased interstitial deposition of collagen (fibrosis).[16-18] However, in a previous study no atrial fibrosis or redistribution of connexins were observed after 4 weeks of AV-block.[6] In the present study, we found a correlation between the length of atrial cells and conduction disturbances during AF (Fig. 7). Computer studies of anisotropic conduction showed that an increase in cell size resulted in local conduction disturbances. It was postulated that cell size was a more important determinant of conduction than the distribution of gap junctions.[19] Another possible explanation for the heterogeneity in conduction in dilated atria is that the higher intra-atrial pressure increases atrial wall stress more in thinner than in thicker parts.[20] This may lead to preferential depression

of conduction between the pectinate muscles, increasing non-uniform tissue anisotropy and facilitating lines of conduction block for reentry.[15;21] The spatial distribution of AF cycle lengths was more heterogeneous in dilated atria. A similar finding was reported in a dog model of chronic mitral regurgitation.[22] Local differences in AF-frequency thus may not only result from spatial differences in refractoriness but also from intra-atrial conduction disturbances.

Interplay between Electrical Remodeling and Atrial Dilatation

In the present study, we found no differences in AF-induced electrical remodeling between dilated and non-dilated atria. Yet, the duration of AF paroxysms was increased much more by electrical remodeling in dilated atria. The AFCL histograms in dilated atria were wider, indicating a higher beat-to-beat variability and a larger excitable gap. An increased temporal variation in AFCL may be explained by a shift from primarily functional reentry, to a mixture of functional and anatomically determined circuits. The short AF intervals, determined by the local refractory period are most likely the result of functional reentry, whereas long AF cycle lengths may result from reentry around dilatation-induced lines of intra-atrial conduction block.[23] The synergistic action of electrical remodeling and atrial dilatation on AF duration thus may be explained by their independent action on two determinants of AF: a shortening of atrial refractoriness (electrical remodeling) and lines of intra-atrial conduction block (atrial dilatation).

However, there are alternative explanations which should be considered: 1) Stretch-induced rapid automaticity or a stable (micro-reentrant) 'mother-rotor' anchored at sites of local conduction delays, may act as a driver for the rest of the atria which is not captured 1:1 due to the high focal rate (fibrillatory conduction).[4] 2) Electrical remodeling may increase AF stability more in dilated than in non-dilated atria, because the $I_{Ca(L)}$ becomes more important for impulse conduction in case of electrical discontinuities between enlarged atrial cells.[19] The reduction of $I_{Ca(L)}$ by AF-induced electrical remodeling[24] might impair atrial conduction and stabilize AF more in dilated atria, than expected from the shortening in refractoriness.

Limitations and Clinical Implications

Mapping of the free wall of the RA and LA was performed under general anesthesia and only in non-remodeled atria. This does not exactly reflect the situation in awake animals subjected to 48h of AF. Although we tried to explain atrial conduction disturbances on the basis of atrial architecture, we did not directly correlate conduction disturbances with changes in the structure of the atrial myocardium. We also did not compare the effects of class I and class III drugs in dilated and non-dilated atria. Our hypothesis that in dilated atria, atrial fibrillation is dominated by anatomically determined reentry is yet mainly based on indirect evidence. In order to conclude that different mechanisms are

operative during atrial fibrillation in dilated and non-dilated atria, more studies will be needed.

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CHAPTER 6

Loss of Atrial Contractility in Dilated Atria due to Chronic Complete AV Block in the Goat

Hans-Ruprecht Neuberger, Maura Greiser, Erik Harks, Sunniva de Haan, Hans Degens, Irina Moshkova, Eva Bodewig, Peter Hanrath, Maurits Allessie, Ulrich Schotten

Submitted

Abstract

Atrial dilatation is an independent risk factor for thromboembolic disease in patients with and without AF. However, the mechanisms underlying thromboembolism in dilated atria are not yet clear. The aim of this study was to investigate, whether in a goat model of chronic atrial enlargement due to complete AV block atrial contractility is impaired, and to describe the underlying cellular mechanisms.

Methods: Twenty-seven female goats were used for this study. In 7 goats (group 1) two right atrial endocardial leads with ultrasound crystals at their tip were used to measure atrial contractility and refractory period (AERP) *in vivo*. AV block was made and the measurements were repeated after 3 weeks of slow idioventricular rhythm. In 10 goats (group 2) AV block was made and after 4 weeks pressure-diameter loops were recorded in an open-chest experiment. Then, the heart was excised and muscle bundles were isolated to measure contractility *in vitro*. Ten goats without AV block served as control.

Results: After 4 weeks of AV block the atria were enlarged (about 18% in one dimension, $p<0.01$). In the awake animals, atrial fractional shortening decreased by 30%, whereas AERP remained unchanged. The atrial work index (AWI) was reduced (8.4±0.9mm*mmHg vs. 18.9±5.3mm*mmHg in control animals ($p=0.02$)). Furthermore, force of contraction (FC) in isolated muscle bundles isometrically contracting at the optimum of the length-tension relationship was reduced by 50% in dilated atria (1Hz: 3.1±0.6 vs. 6.5±1.0mN/mm^2; $p<0.01$) and the effect of rate on FC was similar in both groups. Action potential duration was unchanged. Contractile reserve was reduced by one third and the sarcomere content was slightly lower (46.5±1.1% vs. 55.1±1.7%, $p<0.01$). Furthermore, the Ca load of the sarcoplasmic reticulum assessed by rapid cooling contractures was clearly reduced in bundles from dilated atria (3.4±0.5 vs. 12.2±3.2mN/mm^2, $p<0.01$).

Conclusions: In atria dilated due to chronic complete AV block intrinsic contractility was impaired. This could not be explained by changes in action potential duration or shape. Our findings rather suggest a reduced Ca^{2+} load of the sarcoplasmic reticulum as a mechanism of reduced contractility. In contrast, reduction of contractile reserve plays a minor role.

Introduction

Stroke is the 3rd leading cause of death in Western countries and a leading cause of long-term disability, with important socioeconomic consequences.[1] With aging of our society, the burden associated with stroke will increase. Identification and treatment of the risk factors of stroke is likely to have the largest effect in reducing stroke morbidity and mortality.[2] Of all strokes, 88% are ischemic, mostly caused by cardiac thromboembolism .[3] Atrial dilatation, in turn, is an independent risk factor for thromboembolic disease in patients with and without AF.[4-7] However, the mechanisms underlying thromboembolism in

atrial dilatation are not yet clear. As the size of the atria increases, flow will decrease, and stasis and thrombus formation may occur, increasing the embolic risk. In addition, contractility itself may be impaired in dilated atria representing a "dilated atrial cardiomyopathy". It has been shown, e.g., that after loss of atrioventricular synchrony due to VVI pacing the LA diameter increased while markers for atrial contractility decreased.[8]
The aim of this study was to investigate, whether in a goat model of chronic atrial enlargement atrial contractility is impaired, and to describe the underlying cellular mechanisms.

Methods

Animal Model

Twenty-seven female goats weighing 54.8±1.7kg were used for this study. Animal handling was performed according to the European directive on laboratory animals (86/609/EEC) and the study protocol was approved by the ethical committee of the University of Maastricht.

Group 1
In 7 goats under general anesthesia (thiopental 10-15mg/kg i.v.; halothane 1% and a 1:2 mixture of O_2 and N_2O) two quadripolar screw-in leads with a pair of piezoelectric crystals mounted at their tips were implanted through the jugular vein in the anterolateral and posteroseptal wall of the right atrium (RA, Figure 1). The ultrasound crystals were used to measure the distance between the atrial lead tips. A third unmodified lead was screwed into the right ventricular apex. Three subcutaneously implanted silver plates (diameter 15mm) were used as indifferent electrodes. Cables were subcutaneously tunneled and exteriorized in the neck. The first 2 days after surgery the animals received buprenorphine twice a day (0.01mg/kg, i.m.). Two weeks after lead implantation the animals were anaesthetized again and the His bundle was ablated by radiofrequency energy. This resulted in a slow idioventricular rhythm between 38 and 66bpm. RA and pulmonary wedge pressures were measured by a Swan-Ganz catheter with a pressure transducer at the tip. Two days later in the awake animals the distance between the tips of the two implanted atrial leads (as measured by ultrasound) was recorded during 5 consecutive ventricular cycles. Its mean served as surrogate parameter for RA size. During right atrial pacing at 400 and 300ms cycle length the last isolated atrial contraction between two ventricular actions was used to determine the atrial fractional shortening ($AFS = Diameter_{max}-Diameter_{min})/Diameter_{max}$, Figure 1). Atrial effective refractory period (AERP) was measured at pacing intervals of 400 and 300ms at the anterolateral wall of the RA. Single premature stimuli (4x threshold) were interpolated after every fifth interval, starting at a coupling interval shorter than the AERP. The longest coupling interval (steps 2ms) not resulting in a propagated response was taken as the AERP. Three

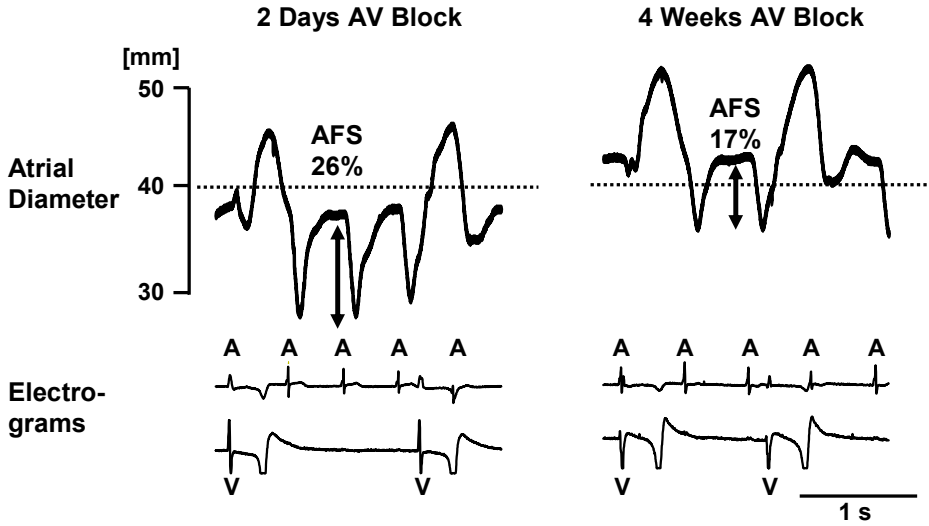

Figure 1
Right atrial diameter as measured by endocardially implanted ultrasound crystals (upper tracings) together with RA and ventricular electrograms during acute and chronic AV block. Note the isolated atrial contractions during the long diastolic pause. The last atrial contraction before a ventricular activation was used to determine atrial fractional shortening (AFS). While the atrial diameter increased, AFS clearly decreased during 3 weeks of AV block.

weeks later these parameters were determined again. Three days later RA and pulmonary wedge pressures were recorded under general anesthesia.

Group 2
In 10 goats (Group 2-AVB) a VVI pacemaker system (lower rate 45bpm) was implanted, chronic AV-block was made and the skin was closed. After 4 weeks the animals were anaesthetized again (thiopental 10-15mg/kg i.v.; halothane 1% and a 1:2 mixture of O_2 and N_2O) and the heart was exposed by a right thoracotomy to obtain RA pressure-diameter-loops. To measure RA diameter one ultrasound crystal was sewn epicardially close to the SCV/RA junction together with a bipolar pacing electrode, another crystal was fixed between the aorta and the auricle. A tip pressure transducer was introduced transvenously in the RA. For ventricular pacing the chronically implanted lead was used. For atrial sensing a bipolar electrode was sewn on the left atrial appendage. During AV-sequential pacing (AV-delay 120ms, pacing interval 300 and 400ms) atrial diameter, atrial pressure and the ECG were digitally recorded to obtain RA pressure-diameter loops. From these loops atrial work indices (AWI_{300} and AWI_{400}) were calculated, as previously reported.[9] The same measurements were performed in 10 control goats without AV block (Group 2-Ctrl) after infusing a plasma expander (polygeline 3.5%, Aventis) during 5min to obtain an atrial pressure/preload comparable to the AVB group.

Thereafter the heart was excised and the atria were isolated. The left atrial free wall was cut along its subjacent rim. The RA free wall was removed by cutting along the AV ring, then lateral towards the inferior caval vein, behind the crista terminalis towards the superior caval vein, then along the septum towards the AV node. The anteroposterior and craniocaudal dimension of the right and left atrial free wall and their weight were determined and RA muscle bundles were isolated.

Muscle Bundle Experiments

After loop recording heparin was administered (10,000 units i.v.), the heart was excised and quickly transferred into cold (+5°C) Ca^{2+}-free Tyrode's solution ($NaHCO_3$ 20.1mM, NaCl 130mM, KCl 4mM, $MgCl_2$ 0.6mM, NaH_2PO_4 1.2mM, Glucose 11.1mM, pH=7.4). The atria were removed and placed in a petri dish with carbogen saturated Tyrode's solution containing a low Ca^{2+}-concentration and BDM ($CaCl_2$ 0.22mM, BDM 29.7mM). Muscle bundles of less than 1mm in diameter were carefully prepared in parallel to the muscle fiber direction. They were connected to an isometric force transducer and superfused with carbogen-saturated Tyrode's solution for 20-30min to equilibrate (CaCl2 2.2mM, 37°C). Electrical stimulation (1Hz) was started and the preload was increased in steps of 0.2 mN until maximal active force generation was reached. The muscles were allowed to equilibrate again for 30min. Muscles with a decline of force of contraction of more than 5% during this period were excluded. Baseline force of contraction (FC) at 1 Hz and force-frequency relation (0.5-3Hz) was measured in 23 bundles of 10 control animals and in 19 bundles of 10 AV block goats.

In 15 preparations from 10 control goats and in 9 preparations from 8 AV block goats the positive inotropic effect of 10.8mM Ca^{2+} was studied.

Contractures after rapid cooling of the bundles from 37 to 1°C (RCCs) were elicited in 10 control and 11 AV block bundles from 7 and 6 animals as described elsewhere.[10] Briefly, the preparations were rapidly (within 1s) transferred from a 37°C to a 0°C bathing solution carefully maintaining the length of the preparations. During the cooling period the muscle was not stimulated.

To obtain transmembrane action potentials (AP) 15 muscle bundles from 9 control goats and 16 bundles from 8 AV block goats were electrically stimulated at rates between 0.5 and 3Hz (cycle length 2000-333ms). Rectangular pulses of 1-3ms were applied between a platinum hook connected to the force transducer and a silver electrode about 1mm apart. Parallel to force measurements APs were recorded with microelectrodes (tip resistance 30-40MOhms, filled with 3M KCl) to determine the resting membrane potential, the AP amplitude and the AP duration at 20, 30, 50, 70 and 90% repolarization.

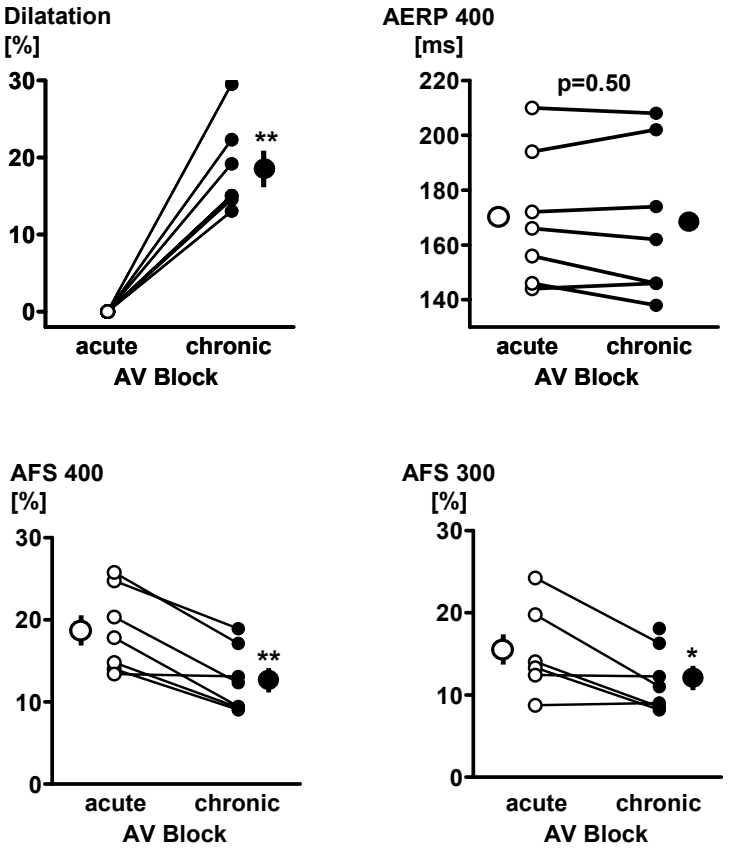

Figure 2
Changes in relative atrial size, AERP and AFS during 3 weeks of AV block for each goat. While atrial size clearly increased, AERP remained unchanged and AFS decreased within 3 weeks of AV block. * $p<0.05$, ** $p<0.01$.

Histology

Morphological assessment was done using electron microscopy as described by Ausma et al.[11] Shortly, parts of the right atrial wall were cut into small blocks (4 mm3), fixed in buffered 3% glutaraldehyde, postfixed in buffered 1% osmium tetroxide, dehydrated, and embedded in epoxy resin. Ultra thin sections were cut from each sample, counterstained with uranium acetate and lead citrate, and examined in a Philips CM100 electron microscope.

Statistics

Results are given as mean±SEM. Student's *t*-test was used to evaluate differences between AV block and control. Multiple groups were compared by an analysis of variance (ANOVA). $P<0.05$ was considered statistically significant.

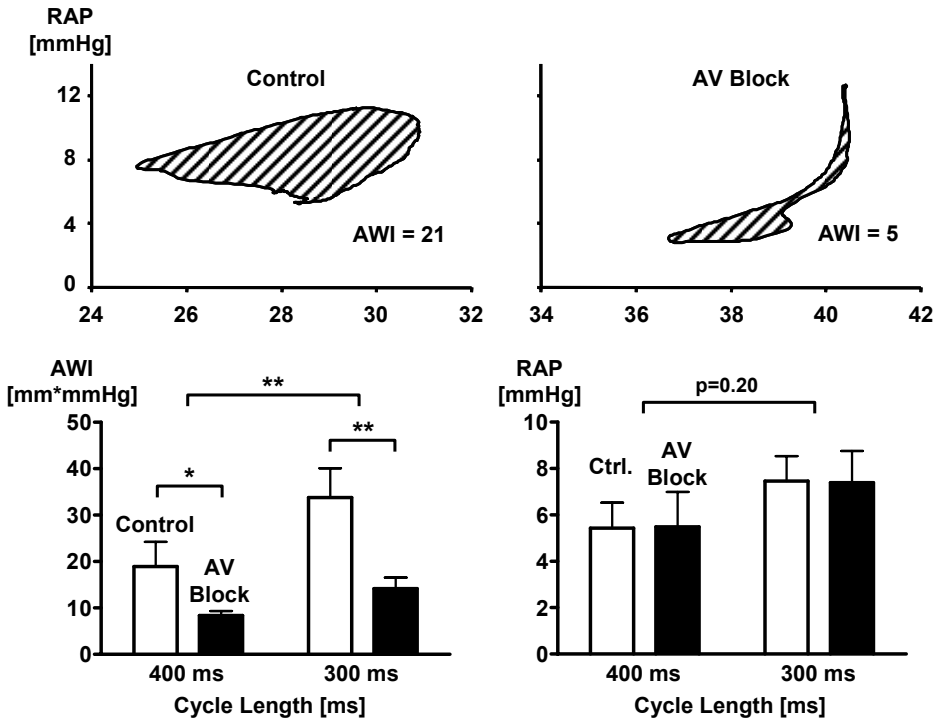

Figure 3
Pressure diameter loops obtained in anaesthetized control goats and after 4 weeks of AV block. The area enclosed by the loop was used to calculate the atrial work index (AWI, mm*mmHg). Chronic AV block significantly reduced the AWI at both cycle lengths. Due to infusion of a plasma expander in control goats atrial pressures were similar in both groups. * $p<0.05$ vs. control, ** $p<0.01$.

Results

Atrial Size, Contractility and Refractoriness in Vivo

The RA diameter in awake goats 2 days after His ablation was 26.6±4.4mm and increased to 31.6±5.5mm after 3 weeks of AV block (+18.4±2.2%, $p<0.01$; Figure 2). At the same time, atrial fractional shortening decreased by 20-30% (AFS_{400} from 18.4±1.7 to 12.8±4.0% ($p<0.01$) and AFS_{300} from 15.4±1.9 to 11.9±1.5% ($p<0.05$); Figure 2). $AERP_{400}$ and $AERP_{300}$ did not change significantly (from 170±9 to 168±11ms and from 163±9 to 161±8ms, $p=0.50$ and $p=0.48$, respectively). Immediately after His bundle ablation, RA pressure was 11.9±1.5mmHg. The pressure did not change throughout 4 weeks of AV block (9.2±1.0mmHg, $p=0.53$), indicating a comparable preload at the times of AFS and AERP measurement. The wedge pressure also remained unchanged (acute AVB 9.7±2.1mmHg vs. 11.7±1.1mmHg 4 weeks later, $p=0.66$),

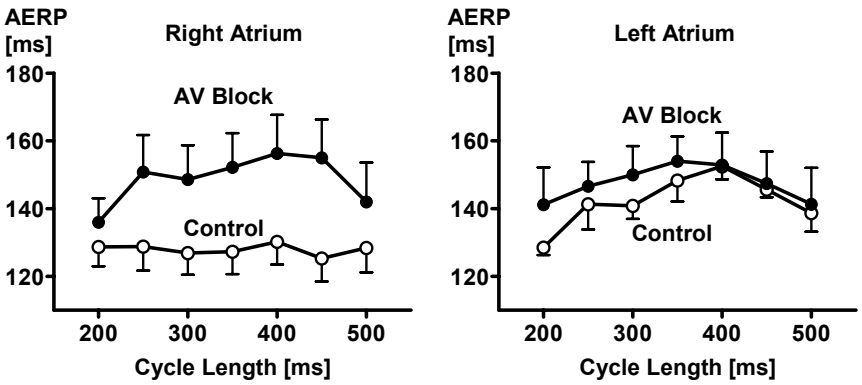

Figure 4
Atrial refractory period as a function of cycle length after 4 weeks of AV block and in control animals measured during anesthesia in the right and left atrium. AERP in RA was significantly longer in dilated atria ($p<0.0001$, 2-way-ANOVA), although statistical significance was not reached for single cycle lengths. Right atrial ERP in control animals did not show any rate adaptation.

indicating that the goats did not suffer from progressive deterioration of the left ventricular pump function.

As assessed in the open chest experiments (Group 2), both atria were macroscopically enlarged in the AV block group. The antero-posterior and craniocaudal dimension of the RA was 6.1±0.2 and 3.3±0.1cm vs. 4.9±0.3 and 2.5±0.1cm in control animals ($p<0.01$), corresponding to an increase in atrial size of about 28% in one dimension. Similar results were obtained in the LA (5.4±0.1 and 4.3±0.2cm vs. 4.1±0.2 and 3.1±0.1cm, $p<0.001$). After 4 weeks of AV block the RA weighed 0.35±0.06 vs. 0.16±0.01g/kgBW in control ($p=0.02$) and the LA weighed 0.26±0.02 vs. 0.12±0.01 ($p=0.002$), respectively.

Figure 3 shows RA pressure-diameter loops from a control and an AV block goat during right atrial pacing (400ms, AV-delay 120ms). The hatched area enclosed by the loop represents the atrial work index (AWI).[9]

To promote comparability between contractility in normal and dilated atria RA pressures in control goats had been adjusted to RA pressures in chronically dilated atria by volume loading (RAP_{400}: 5.5±1.5 vs. 5.4±1.1mmHg, $p=0.98$; RAP_{300}: 7.4±1.4 vs. 7.5±1.1mmHg, $p=0.97$). In the dilated atrium the loop is almost closed, indicating impaired contractility and mainly passive atrial movement. On average, AWI_{400} was reduced by ~50% after 4 weeks of AV block (8.4±0.9mm*mmHg vs. 18.9±5.3mm*mmHg in control animals ($p=0.02$)). AWI_{300} in dilated atria was 14.2±2.4 vs. 33.8±6.3mm*mmHg in control ($p=0.007$). Qualitatively similar results were obtained after normalization for atrial size. In dilated atria the normalized AWI_{400} and AWI_{300} were reduced to 0.22±0.03 and 0.37±0.06mmHg vs. 0.53±0.14 and 1.02±0.13mmHg in control goats ($p=0.03$ and $p=0.004$). These results were in line with the AFS measurements in the awake animals. However, in contrast to

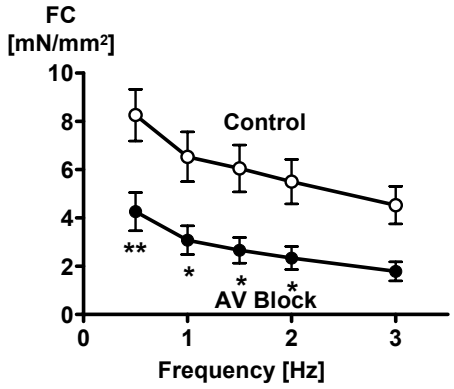

Figure 5
Contractile force of isolated muscle bundles was halved after 4 weeks of AV block. The effect of rate on force was similar in both groups (negative force-frequency relationship). * $p<0.05$, ** $p<0.01$ vs. control.

AFS, AWI increased with increasing stimulation frequency (positive force-frequency relationship, $p<0.01$).
In contrast to the measurements in the awake state, during the open chest experiment the right atrial ERP was slightly prolonged after 4 weeks of AV block ($AERP_{400}$: 156±11 vs. 130±7ms, $AERP_{300}$ 149±10 vs. 127±6ms, $p<0.01$ [Two-way-ANOVA]; see Figure 4, left panel). ERP was unchanged in the left atrium (right panel). Action potential duration at 70% and 90% of repolarization as measured in isolated right atrial muscle bundles tended to be longer in the AV block group (Figure 8; APD70 111±7 vs. 95±7ms and APD90 165±7 vs. 153±10ms, p= 0.09 and 0.26, respectively).

Contractility and Action Potentials in Isolated Muscle Bundles, Histology

Figure 5 shows that in muscle strips from goats after 4 weeks of AV block isometric force of contraction (FC) measured at the optimum of the length-tension relationship was reduced by 50% (at 1Hz from 6.5±1.0 to 3.1±0.6mN/mm^2; $p<0.01$). This was irrespective of rate: as stimulation frequency was increased, isometric FC declined in both groups (negative force-frequency relationship).
The contractile reserve (FC at 10.8mM Ca^{2+}) tended to be reduced by one third in bundles from dilated atria (7.2±2.2 vs, 11.4±1.3mN/mm^2, p=0.10, Figure 6). Electron microscopy (Figure 6) showed a reduction of contractile material (sarcomeres) per cell-surface from 55.1±1.7% to 46.5±1.1% ($p<0.01$) and a perinuclear accumulation of glycogen from 16.9±1.2% to 28.4±1.5% ($p<0.01$).
Figure 7 shows twitch forces at 1Hz and 2.5Hz together with rapid cooling contractures in muscle bundles from normal and dilated atria. At a stimulation rate of 1Hz contractile force is about halved in AV block animals (2.2±0.6 vs. 5.1±0.7mN/mm^2, $p<0.01$). The calcium content of the sarcoplasmic reticulum (SR), as assessed by RCCs, tended to be reduced in dilated atria (4.3±1.1 vs. 6.4±1.1, p=0.13). In control goats, increasing the rate to a physiologic frequency (2.5Hz) did not change FC (5.0±0.8 vs. 5.1±0.7mN/mm^2), whereas RCCs

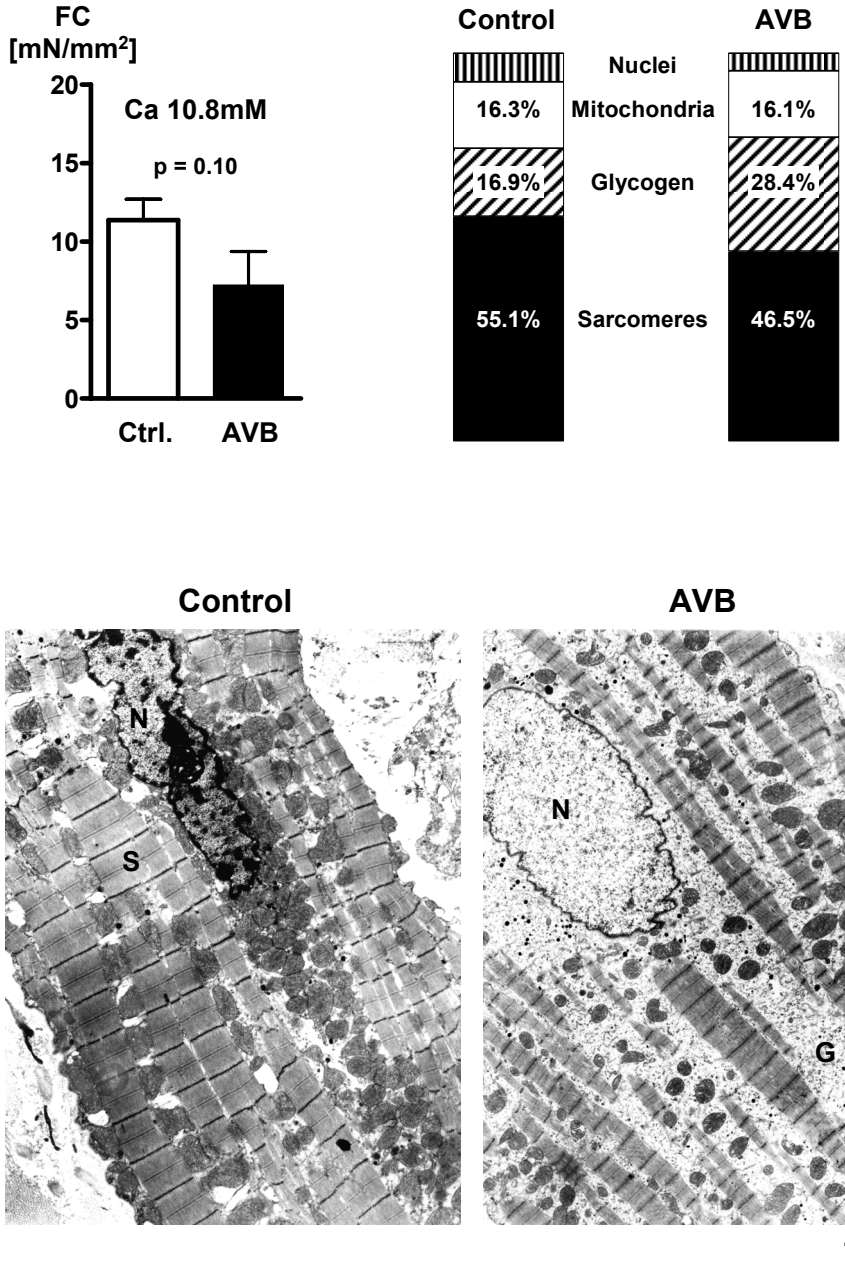

Figure 6
Above: Contractile reserve (determined by a high extracellular calcium concentration) tended to be reduced by one third in AV block. As assessed by morphometry using electron microscopy, contractile material (sarcomeres) was reduced by ~16% per cell. *Below:* Electron microscopy of atrial myocardium from a control and an AV Block goat. Note the reduction of sarcomeres (S) and glycogen accumulation (G) in sarcomere-depleted areas.

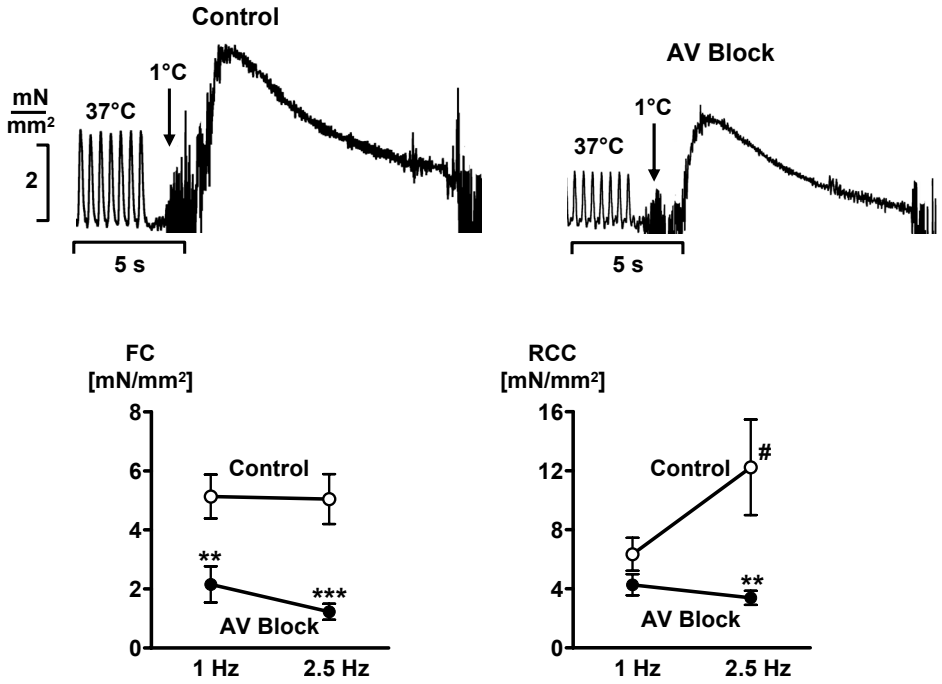

Figure 7
Upper panels: Steady-state twitch at 2.5Hz followed by a rapid cooling contracture (RCC). In the AV block bundle, steady-state contractility and RCC amplitude were reduced. *Lower panels:* Twitch force and RCCs in control and AV block bundles at 1Hz and 2.5Hz. Twitch force was reduced in the AV block group. RCCs in AV block bundles were comparable at 1Hz, but failed to increase at higher rate. ** $p<0.01$, *** $p<0.001$ vs. control. # $p<0.05$ vs. 1Hz.

increased (12.2±3.2 vs. 6.4±1.1mN/mm^2, $p<0.05$). In bundles from dilated atria, RCCs failed to increase at 2.5Hz (4.3±1.1 at 1Hz and 3.4±0.5mN/mm2 at 2.5Hz, $p<0.01$ vs. control) and were much smaller than in control.
Averaged transmembrane action potentials obtained in bundles from normal and dilated atria are given in Figure 8. The right panel shows APs normalized for amplitude. Diastolic potential and AP amplitude did not differ significantly between the groups. After 4 weeks of AV block atrial contractility was reduced despite an increased action potential duration at 20% depolarization (APD20 24.5±3.9 vs. 13.4±1.5ms, $p<0.05$). Furthermore, the plateau potential (average potential between 10 and 50ms) was not lower (-13.5±2.8 in AV block vs. -16.6±2.2mV in control, $p=0.29$). The rate adaptation of the APD was preserved in the AV block group. The curves of the APD at 70% and 90% repolarization as a function of cycle length were significantly shifted upwards in the AV block group ($p<0.0001$, 2-way-ANOVA).

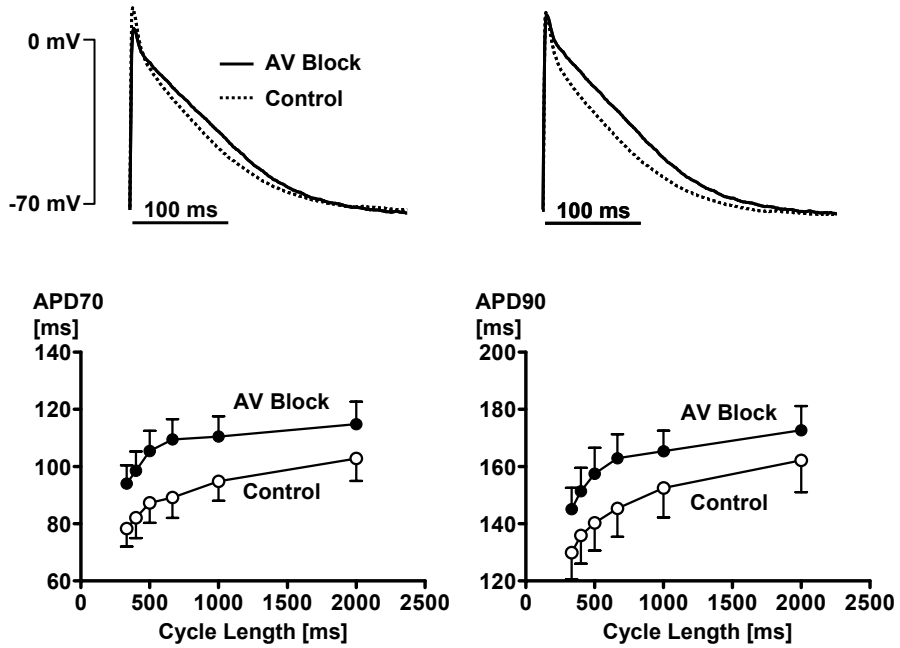

Figure 8
Mean transmembrane action potential of 15 control (dotted line) and 16 AV block bundles. Repolarization is slightly prolonged in muscles from dilated atria. *Right:* same action potentials, normalized for amplitude. *Below:* APD70 and APD90 as a function of cycle length were significantly longer in the AV block group ($p<0.0001$, 2-way-ANOVA).

Discussion

Atrial dilatation is a clinically important risk factor for thromboembolic disease like ischemic stroke.[4-7] Concerning the underlying mechanisms, different hypotheses have been developed including atrial contractile dysfunction. To our knowledge, this is the first study to demonstrate that atrial contractility indeed is impaired in a model without heart failure but chronic atrial enlargement.

In awake goats 3 weeks of slow idioventricular rhythm induced right atrial dilatation by about 20% in one dimension. This was accompanied by a decrease in atrial fractional shortening of about 30%. Measurements were performed by use of implanted ultrasound crystals 2 days after His bundle ablation and 3 weeks later. During the long diastolic pause of the slow idioventricular rhythm, isolated atrial contractions occurred without the complex interaction with ventricular contraction (Figure 1).[12] This allowed simple and reproducible assessment of the atrial shortening fraction. Atrial pressure as marker for atrial preload was similarly elevated early after His bundle ablation and 4 weeks later. Thus, impaired contractility is not likely due to changes in preload. This finding was confirmed during AV-sequential pacing in anesthetized animals by atrial pressure diameter loops. After 4 weeks of AV-block, atrial work index was reduced by 50%.

Four weeks of AV block reduced atrial contractility not only in vivo but also in isolated myocardium. In muscle bundles from dilated atria isometric force of contraction measured at the optimum of the length-tension relationship was 50% lower, irrespective of rate. Thus, intrinsic atrial contractility was impaired in atrial enlargement independent from changes in preload.

The loss of atrial contractility could not be attributed to changes in action potential shape or duration. Measurements in the anesthetized goats and in isolated right atrial muscle bundles rather showed an increase in AERP and action potential duration in dilated atria. Furthermore, the plateau potential was unchanged. This is in sharp contrast to AF-induced contractile dysfunction. During the first days, AF leads to a shortening of atrial refractoriness and action potential duration (electrical remodeling), which goes hand in hand with the decline in contractile force.[9] Probably, the reduction of I_{CaL} during electrical remodeling also causes this contractile remodeling. Because a shortening of the action potential does not occur in chronic atrial enlargement, different mechanisms seem to be the basis of the "dilated atrial cardiomyopathy".

Atrial contractile dysfunction in this model could simply be the consequence of a reduced amount of sarcomeres per cross sectional area. However, whereas atrial contractility was reduced by 50%, the sarcomere content per cell was reduced only by 16% (Figure 6). Moreover, atrial histology in AV block goats showed an even reduced content of extracellular matrix and an increase of surface area covered by cardiomyocytes by ~5% .[12] Thus, the relative reduction in contractile material rather equals 11%. The contractile reserve as measured in the presence of high calcium concentrations tended to be reduced by only one third in this model. Therefore, a reduction in contractile material or contractile reserve can only partly explain the contractile dysfunction. However, reduced rapid cooling contractures suggest a reduced calcium load of the sarcoplasmic reticulum as an important cause of impaired contractility. In human ventricular myocardium of patients with heart failure, reduced Ca load of the sarcoplasmic reticulum has been demonstrated to contribute to diminished Ca release from the sarcoplasmic reticulum and to impaired force generation.[13]

Limitations and Implications

(1) Contractility in vivo and in vitro was studied in the right atrium only. However, concerning stroke the left atrium is clinically more relevant. Chronic endocardial instrumentation of the LA is more risky and preparation of LA muscle bundles was not successful due to the thick endocardial layer. (2) Real preload during in vivo measurements of contractility is difficult to asses because of the complex interaction of the thoracic pressure, the pericardium, the intra-cardiac pressure and the wall stress, especially when cardiomyocytes (and the pericardium) enlarge. Nevertheless, fractional shortening itself seems to be a relevant parameter in describing reduced blood flow and should therefore correlate with thromboembolic risk.

Discovery of contractile dysfunction in a model of atrial dilatation adds to our knowledge of possible mechanisms involved in stroke. Strategies aimed at preventing atrial dilatation or treating the associated contractile dysfunction can be tested in models like this and may provide means for primary and secondary prevention of stroke.

Conclusions

Chronic complete AV block in the goat caused atrial dilatation and reduced atrial contractility within the first weeks. The mechanisms underlying this "dilated atrial cardiomyopathy" differ from the contractile dysfunction due to reduced calcium currents as seen after conversion of atrial fibrillation. Data from this study suggest an impaired SR-calcium load and release together with a moderate reduction of the contractile reserve as mechanisms of impaired contractility in dilated atria.

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CHAPTER 7

Clinical Implications of Atrial Dilatation

Atrial dilatation is an independent predictor of mortality. This article reviews causes, consequences, and treatment options of atrial dilatation. Determinants of atrial size are discussed, and the important difference between acute and chronic dilatation is highlighted. After remarks on the measurement of atrial size, consequences of dilated atria like arrhythmias, contractile dysfunction, and thromboembolism are addressed. Finally, established and experimental, pharmacological and surgical treatment options are described.

Determinants of Atrial Size

Acute Atrial Dilatation

Atrial enlargement or dilatation is observed when the atrial pressure becomes elevated. This can occur acutely, e.g. due to myocardial infarction with reduced pump function or due to acute valve regurgitation. The degree of the resultant acute dilatation depends on atrial compliance. One important determinant of atrial compliance is the pericardial sac, which acutely limits atrial dilatation and the increase in wall stress. Taking into account the physiological constraint of the relatively stiff pericardium, dilatation of one atrium also depends on the relative pressure and compliance of the other and of the ventricles. Especially when the filling pressures of all four heart chambers increase simultaneously, the pericardium plays an important role in the mechanical interactions and limits overall cardiac dilatation. Maruyama et al. showed that an acute increase of pericardial pressure from 5 to 10 mmHg results in a volume increase of only 5.8% (about 2% increase in diameter), and even an acute rise to 20 mmHg augments pericardial volume by only 11.7% (about 4% in diameter).[1] Traboulsi et al. found in dogs, that a rise of right or left ventricular end-diastolic pressure from zero to 20 mmHg increased the transmural pressures only from 0.2 mmHg to 2.5 mmHg or from 0.3 mmHg to 6.0 mmHg, respectively.[2] These experiments have been performed after closure of the pericardium and the thorax and are likely to reflect the conditions of an acute rise in diastolic pressure also in human ventricles. To our knowledge, such measurements have not yet been performed in the atria.

Chronic Atrial Dilatation

In contrast to acute atrial dilatation, chronic atrial dilatation involves further mechanisms. Because of the increased functional demand (pressure and/or volume overload), hypertrophy will occur. This is associated with parallel increases in pericardial surface area and mass, allowing the whole heart to dilate.[3] Cardiac hypertrophy is characterized by an increase in cell size accompanied by an augmented functional capacity. These changes in cellular phenotype are associated with the re-induction of the so-called fetal gene program.[4] When the hypertrophic responses are unsuccessful in normalizing wall stress and suppressing the stimulus, heart failure will occur. Some clinical conditions associated with atrial enlargement are listed in Table 1.

Table 1: Causes of Atrial Enlargement

Main Mechanism	Caused by	LA	RA
Volume Overload	Mitral regurgitation	●	
	Tricuspid regurgitation		●
	Hypervolemia	●	●
	Congenital AV block	●	●
	Atrial septum defect		●
	Ventricular septal defect	●	
	Persistent truncus arteriosus	●	
	Tricuspid atresia		●
	Epstein's anomaly		●
	Complete transposition of the great arteries		●
Pressure overload	Mitral stenosis	●	
	Tricuspid stenosis		●
	Aortic valve disease	●	
	Pulmonic valve disease		●
	Left ventricular hypertrophy	●	
	COPD, pulmonary embolism		●
	Paroxysmal SVT	●	●
	Constrictive pericarditis	●	
	Heart failure	●	●
	Hypertrophic cardiomyopathy	●	
	Age	●	
Atrial contractile dysfunction	Atrial fibrillation	●	●

The underlying hemodynamic mechanism can be described as an overload either primarily in volume or in pressure. E.g., AV-valve regurgitation increases atrial volume load, whereas stenosis causes pressure overload. Atrial enlargement may be limited to one atrium (e.g. single valve disease) or affect both atria (e.g. heart failure). Normal aging does not seem to increase atrial size. Rather, the atrium compensates for age-induced changes in LV diastolic properties by augmenting active atrial contraction.[5]

Measurement of Atrial Size

In clinical practice, left atrial (LA) size is usually measured by 2-D or M-mode echocardiography. Right atrial (RA) size can be evaluated with 2-D echocardiography. Transesophageal echocardiography provides excellent examination of both atria. In routine, LA size is reported as LA anteroposterior dimension. However, three-dimensional echocardiographic reconstruction

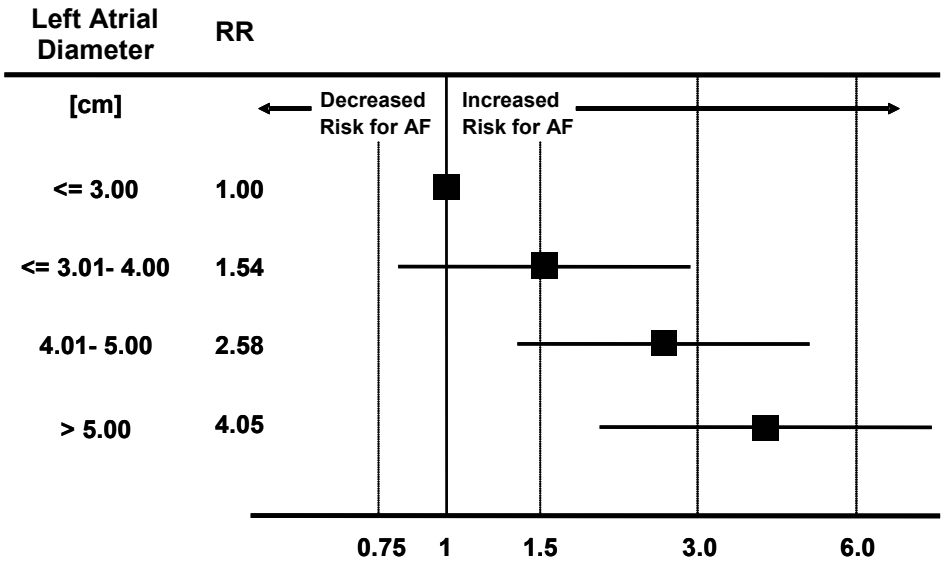

Figure 1
Association between left atrial size and the incidence of AF in the Cardiovascular Health Study. RR: relative risk. From Psaty et al.[12]

provides a more reliable measurement, comparable to magnetic resonance imaging.[6;7]

P-wave duration (PWD) has been regarded as a parameter associated with atrial size. Indeed, Ehrlich et al. showed in 100 persons without cardiac disease that signal-averaged PWD correlates with LA and left ventricular end-diastolic diameter. However, multivariate analysis showed that age was the only independent predictor of PWD.[8] In a study of patients with paroxysmal AF, PWD was not correlated with atrial volumes as assessed by cine MRI scans.[9] Michelucci et al. found that RA volume was correlated with PWD, whereas LA dimensions were correlated with age but not with PWD.[10] In patients with heart failure Faggiano et al. observed a correlation of left atrial size and pressure with PWD, however, age was not included in the analysis.[11] In summary, P-wave duration does not seem to be a useful parameter for assessment of atrial size. It rather reflects atrial conduction disturbances.

Atrial Enlargement and Atrial Arrhythmias

"When the palpitations are irregular they form a veritable malady of the beat of the heart acting on the great arteries. The primary cause of the disorder is an irritation of the heart and a reflux of blood, which is directed against the auricles with more violence. [...] If the auricles are strained and increased in volume they cause palpitations." In 1783, De Senac made this early statement proposing a causal relationship between atrial enlargement and atrial arrhythmias.[12] More than 200 years later large prospective clinical trials showed

that atrial dilatation is an independent risk factor for the development of atrial fibrillation (Figure 1).[13-15] The enlarged atrial size itself may represent a substrate for AF. According to Moe's multiple wavelet hypothesis a larger atrial surface or mass will allow more reentrant circuits to coexist simultaneously, thereby stabilizing AF. For instance, Grigioni found in patients with mitral regurgitation that the risk to develop AF depended on the atrial diameter.[16]

Several animal models revealed further electrophysiological mechanisms that may explain an AF substrate in dilated atria. Mostly, the atrium was distended after opening the chest and the pericardium or in isolated hearts. These models are characterized by an acutely and severely increased atrial wall stress. Regarding atrial refractory period (AERP) or action potential duration, the results are somewhat inconsistent: a prolongation as well as a shortening have been measured.[17-25] Atrial conduction was regionally depressed in acutely dilated hearts.[17;26] Additionally, acute atrial stretch can provoke premature depolarizations in normal atria,[20] but also in atria hypertrophied due to chronic myocardial infarction.[18]

As described above, acute atrial dilatation is fundamentally different from the frequent clinical condition of chronically progressive atrial enlargement. However, even in the presence of hypertrophy (thickening of the wall), atrial wall stress can be increased due to increased atrial size and pressure. This holds true particularly for later stages of cardiac disease with severe hemodynamic alterations. Studies of chronic atrial dilatation described substrates with marked atrial fibrosis, e.g. in progressive heart failure. These substrates of AF did not show a shortened AERP or an increased heterogeneity of refractoriness.[27-30] Rather, heterogeneity in conduction was regarded to account for an increased AF inducibility.[27;31] Regional conduction disturbances were also found in a goat model of chronic atrial enlargement due to complete AV block (Chapter 4, Figure 6). These atrial conduction disturbances were not associated with atrial fibrosis or altered expression of connexins.[32] In this model, locally increased atrial wall stretch might impair local conduction.[26] The heterogeneity of the architecture of the atrial wall is known to cause unequal stretch and heterogeneous electrophysiological characteristics.[22] At a later stage of disease, increased wall stretch may result in atrial fibrosis to reduce the stretch of adjacent cardiomyocytes, but impairing conduction.

Also in humans, acute atrial stretch may create a substrate for AF.[33;34] However, like in animal studies, the effect on atrial refractoriness is inconsistent.[34-38] Kamkin et al. described in isolated atrial cells that acute longitudinal stretch causes extra depolarizations.[38] *Chronic* atrial enlargement in humans seems to prolong atrial refractoriness, which would be consistent with the electrophysiological effects of hypertrophy on the ventricle. In patients with atrial arrhythmias Chen et al. showed that in dilated atria the AERP was prolonged.[39] Morton et al. found that patients with enlarged atria due to an atrial septum defect also had a prolonged AERP, and Sanders et al. described the same observation for patients with congestive heart failure.[40;41] In addition, all

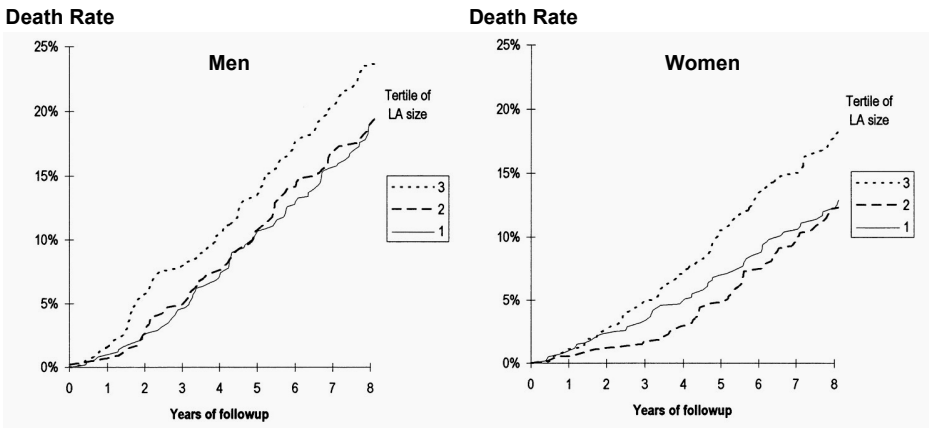

Figure 2
Age-adjusted cumulative death rate by tertile of left atrial (LA) size in men and women from the Framingham Heart Study. From Benjamin et al.[53]

these studies reported conduction disturbances in chronically dilated human atria.

Since a prolongation of the AERP does not promote AF, the available data suggest that in chronically enlarged human atria the atrial size itself and conduction disturbances play a prominent role for the development of an arrhythmic substrate. The role of changes in refractoriness is less clear, but it may be that acute mechanoelectrical feedback plays a role in the initiation of atrial arrhythmias.

Atrial enlargement is not only a cause, but also a consequence of atrial arrhythmias. For the SPAF investigators Dittrich et al. reported that prolonged AF independently contributes to the LA diameter, and Sanfilippo et al. found atrial dilatation after 20 months of lone atrial fibrillation.[42;43] Probst and co-workers and Keren et al. also described a contribution of AF to atrial enlargement, which they assessed in patients with mitral stenosis.[44;45] However, in paroxysmal or short term AF this correlation was not found.[44;46-48] In so-called lone AF Jaïs et al. reported hemodynamic signs of diastolic dysfunction including elevated LA pressures, and echocardiography showed an enlarged inferosuperior LA dimension, but was otherwise normal.[49] Atrial enlargement and chronic AF may be a mutual cause and consequence and seem to be part of a vicious circle stabilizing the arrhythmia. Because AF increases mortality and morbidity, an interruption of this circle theoretically offers the chance of improving survival and quality of life in many patients.

Impact of Atrial Enlargement on Mortality

Atrial enlargement is almost always associated with cardiac disease (Table 1), and idiopathic atrial dilatation is extremely rare[50-52]. Thus, atrial enlargement

may simply indicate the increased morbidity and mortality due to heart disease. However, atrial size itself could also be a determinant of prognosis. Indeed, in the population based Framingham Heart Study LA enlargement was a predictor not only of stroke but also of death (Figure 2). This was still the case after multivariable adjustment.[53] Also in patients with dilated cardiomyopathy, LA volume had an independent and incremental prognostic value, compared with its determinants (e.g., AF, left ventricular end-diastolic volume, degree of mitral regurgitation).[54] Other studies in patients with left ventricular dysfunction showed similar results.[55-57] In hypertrophic cardiomyopathy in the elderly, LA size was most strongly associated with reduced survival.[58] Furthermore, in patients with acute myocardial infarction LA volume powerfully and independently predicted mortality during a follow-up of 15 months. Again, this remained true after adjustment for clinical factors and parameters of LV systolic and diastolic function.[59]

What are the underlying mechanisms of increased mortality in atrial dilatation? Atrial contractile dysfunction and its hemodynamic consequences is one candidate, another is hypercoagulability and thromboembolism.

Atrial Enlargement and Contractility

While there is a considerable body of evidence that "atrial paralysis" occurs due to atrial fibrillation,[60] it is controversial, whether loss of atrial contractility can also be caused by atrial enlargement. Sparks et al. conducted a prospective clinical trial in 21 patients with AV block or sinus bradycardia requiring a pacemaker. They showed that the loss of atrioventricular synchrony (VVI pacing) during 3 months increases atrial size by 10% and reduces the left atrial appendage (LAA) emptying velocity by 50% and the LAA fractional area change by 30%. Besides, 4 of 21 patients developed spontaneous echo contrast. These changes were reversible after 3 months of AV synchronous pacing (DDD).[61] In a cardioversion study of 68 AF patients a normal left atrial size (<40mm) was associated with earlier recovery of LA mechanical function.[62] However, others could not confirm this.[63]

Besides, there are conflicting interpretations of experimental data. In a ventricular tachypacing-induced heart failure model Shi et al. found a reduced atrial fractional area shortening and suggested atrial hypocontractility as cause.[64] Yet, Hoit et al. found an increased atrial mechanical work and unchanged force generation when recording pressure-volume loops in a similar dog model.[65] To study whether atrial enlargement is associated with atrial contractile dysfunction, we used a goat model of atrial dilatation without clinical signs of heart failure (chronic complete AV block). As described in Chapter 6 of this thesis, the increase in atrial size was accompanied by atrial hypocontractility. In contrast to AF induced atrial contractile remodeling, this was neither associated with a shortening of the AERP nor with changes in action potential shape. Furthermore, in this "dilated atrial cardiomyopathy" contractility showed a different rate response compared to AF-induced

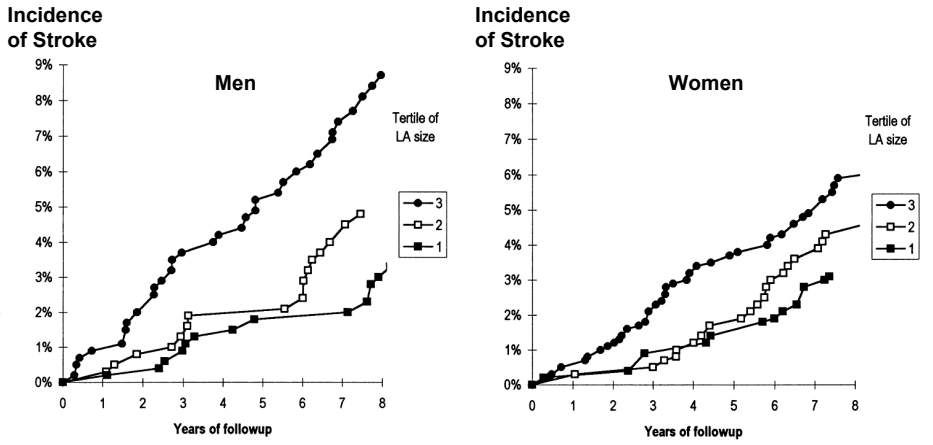

Figure 3
Age-adjusted cumulative incidence of stroke by tertile of left atrial (LA) size in men and women from the Framingham Heart Study. From Benjamin et al.[53]

hypocontractility, indicating different underlying mechanisms.[66] We also found a decrease in intrinsic contractility of atrial trabeculae contracting under isometric conditions at the optimum of the length-tension relationship (50% reduction of contractile force of muscle bundles isolated from dilated atria). The loss of atrial contraction could only partly be attributed to a reduction of contractile reserve or to loss of contractile material. Also, changes in action potential configuration could not account for the decrease in atrial contractility. Rather, calcium load and release of the sarcoplasmic reticulum was impaired.

Atrial Enlargement and Thromboembolism

Atrial dilatation is an important risk factor for the development of AF, which impairs atrial contractility and increases the thromboembolic risk. Furthermore, as described above, atrial dilatation itself is associated with the development of atrial contractile dysfunction. Consequently, stasis occurs and increases the risk of intravascular coagulation and thromboembolism. Additionally, at a given cardiac output atrial enlargement (i.e. an increased atrial volume) reduces the blood flow within the atria. Biochemical markers of hypercoagulability can be elevated in patients with dilated atria. In hypertension high plasma fibrinogen levels were related to left atrial size.[67] In patients with mitral stenosis, fibrinopeptide A and thrombin-antithrombin III complex (markers for thrombin generation) were higher in the left than in the right atrium.[68] In persons 50 years of age or older from the Framingham Heart Study LA enlargement was a predictor of stroke in men (Figure 3).[53] The SPAF (Stroke Prevention in Atrial Fibrillation) trial showed that atrial size is a strong and independent predictor of later thromboembolism in patients with nonrheumatic AF.[69] A similar finding was reported by Cabin et al. who found in 272 patients without mitral stenosis

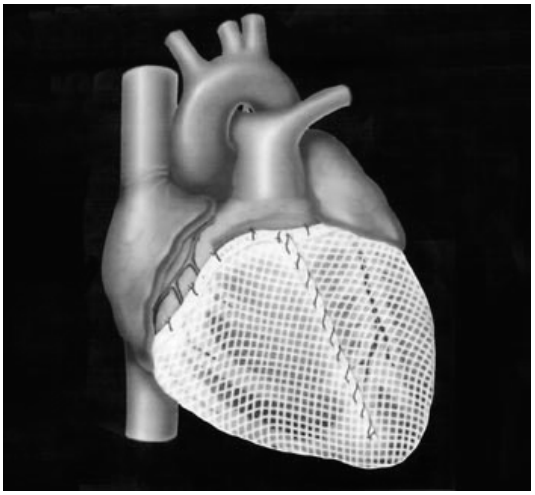

Figure 4
Passive cardiac support device (preformed-knitted polyester, Acorn Inc., St. Paul, Minnesota) placed around the ventricles to prevent further dilatation and to improve function in congestive heart failure.

or prosthetic valves LA size ≥40 mm to be the strongest predictor of increased risk for embolization.[70] In an ethnically mixed population, DiTullio et al. reported an increased risk of stroke associated with LA enlargement after adjustment for other stroke risk factors.[71] This association was observed in men, but was attenuated in women.

Options for Therapy

The abovementioned experimental and clinical studies suggest a causal relationship between chronic atrial enlargement on the one hand and morbidity and mortality on the other. Conversely, this would imply that interventions reducing atrial size are prognostically beneficial.

Non-Pharmacologic Strategies

Because AF induces atrial dilatation, cardioversion of AF should reduce atrial size. Indeed, several (rather small) clinical studies demonstrated this.[72-75] The restoration of sinus rhythm can reverse AF-induced electrical, structural, and contractile remodeling. Thus, a consequent cardioversion strategy should allow interrupting the vicious circles involved in the self-perpetuation of AF.[60;76] However, attempts to achieve and maintain sinus rhythm with currently available strategies are not superior to rate control strategies in patients with AF.[77-79] This may be due to adverse effects of antiarrhythmic drugs.[80] On the other hand, reversion of AF-induced atrial remodeling alone may not be enough to eliminate the substrate of the arrhythmia.

In recent years, multiple studies in severe heart failure showed that reducing global or regional left ventricular loading conditions by so-called assist devices (LVAD) promotes regression of pathological hypertrophy or dilatation ("reverse remodeling"). It seems to be the reduction of wall stress by these devices, which

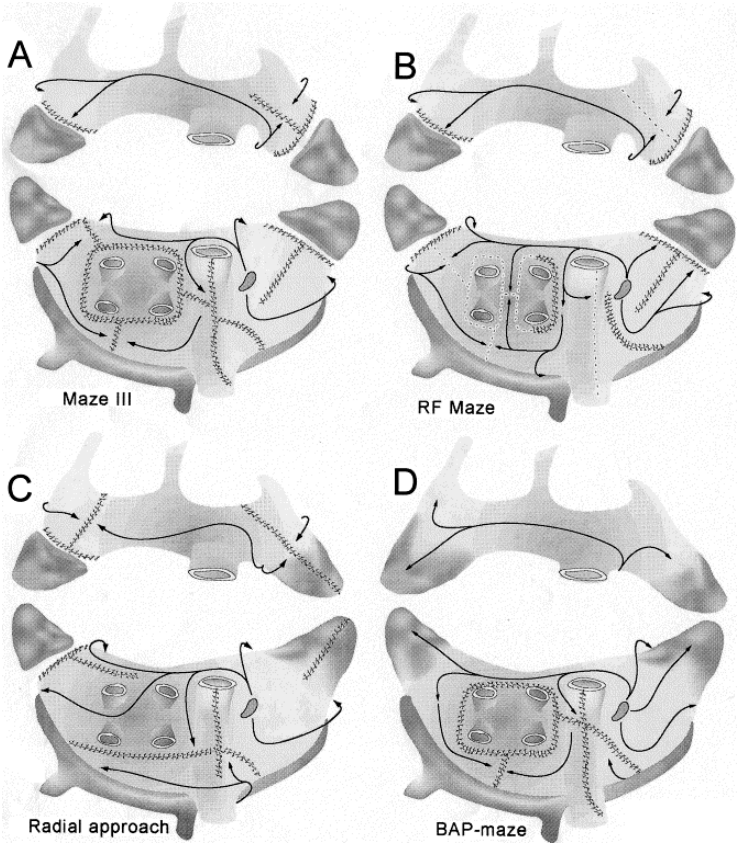

Figure 5
(A) Maze III procedure: the cephalad to caudad view of the atria (upper diagram) and view of the dorsal aspect of the atria (lower diagram). Black arrows indicate lines of electrical activation; the zigzag lines depicting the surgical incisions and sewing in the atria. (B) Radiofrequency modified Maze procedure. The dotted lines indicate the endocardial radiofrequency ablation lines. (C) Radial approach. (D) Bilateral appendage preserving Maze procedure (BAP Maze). From Sie et al.[93]

induces regression of hypertrophy, action potential changes, contractile dysfunction, fibrosis, and the expression of fetal gene programs.[81-87] A less invasive strategy is the regional re-synchronization of left ventricular contraction by multisite ventricular pacing. A decrease in LV size and mass after 6 months could be achieved.[88;89] Similar results could be attained by a passive cardiac support device (Figure 4).[90;91] Ventricular unloading by these strategies should also unload the atria. Indeed, this has been shown for the left atrium.[92] Parallel to the ventricle, the resulting reduction in atrial wall stress may promote reverse atrial structural remodeling. However, this has not been investigated so far. Theoretically, the method of passive epicardial containment

using a preformed-knitted polyester device could also be applied on the atria in case of open-heart surgery for valve disease or coronary revascularization.
Another and already established way to directly reduce atrial size is the so-called Maze procedure (Figure 5).[93] It compartmentalizes both atria in order to reduce the atrial mass available to sustain AF. Restoration of sinus rhythm during long-term follow-up (3 months to 8 years) can be achieved in more than 90% without antiarrhythmic medication.[94] The rate of restoring atrial contraction varies in different series from 21-100%.[94;95] The Maze procedure includes amputation of both atrial appendages and the stroke rate seems to be low. Of 265 patients followed by Cox et al. for 11.5 years after surgery, 2 patients had a perioperative stroke and only 1 patient had a stroke during follow-up.[96] The success rate of the Maze-procedure in restoring sinus rhythm is not only related to reduction in atrial size[97] but also to the atrial compartmentalization that prevents reentrant wavelets and/or isolates pulmonary vein triggers. A simple surgical size reduction in patients undergoing mitral valve surgery restored sinus rhythm in only 63% at 1 year post-operatively.[98] Furthermore, in large atria restoration of sinus rhythm as well as atrial contraction is less likely after the Maze operation.[99;100] However, isolation of the pulmonary veins together with a surgical reduction of left atrial size seems to restore sinus rhythm in patients with mitral valve disease, although it does not include all left-sided incisions of the Maze III procedure.[101;102]
While these procedures require open-heart surgery, catheter based endocardial approaches have been developed. E.g., the method of circumferential radiofrequency (RF) pulmonary vein ablation, as proposed by Pappone et al., may not only isolate triggers but also reduces electrically functional atrial mass. The area encircled by RF ablation was larger in patients without AF recurrence compared to patients with AF recurrence.[103] However, such minimally invasive catheter approaches are technically challenging and success rates seem to be lower than in Maze operations.[104]

Drug Therapy

Depending on the substrate different types of AF can occur. In apparently normal atria different types of acutely induced AF have been described, based on the complexity of atrial activation.[105] In a goat model, atrial dilatation widened the excitable gap during AF.[106] Further studies will be necessary to show whether different types of AF require different therapies. Theoretically, a more specific antiarrhythmic drug therapy may improve the risk-benefit ratio of anti-arrhythmic drugs (AADs). Some new promising substances are currently being developed.[107;108]
Medications, which reduce atrial size and wall stress, may also reduce the recurrence and stability of AF. Thus, pharmacologic antiarrhythmic therapy may be possible without using specific AADs. Given the potentially serious arrhythmogenic and non-arrhythmogenic side effects of currently available

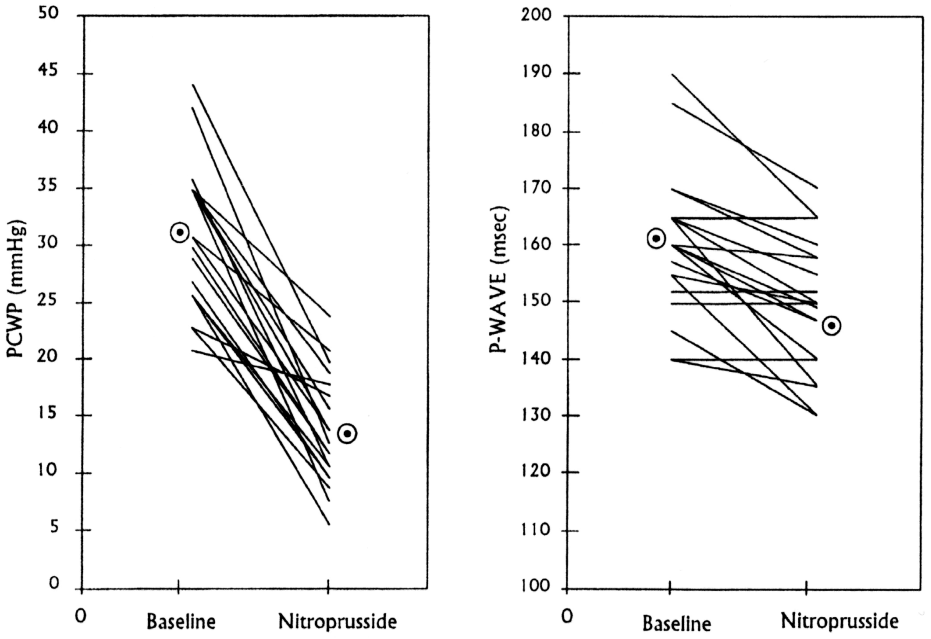

Figure 6
Acute effects of sodium nitroprusside administration on mean pulmonary capillary wedge pressure (PCWP) and P-wave duration in 19 patients with chronic heart failure. From Faggiano et al.[11]

AADs, this could be a successful strategy not only for treating AF as a rhythm disorder but also for improving morbidity and prognosis.
According to experimental data from the isolated rabbit heart, acute reduction of atrial pressure has been shown to improve atrial conduction in humans.[26] Faggiano et al. infused nitroprusside in patients with chronic congestive heart failure to reduce cardiac pre- and after-load. As a result, the pulmonary capillary wedge pressure declined and the filtered P-wave became shorter (Figure 6).[11] The cardiac effects of hypertension include atrial enlargement.[42;109] Most studies have reported that the degree of atrial dilatation correlates with the degree of hypertension.[110;111] Thus, antihypertensive agents may reduce atrial size. In a clinical study of Gottdiener et al. the effects of atenolol, captopril, clonidine, diltiazem, hydrochlorothiazide and prazosin on left atrial size were investigated.[112] Hydrochlorothiazide turned out to be most effective in reducing left atrial size in enlarged atria. It was the only drug, that also reduced atrial dimensions in patients with normal atrial size at baseline. ACE inhibitors not only reduced atrial size in dilated atria.[112] In a dog model, enalapril also attenuated the effect of tachycardiomyopathy on atrial fibrosis, atrial conduction and stability of induced AF episodes.[113] The angiotensin I type 1 receptor blocker irbesartan reduced the recurrence of AF after cardioversion.[114] Two other studies showed that ACE inhibitors decrease the incidence of AF in

patients with left ventricular dysfunction.[115;116] However, effects on atrial size were not reported. In general, new pharmacological approaches in heart failure therapy are of potential interest in treating or preventing atrial dilatation and its consequences. Novel drugs interacting with the sympathetic nervous system or with endothelin, vasopeptidase inhibitors, cytokine antagonists, calcium sensitizers, or gene therapy are some of the possible future approaches. In the meantime, primary and secondary stroke prevention in dilated and fibrillating atria by anticoagulation remains the cornerstone of drug therapy.

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Summary

The goal of the present study was twofold: First, to study the effects of chronic atrial dilatation on atrial electrophysiology, focusing on atrial fibrillation (AF); second, to characterize contractility of enlarged atria.

Chapter 1 provides the clinical and experimental background for the study.

Chapter 2 illustrates the interplay between atrial arrhythmias, cardiac function and dimensions. It describes the case of a patient suffering from focal atrial arrhythmia originating from a pulmonary vein and causing atrial fibrillation, atrial flutter and atrial tachycardia. The resulting rapid ventricular rate induced tachycardiomyopathy. Radiofrequency ablation in a pulmonary vein cured the supraventricular arrhythmia and normalized ventricular function. This is one of the early reports of percutaneous AF therapy.

In **Chapter 3** the interaction between atrial dilatation and atrial fibrillation is systematically reviewed. Epidemiological data show that atrial dilatation is an independent risk factor for the development of atrial fibrillation. On the other hand, atrial dilatation can be a consequence of atrial fibrillation. This implies a mechano-electric vicious circle.

Chapter 4 describes the development of a substrate of atrial fibrillation during chronic atrial dilatation. For this purpose a goat model of atrial enlargement without clinical signs of heart failure was developed. Ablation of the His bundle (complete AV block) caused a slow idioventricular rhythm, leading to cardiac volume overload. Measurement of atrial size by endocardially implanted ultrasound crystals showed slowly progressive atrial enlargement during 4 weeks. As the atria became larger, stability of induced AF episodes increased. This was not due to a shortening of atrial refractoriness (AERP). Rather, local conduction disturbances and the increased atrial surface itself seemed to stabilize the arrhythmia.

In **Chapter 5** the mutual effects of chronic atrial dilatation and electrical remodeling on the characteristics of AF were investigated. In 7 goats AF was induced during 48h by burst pacing, both at baseline and after 4 weeks of slow idioventricular rhythm. At baseline, AF-induced electrical remodeling shortened AERP and AF cycle length (AFCL) to the same extent. After 4 weeks of AV-block the right atrial diameter had increased. Surprisingly, in dilated atria electrical remodeling still shortened AERP, but failed to shorten the AFCL. Mapping revealed a higher incidence of intra-atrial conduction delays during AF. Histological analysis showed no atrial fibrosis, but a positive correlation between the size of atrial myocytes and the incidence of intra-atrial conduction block. Since in dilated atria AFCL no longer shortened during electrical remodeling, a wider excitable gap exists during AF, probably caused by intra-atrial conduction defects and a higher contribution of anatomically defined reentrant circuits.

Chapter 6 focuses on the effects of chronic atrial dilatation on atrial contractility. Atrial dilatation is an independent risk factor for thromboembolic disease in patients with and without AF. However, the mechanisms underlying thromboembolism in dilated atria are not yet clear. The aim of this study was to investigate, whether in the goat model of chronic atrial enlargement atrial contractility is impaired, and to describe the underlying cellular mechanisms. In dilated atria of awake animals, atrial fractional shortening decreased by 30%, whereas AERP remained unchanged. The atrial work index (AWI) was reduced. Furthermore, force of contraction (FC) in isolated muscle bundles from dilated atria was reduced by 50%. Action potential duration was unchanged. Contractile reserve was reduced by one third and the sarcomere content was slightly lower. Furthermore, the calcium load of the sarcoplasmic reticulum assessed by rapid cooling contractures was clearly reduced in bundles from dilated atria. In conclusion, in dilated atria intrinsic contractility was impaired. This could not be explained by changes in action potential duration or shape. The findings rather suggest a reduced Ca^{2+} load of the sarcoplasmic reticulum as a mechanism of reduced contractility. In contrast, reduction of contractile reserve plays a minor role.

Atrial dilatation is an independent predictor of mortality. Thus, the last chapter (**Chapter 7**) reviews causes, consequences, and treatment options of atrial dilatation. Determinants of atrial size are discussed, and the important difference between acute and chronic dilatation is highlighted. After remarks on the measurement of atrial size, consequences of dilated atria like arrhythmias, contractile dysfunction, and thromboembolism are addressed. Finally, established and experimental, pharmacological and surgical treatment options are described.

Samenvatting

Het doel van deze studie was tweeledig. Ten eerste, het bestuderen van de effecten van chronische atriale dilatatie op de atriale electrofysiologie en meer bepaald tijdens atriumfibrilleren (AF) en ten tweede, het karakteriseren van de contractiliteit bij gedilateerde atria.

Hoofdstuk 1 beschrijft de klinische en experimentele achtergrond van de studie. **Hoofdstuk 2** licht het verband toe tussen atriale ritmestoornissen, de hartfunctie en afmetingen van de atria. Hierin wordt een casus beschreven van een patiënt die lijdt aan een focale atriale ritmestoornis die zijn oorsprong vindt in de pulmonaal venen en atriumfibrilleren, atriumfladderen en atriumtachycardie veroorzaakte. Het verhoogde kamerritme dat hiermee samenhing veroorzaakte tachycardiomyopathie. Deze voorkamer ritmestoornis kon ongedaan gemaakt worden d.m.v. radiofrequency ablatie in een pulmonaal vene en de kamerfunctie werd bijgevolg hersteld. Dit is een beschrijving van een van de vroege rapporteringen m.b.t. percutane therapie van atriumfibrilleren.

In hoofdstuk 3 werd systematisch een overzicht gegeven van de interactie tussen atriale dilatatie en AF. Epidemiologische gegevens tonen aan dat atriale dilatatie een onafhankelijke risico factor vormt voor de ontwikkeling van AF. Anderzijds kan atriale dilatatie een gevolg zijn van AF. Met andere woorden, er bestaat een mechano-electrische vicieuze cirkel.

Hoofdstuk 4 beschrijft de ontwikkeling van een substraat van AF tijdens chronische atriale dilatatie. Hiervoor werd een geitenmodel ontwikkeld met vergrootte atria, maar zonder klinische tekens van hartfalen. Ablatie van de His bundel (volledig AV blok) veroorzaakte een traag idioventriculair ritme met een hartvolume overload tot gevolg. Bepaling van de atriale afmetingen m.b.v. endocardiale geïnplanteerde ultrasound kristallen toonde aan dat er een trage toename was in de vergroting van de atria gedurende 4 weken. Naar mate de atria groter werden nam ook de stabiliteit van de geïnduceerde AF episodes toe. Dit was niet ten gevolge van een verkorting van de refractaire periode van de boezems. Echter, lokale geleidingsstoornissen en het toegenomen oppervlak van de atria bleken verantwoordelijk voor de stabilisatie van de ritmestoornis.

In **Hoofdstuk 5** werden de gemeenschappelijke effecten van chronische atriale dilatatie en de electrische remodeling op de eigenschappen van AF onderzocht. AF werd in 7 geiten geïnduceerd d.m.v. burst pacing gedurende 48u, zowel tijdens baseline als na 4 weken traag idioventriculair ritme. Bij de baseline werd de refractaire periode en de fibrillatie cyclus lengte in dezelfde mate verkort door AF-geïnduceerde electrische remodeling. Na 4 weken AV-blok was de diameter van de rechter boezem toegenomen. De electrische remodeling verkortte verrassend genoeg de refractaire periode in gedilateerde atria maar er was geen verkorting van de AF cyclus lengte. Mapping toonde aan dat er meer

intra-atriale geleidingsvertragingen voorkwamen tijdens AF. Histologische analyse vertoonde geen fibrose in de boezems maar liet wel een positieve correlatie zien tussen de grootte van de atriale myocyten en de incidentie van intra-atriaal geleidingsblok. Het feit dat de AF cyclus lengte in gedilateerde atria niet verder verkort door electrische remodeling geeft aan dat er een bredere excitable gap bestaat tijdens AF die waarschijnlijk veroorzaakt wordt door intra-atriale geleidingsdefecten en een toegenomen bijdrage van anatomisch gedefiniëerde reentrants circuits.

Hoofdstuk 6 concentreert zich op de effecten van chronische atriale dilatatie en contractiliteit. Atriale dilatatie is een onafhankelijke risicofactor voor trombo-embolische ziekten in patiënten met en zonder AF. De mechanismen echter die ten grondslag liggen aan trombo-embolische incidenten in gedilateerde atria zijn nog niet helemaal duidelijk. Het doel van deze studie was enerzijds te onderzoeken of de atriale contractiliteit verzwakt was in het geitenmodel van chronische atriale vergroting en anderzijds het beschrijven van de onderliggende mechanismen. In gedilateerde atria van wakkere dieren was de atriale fractionele verkorting gedaald met 30% terwijl de refractaire periode onveranderd bleef. De atriale werk index was verminderd. Evenals was de contractiekracht in geïsoleerde spierbundels van gedilateerde atria gedaald met 50%. De duur van de actiepotentiaal was niet veranderd. De contractiele reserve was verminderd met een derde en de sarcomeer hoeveelheid was licht gedaald. Hierbij komt nog dat de calcium load van het sacroplasmatisch reticulum, vastgesteld m.b.v. rapid cooling contractures, duidelijk verminderd was in de bundels van gedilateerde atria. We kunnen besluiten dat de intrinsieke contractiliteit in gedilateerde atria verzwakt was. Dit kon niet verklaard worden door veranderingen in de duur of de vorm van de actiepotentiaal. Deze bevindingen suggereren eerder een verminderde calcium load van het sacroplasmatisch reticulum als onderliggend mechanisme wat betreft de verzwakking van de contractiliteit. Een vermindering van de contractiele reserve speelt in mindere mate een rol.

Atriale dilatatie is een onafhankelijke voorspeller voor sterfte. Daarom wordt in het laatste hoofdstuk **(Hoofdstuk 7)** een overzicht gegeven van de oorzaken, de gevolgen en de mogelijke behandelingen van atriale dilatatie. Bepalingen van de atriale grootte worden besproken en het belangrijke verschil tussen acute en chronische dilatatie wordt benadrukt. Na opmerkingen over de bepaling van de atriale grootte worden de gevolgen van atriale dilatatie zoals ritmestoornissen, contractiele dysfunctie en trombo-embolisatie toegelicht. Ten slotte worden zowel gevestigde als experimentele farmacologische en chirurgische behandelingen beschreven.

Epilogue

I am well aware, as I write this epilogue, that no other part of a thesis may be so carefully read. That realization is something of a relief, as far as the previous chapters are concerned…

The adventure began in 1999 when my colleagues in Tübingen (Professor Kühlkamp, Ralph Bosch, and Christian Mewis) suggested Professor Maurits Allessie as mentor of a research fellowship in electrophysiology. I had just started doing EP studies and simple ablation procedures in patients, a new and exciting field for me. Already at our first meeting Maurits surprised me with the question: "Hans, what is the project you plan to do and why do you think you can do this only in our lab in Maastricht?" I had hoped to get some ideas for a research project from him… He asked simple and scientifically radical questions, and he did not accept vague answers. I was a bit startled but challenged, too.

Dear Maurits, to be able to work and especially to discuss with you is an extraordinary experience. I enjoyed it enormously (even when I got hungry after 4 or 5 hours of our scientific dialogue…) and I regarded it not only as a personal but also a historical opportunity. You taught me to accept scientific and experimental failure and to believe in eventual success. Your pursuit of perfection in the writing of articles is impressive as is the time you customarily invest in your co-workers. Last but not least, Thea and you are exceptionally hospitable – I remember wonderful festivities at your home in Eindhoven. I thank you very much for all that.

Ulrich Schotten, my co-promotor, was the other person indispensable for this thesis. Lieber Uli, was wäre nur geworden, wären wir nicht 1 Jahr lang beinahe jeden Morgen und Abend zusammen im Auto zwischen Aachen und Maastricht unterwegs gewesen (auch wenn es mir schwer fiel, um 6:30 Uhr zu starten…). Durch unsere Diskussionen hat das ganze Projekt erst konkrete Formen angenommen – Dein Enthusiasmus hat mich irgendwann auch glauben lassen, dass sich eine endokardiale Instrumentierung für sonographische und elektrophysiologische Messungen entwickeln lässt (s. Chapter 4). Doch nicht zuletzt habe ich unsere politischen und grundsätzlichen Dialoge genossen. Für all Deinen Einsatz danke ich Dir herzlich!

Furthermore, I would like to thank the assessment committee for reading and evaluating this thesis: Prof. H.J.G.M. Crijns, Prof. M. Böhm, Prof. D.J. Duncker, and Prof. J. Smits. Your participation in the defense is also very much appreciated.

Crucial for the success of a project is the atmosphere; and one's colleagues are therefore an important factor. That I always liked working in this group was thanks to Yuri, Dirk, Sabine, Natasja, Sander, Jan, Jannie, Pepijn, Robert, Sunniva, Els, Maura, Erik, Hans, Volkert and Richard. You all are the reason why I feel nostalgic when thinking of Maastricht, I thank you for that. Dear Yuri, our desk was in the same room and we shared some ups and downs in our

experiments, in data analysis and writing articles. You were enormously disciplined and hard-working (Lance Armstrong's book "Door de pijngrens" was not by chance on your bookshelf), and you asked (somehow like Maurits) very intelligent and fundamental questions. Dear Dirk, you joined us a bit later, and when I asked a (of course, scientific) question into the room, a brilliant and refreshing discussion started. Dear Sabine, without you I never would have gone to the outstanding fish-market in Maastricht, I would not have known the names of many spices and food in Dutch and I would have had many more problems in mapping atrial activation. Dear Natasja, I still admire your industriousness – you could have written two theses. Yet I always found you open-minded and cooperative; in addition, you are an expert user of Maurits' mapping program and helped me a lot. Dear Sander, you were the encyclopedia next door, not only in biomedical but also in computer science, classical music and English; I enjoyed every meeting with you. Jan, you are the technical backbone of the lab. Many experiments would not have succeeded without your willing help, and I am a bit nervous about my future experiments in Homburg without your sitting nearby. Dear Maura and Els, thank you for being the "paranimfen". It is a great honor for me and it is good luck that we are not in ancient Greece, for I am sure that women would not have been accepted. Thank you, Els, for translating the summary into Dutch (I can read it, but writing is awfully difficult…) and thank you, Maura, for your perfect cooperation in characterizing the "atrial dilative cardiomyopathy". Dear Volkert, you helped me practically and theoretically with instrumenting the goats; I got a great deal of valuable advice from you. I thank Arne, Marion, Theo, and Ruud for the excellent technical help and general support in my experiments in the OR; you are part of the success of this work. Dear Arne, you quickly learned to do complex and new procedures and you were constantly thinking about how to improve instrumentation and experiments. These discussions helped me a lot. Last but not least I would like to thank Joyce, Frans, Monique, May and the whole department for their valuable advice and perfect care of our goats; and the secretaries Claire, Jos, Vivian and Sonia for their constant help.

Den größten Dank schulde ich meiner Frau Anne Christina, die bereit war, von Tübingen weg zu ziehen, mit zwei kleinen Kindern ein neues soziales Netz in Aachen aufzubauen und die mit einigen Entsagungen und viel Flexibilität diese Arbeit bis zuletzt unterstützt hat. Ohne sie und ohne unsere Kinder hätte ich die Motivation für dieses Projekt nicht aufgebracht. Die Hilfe unserer Eltern war in dieser Zeit immer wieder und oft kurzfristig nötig. Sie haben keinen Aufwand gescheut, sie uns zuteil werden zu lassen! Auch sie haben großen Anteil an dieser Dissertation. Meinen Eltern gilt der besondere Dank, mich und uns im Studium, in den ersten Berufsjahren, aber auch während und nach dieser Promotion bedingungslos unterstützt zu haben. Das war mir immer Rückhalt und Erleichterung.

In the last analysis, this epilogue shows that this thesis has had many co-authors, and I ask forgiveness in case I have failed to mention them all…

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Curriculum vitae

Hans-Ruprecht Neuberger

16.08.1968	Born in Ulm/Donau (Germany)
1988	High school graduation (Abitur)
1988 - 1995	Study at the Medical School of the University of Würzburg (Germany) and Bern (Switzerland)
1995	State examination in medicine ("MD")
1996	Conferral of doctorate (Dr. med.)
1995 – 2000	Resident of internal medicine (University of Tübingen), Training in Cardiology and Clinical Electrophysiology
2001 – 2004	Research Fellow at the Department of Physiology, University of Maastricht (Post-doctoral Marie-Curie Individual Fellowship and Post-doctoral Research Grant, German Heart Foundation).
2004 – present	Resident of internal medicine / cardiology (Universitätsklinikum des Saarlandes)

Awards:

2004	Poster Prize of the European Society of Cardiology
2006	"Bruno-Kisch-Forschungspreis" of the German Society of Cardiology