Atrial remodeling due to atrial tachycardia and heart failure
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Chapter 1

Introduction: Atrial Remodeling Due to Atrial Tachycardia and Heart Failure

A Review of Experimental and Clinical Studies

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I. INTRODUCTION

Chronic heart failure (CHF) is a major health problem. With an incidence of 1.32% and a prevalence of 3.0% in the Dutch population over 55 years of age, CHF was responsible for more than 24,000 hospital admissions in the Netherlands in the year 2000. Atrial fibrillation (AF) is a frequently occurring arrhythmia and is often associated with CHF. Improved treatment of acute cardiac conditions resulting in an improved survival and an overall increase of the average age of the population has increased both the incidence and prevalence of these two cardiac disorders. AF may occur as a consequence of CHF due to hemodynamic and neurohormonal conditions caused by CHF or due to a progressive common underlying condition. However, AF may also be the cause of CHF due to rapid ventricular rates resulting in a tachycardia-induced cardiomyopathy. Both AF and CHF are known to result in changes in atrial function and/or structure, a series of processes known as atrial remodeling. This chapter provides a review of experimental and clinical data on atrial remodeling due to these two frequently occurring cardiac entities, discusses their reciprocal relationship and provides the rationale of this thesis.

II. ATRIAL REMODELING

Atrial remodeling comprises a number of changes in atrial function and structure which may occur due to different conditions including AF and CHF. Among these changes are alterations in atrial electrophysiology, atrial dimensions, atrial contraction, atrial ultrastructure and the secretion of atrial natriuretic peptides.

III. ATRIAL REMODELING DUE TO ATRIAL TACHYCARDIA AND FIBRILLATION

In recent years, atrial remodeling due to chronic high atrial rates has been the subject of many experimental and clinical studies. It was well known from clinical practice that AF is a progressive arrhythmia in terms of duration and frequency of episodes in patients in which the arrhythmia is paroxysmal. Finally, in 14-24% of patients with paroxysmal AF persistent AF will develop, also in the absence of progressive underlying heart disease. Furthermore, conversion of AF to sinus rhythm, either electrically or pharmacologically, becomes more difficult when the arrhythmia has been present for a longer period of time. This indicates that the arrhythmia itself causes changes in the function and structure of the atria which could explain its perpetuating character (“AF begets AF”).
III.A.1. Atrial electrical remodeling – experimental data

In 1972, Olsson et al. found short right atrial monophasic action potentials in patients immediately after conversion of AF to sinus rhythm. Ten years later, Attuel et al. described the loss of the physiological adaptation of the atrial refractory period to rate in patients susceptible to atrial arrhythmia. Boutjdir et al. and Le Heuzey et al. found short atrial refractory periods with loss of physiological adaptation to rate in atrial appendages of patients with chronic AF undergoing surgery. At that time, these findings were interpreted as an important cause of AF in these patients. However, in 1995 two independent experimental studies first denominated changes in atrial electrophysiology as a consequence of AF. Wijffels et al. demonstrated that repeated induction of AF in goats resulted in progressive duration of the induced paroxysms together with shortening of the atrial refractory period and loss or even reversal of its physiological adaptation to rate. Similarly, Morillo et al. demonstrated that rapid atrial pacing during 6 weeks in dogs resulted in shortening of atrial refractory periods, an increased inducibility and stability of AF together with a increase in P wave duration and a decrease in atrial conduction velocity. In addition, also other investigators found a decrease in atrial conduction velocity after long term rapid atrial pacing.

Shortening of refractoriness in combination with a decrease in conduction velocity results in a shorter atrial wavelength which is the product of these two parameters. This could be an explanation for the increased duration of AF since, according to the multiple wavelet theory, a short wavelength will result in smaller wavelets which would increase the maximum number of wavelets, given a certain atrial surface. Furthermore, it was demonstrated that chronic atrial tachycardia depresses sinus node function which may reduce the stability of sinus rhythm and increase the stability of AF.

Apart of these changes which may increase the stability of AF, changes in atrial electrophysiology favoring an increased inducibility of AF have been described as a consequence of long term pacing or repeated induction of the arrhythmia. An increased heterogeneity of atrial conduction and atrial refractoriness which provides a substrate for reentry have been described already after 24 hours of rapid atrial pacing.

III.A.2. Atrial electrical remodeling – clinical data

Besides these experimental data, several studies have also investigated atrial electrical remodeling in patients with AF. Short-term artificially induced AF in humans results in shortening of atrial refractoriness. Additionally, in patients with persistent AF, atrial refractoriness has been shown to be shorter when compared to controls and to prolong after conversion to sinus rhythm. However, despite these findings, a pivotal role of atrial electrical remodeling in the progressive nature of clinical AF has never been proven. Furthermore, experimental atrial electrical remodeling is complete within hours to days while the development of sustained AF generally takes at least one week. This indicates that other factors are involved.
III.A.3. Atrial electrical remodeling - changes in ion currents and channels

Shortening of the atrial refractory period and the atrial action potential may be caused by a net decrease of inward ionic currents (Na\(^+\) or Ca\(^{2+}\)), a net increase in outward currents (K\(^+\)) or a combination of both. The changes of these currents and the expression of the responsible channels in atrial electrical remodeling have been investigated both in experimental and clinical studies.

In dogs subjected to 42 days of rapid atrial pacing, Yue et al. demonstrated a reduction in the L-type calcium current (I\(_{Ca,L}\)) and the transient outward potassium current (I\(_{to}\)). The inward rectifier K\(^+\) current (I\(_{K1}\)) and the components of the delayed rectifier current (I\(_{Kur}\), I\(_{Kr}\), I\(_{Ks}\)) were unchanged.\(^{21}\) In addition, they demonstrated a decrease of the mRNA expression of the L-type calcium channel α\(_{1c}\)-subunit, as well as Kv4.3 (encoding for I\(_{to}\)).\(^{22}\) The decrease of I\(_{Ca,L}\) is responsible for shortening of the atrial action potential whereas the decrease in I\(_{to}\) is considered to result in the loss of physiological rate adaptation of the action potential. In humans, these findings have been largely confirmed. Several studies demonstrated a decrease in I\(_{Ca,L}\) and I\(_{to}\) in patients with AF undergoing cardiac surgery.\(^{23-26}\) Brundel et al.\(^{18}\) additionally reported a decreased protein expression of the L-type calcium channel, a finding that could not be confirmed by others.\(^{30}\) Reduced mRNA and/or protein concentrations of several potassium channels have also been reported.\(^{18,31,32}\)

Changes in conduction velocity can in part be explained by changes in I\(_{Na}\) density. In dogs subjected to rapid atrial pacing, I\(_{Na}\) was reduced by 52% after 42 days\(^{33}\) which was associated with a decreased mRNA content of the Na\(^+\) channel α-subunit.\(^{22}\) In goats with AF, however, the latter finding was not reproduced.\(^{34}\) In humans with AF, no change in I\(_{Na}\)\(^{24}\) or mRNA of the Na\(^+\) channel α-subunit\(^{18}\) was found.

III.B. Changes in atrial diameter and contractility due to AF

In clinical practice there is a clear relationship between AF and atrial dilatation. However, in individual patients it is often not recognizable whether the atria are dilated as a cause or consequence of the arrhythmia. Atrial dilatation as a predictive factor for the development of AF has been recognized since some decades.\(^{35,36}\) On the other hand, atrial diameters have been shown to further increase when AF is present. In patients with AF in the absence of structural heart disease Sanfillipo et al. demonstrated an increase in atrial diameters of almost 40% during a mean follow up of 20.6 months.\(^{37}\) Additionally, it has been demonstrated that atrial diameters may decrease after conversion of AF to sinus rhythm.\(^{38,39}\) Likewise, rapid atrial pacing during 6 weeks in healthy dogs was shown to result in progressive bi-atrial enlargement.\(^{12}\)

AF results in absence of atrial contraction which only reappears gradually after conversion of long-term AF.\(^{40}\) This phenomenon is known as atrial stunning and is considered to be one of the factors responsible for the occurrence of thromboembolic complications during AF but also after a period of AF.\(^{41}\) Already after a few minutes of
experimental AF, atrial contractility is impaired. In 1964 it was demonstrated that the a-wave was missing in patients after conversion to sinus rhythm. Later, after the introduction of echocardiography, the time course of restoration of atrial contractile function after cardioversion could be monitored. It was demonstrated that the recovery of the atrial contraction after AF can take weeks to even months and is related to the duration of the previous episode of AF.

III.C. Changes in atrial (ultra)structure due to high atrial rates

Chronic experimental AF leads to extensive changes in atrial (ultra)structure. The nature and time course of these alterations have been extensively investigated in goats by Ausma and coworkers. After 9 to 23 weeks of artificially maintained AF, they found marked changes in atrial cellular substructures, including loss of myofibrils, accumulation of glycogen, changes in mitochondrial shape and size, fragmentation of sarcoplasmic reticulum and dispersion of nuclear chromatin. These changes were present in up to 92% of studied atrial cells and are considered to be a sign of dedifferentiation rather than degeneration i.e. the cells seemed to have changed to a fetal phenotype.

There are few data on changes in atrial ultrastructure in humans suffering from AF. Bailey et al. reported the first study in which atrial myocardium of living patients with AF was examined. They obtained atrial tissue from patients undergoing valve surgery for rheumatic valve disease. Of the 44 patients included, 32 were in AF of whom 18 had AF for more than 5 years at the time of surgery. They observed that long term AF was characterized by loss of muscle mass which they described as diffuse atrophy. The presence of rheumatic heart disease however may have importantly influenced the structural abnormalities they saw. Mary-Rabine et al. described the relationship between atrial cellular electrophysiology, function and ultrastructure in 121 patients undergoing cardiac surgery of which 23 had AF. Atrial biopsies obtained from patients with AF showed ultrastructural abnormalities such as loss of myofibrils and disorganization of sarcoplasmic reticulum. However, interpretation of these changes is difficult since AF was associated with higher patient age and atrial dilatation, factors independently associated with these structural changes. One paper has been published describing atrial ultrastructural changes in patients with lone AF (i.e. AF in the absence of a detectable underlying cause). These included inflammatory infiltrates, myocyte hypertrophy, myocyte degeneration and fibrosis. Brundel et al. evaluated atrial tissue of patients with a normal ventricular function undergoing coronary artery bypass grafting and compared patients with persistent AF, paroxysmal AF and sinus rhythm. In patients with paroxysmal and persistent AF, contraction bands were observed which were virtually absent in patients with sinus rhythm. In patients with AF, degenerative features such as clumping of nuclear chromatin and the presence of lysosomalike bodies were present. Furthermore, only in patients with persistent AF, hibernating atrial myocytes were found, characterized by glycogen accumulation and the dispersion of nuclear chromatin.
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III.D. Neurohormonal changes: The natriuretic peptide system
Apart from the role in the electrophysiologic and hemodynamic function of the heart, the atria also have an endocrinologic function. In situations in which there is an increased hemodynamic burden on the heart, the atria secrete atrial natriuretic peptide (ANP). Besides its diuretic effects, ANP reduces peripheral vascular resistance, reduces the sympathetic tone and suppresses the renin-angiotensin-aldosteron axis. Thus, by releasing ANP into the circulation, the preload is reduced and the atria protect themselves against hemodynamic overload. AF is associated with elevated levels of plasma ANP in the acute phase but also when the arrhythmia is chronic. The exact mechanism by which atrial arrhythmia results in secretion of ANP is unknown, although it has been demonstrated that atrial stretch is an important factor. Furthermore, the increased atrial rate itself has been proposed to result in ANP release.

IV. ATRIAL REMODELING IN HEART FAILURE AND/OR HEMODYNAMIC OVERLOAD

IV.A.1. Experimental models of CHF induced atrial electrical remodeling
Increased ventricular and atrial pressures during the development of CHF may modulate atrial electrophysiology by causing myocardial stretch. This phenomenon is called mechanoelectric feedback or contraction-excitation coupling and has been demonstrated in animal studies as well as in humans.

Several experimental studies have demonstrated changes in atrial refractoriness as a result of an acute rise in atrial pressure. However, there is disagreement whether refractory periods shorten or prolong. In dogs, an acute rise in atrial pressure caused by (near) simultaneous atrioventricular pacing resulted in prolongation of AERP. In contrast, Solti et al. reported a decrease of AERP along with an increase of atrial conduction velocity. Similarly, acute atrial volume overload in rabbits resulted in shortening of AERP but in a decrease of atrial conduction velocity. Although the results of these studies are conflicting, all report an enhanced susceptibility to AF during an acute rise in atrial pressure.

The effects of chronic heart failure, resulting in long standing atrial hemodynamic overload, on atrial electrophysiologic properties are even less well established. Li et al. evaluated the processes underlying the enhanced propensity to AF during the development of pacing induced CHF in a dog model. They induced CHF by rapid ventricular pacing during 5 weeks. When compared to control dogs, the dogs with CHF had a dramatically increased duration of AF induced by burst pacing when compared to control dogs (535±82 seconds versus 8±4 seconds). When comparing the atrial effective refractory periods (AERP) between the groups, at longer basic cycle lengths AERP was comparable.
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between both groups while at shorter cycle lengths AERP was slightly longer in the CHF group. However, this prolongation of AERP is not likely responsible for the enhanced inducibility and sustenance of AF during CHF. According to the multiple wavelet theory, AF should be attenuated by a prolongation of AERP since the wavelength (which equals conduction velocity x AERP) prolongs concurrently, resulting in a decreased maximum number of wavelets during AF. However, they observed a dispersion of atrial conduction in the CHF dogs, caused by extensive interstitial atrial fibrosis, resulting in an environment vulnerable to reentry. Comparable results were obtained in sheep with ventricular pacing induced CHF. During 6 weeks of pacing left atrial but not right atrial AERP prolonged. The susceptibility to AF initially increased. However, subsequently, the sheep became less susceptible to AF induced by an extrastimulus although the duration of AF, when induced, was longer.

Boyden et al. found no differences in the action potential duration and shape in the right atrium and only a slightly increased duration in the left atrium of cats with cardiomyopathy when compared to controls. However, the diseased atria had a substantially increased amount of inexitable cells and showed structural abnormalities including fibrosis, cellular hypertrophy and degeneration. In dogs with artificially induced right atrial enlargement caused by tricuspid regurgitation they found no difference in the right atrial action potential although the susceptibility to, and duration of AF was significantly increased when compared to control dogs. However, there was no spontaneously occurring AF. In contrast, Verheule et al. found prolonged atrial refractory periods but unchanged atrial conduction velocity in dogs one month after the induction of mitral regurgitation. Dogs with pacing induced CHF have an enhanced inducibility of atrial tachycardia with foci located along the crista terminalis and pulmonary veins. The focal nature of specific types of AF recently has gained a lot of interest. These findings, although preliminary, indicate that the development of CHF may evoke atrial foci, leading to AF.

IV.A.2. The influence of hemodynamic overload on atrial electrophysiology in patients

There are few data on the influence of atrial disease, characterized by atrial dilatation, or atrial mechanoelectric feedback in patients. Patients with dilated atria have been shown to have a shorter atrial action potential with a lower amplitude than patients in whom the atria have normal dimensions. However, this finding may partly be due to the presence of AF in 25% of patients with the dilated atria, which, apart from underlying heart disease, shortens AERP.

Simultaneous atrioventricular pacing in patients has been reported to prolong AERP. In contrast, Calkins et al. found no change in AERP during simultaneous AV pacing. However, an acute increase of the atrial pressure by two simultaneous AV beats resulted in a shortening of AERP. These results were not influenced by the presence or absence of autonomic blockade. We previously reported a case of a patient who had exercise
induced AF presumably caused by an acute increase of atrial pressure due to left ventricular ischemia due to a coronary stenosis. After angioplasty, this patient had no recurrence of AF. However, we did not prove this hypothesis by confirming changes in atrial refractoriness.

Also chronic hemodynamic load may lead to changes in atrial electrophysiology. Patients with AF and mitral valve regurgitation were shown to have an increased AERP. This prolongation was not related to arrhythmia history, i.e. also patients with chronic or paroxysmal AF and mitral regurgitation had longer AERP than patients suffering from the same arrhythmia without valve disease. Sparks et al. investigated the effect of VVI pacing in patients during sinus rhythm in the presence of an AV block. Chronic AV dissociation also resulted in prolongation of AERP and an impairment of left atrial contractility, processes which were reversible after reestablishing AV synchrony by DDD pacing. In patients with an atrial septum defect, the chronic right atrial stretch results in prolonged right AERP, conduction delay and sinus node dysfunction. Although these studies provide evidence for mechanoelectric feedback in human atria, data on these processes in patients with CHF are lacking.

IV.A.3. CHF induced atrial electrical remodeling – changes in ion currents and channels
Experimental CHF in dogs decreases the densities of atrial $I_{Ca,L}$, $I_{to}$ and $I_{Ks}$. The net result of the decrease of repolarizing potassium currents and the decrease of depolarizing calcium current resulted in a slight prolongation of the atrial refractory period and action potential duration but only at higher rates. Furthermore, the $Na^+/Ca^{2+}$ exchanger (NCX) current was increased which may promote delayed afterdepolarization induced ectopic activity.

In humans with dilated atria, Le Grand et al. found a decrease in $I_{Ca,L}$ while others found no change. Also, reported changes in $I_{to}$ and other potassium currents are conflicting. Some authors have reported an increase, others have found a decrease of $I_{to}$ in dilated atria. Additionally, the inward rectifier current $I_{K1}$ was found to be reduced or unchanged. The discrepancies of these findings may be explained by the variety of underlying cardiac diseases, use of medication and the presence of AF in some of these patients.

IV.B. Changes in atrial diameters and contractility due hemodynamic overload
Clinical CHF is associated with bi-atrial enlargement which is considered as an important factor in the genesis of atrial arrhythmias in patients with CHF. Although there are numerous experimental ventricular pacing induced CHF studies, only few have evaluated atrial dilatation during the development of pacing induced CHF. Five weeks of rapid ventricular pacing (220-240 bpm) in dogs resulted in a 80.2% and 61.2% increase in left and right atrial diastolic area, respectively, as measured by transthoracic
echocardiography. This bi-atrial dilatation was associated with a decrease in atrial contractile function which was reflected by a decrease in left and right fractional area shortening of 41.8% and 33.7%, respectively. Similar results were found by Power et al. who found a 100% increase of diastolic left atrial cross-sectional area after 6 weeks of rapid ventricular pacing in sheep.

In a study performed in 21 patients, loss of AV-synchrony due to VVI pacing during sinus rhythm resulted in an increase of mean left atrial diameter from 3.96 to 4.40 cm. Additionally, loss of atrial contractility was observed since the mitral A-wave velocity decreased from 74.1 to 39.3 cm/s. Both atrial dilatation and loss of atrial contractility were shown to be completely reversible after 3 months of reestablishment of AV-synchrony by D D D pacing.

IV.C. Changes in atrial ultrastructure due to hemodynamic overload
Atrial volume- or pressure overload results in atrial dilatation which is accompanied by changes in atrial ultrastructure, also in the absence of atrial arrhythmia.

The development of rapid ventricular pacing induced heart failure in dogs is associated with atrial interstitial fibrosis, cellular hypertrophy, loss of myofibrils, and signs of necrosis, processes that were shown to be irreversible after cessation of pacing and consequent recovery of the systolic ventricular function. Similarly, chronic atrial dilatation in dogs due to experimental mitral regurgitation in the absence of overt CHF results in atrial fibrosis, signs of chronic inflammation and increased accumulation of glycogen. Boydén et al. found marked structural abnormalities in cats with spontaneously occurring cardiomyopathy. These abnormalities included large amounts of interstitial fibrosis, cellular hypertrophy and degeneration, and thickened basement membranes. The degree of structural pathology was related to the degree of left atrial enlargement. However, part of the animals also suffered from AF which presence was also related to the magnitude of atrial dilatation.

The interpretation of changes in atrial ultrastructure in patients is hampered by the often obscure arrhythmia history of an individual patient. Aimé-Sempé et al. investigated human specimens of dilated right atrial myocardium and found signs of apoptosis and myolysis in patients with AF as well as in patients with a decreased left ventricular ejection fraction who were in sinus rhythm. These included a disrupted sarcomeric apparatus with replacement by glycogen granules, the presence of large TUNEL positive nuclei with condensed chromatin indicating the presence of DNA breakage and the decreased expression of antiapoptotic proteins. Fenoglio et al. studied right atrial samples of patients with an atrial septal defect. Although all patients had enlarged right atria, structural abnormalities including hypertrophy and cell degeneration were only observed in the presence of elevated right atrial pressures. Of note, all these 15 patients were in sinus rhythm.
IV.D. The natriuretic peptide system during CHF
Natriuretic peptides defend against excess salt and water retention, inhibit vasoconstrictor peptides, promote vascular relaxation and inhibit the sympathetic neural system. These neurohormones have been shown to be important markers in the assessment of clinical severity and prognosis of CHF.88,89 Patients with CHF have high plasma concentrations of both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). These concentrations are associated with the degree of left ventricular dysfunction and may rise a factor 30 in patients with New York Heart Association class IV CHF.90 ANP is mainly secreted from the cardiac atria but during CHF a proportion is also produced in the ventricles.91 Several experimental pacing induced heart failure studies have demonstrated an increase in circulating ANP and BNP during the development of CHF.92-95

In conclusion, it has been established that both acute and chronic atrial stretch cause changes in the electrophysiologic and structural substrate which may form an environment vulnerable to AF. However, the data are scarce and conflicting. Furthermore, other mechanisms such as neurohormonal activation and medication in patients with structural heart disease certainly will play a role. Therefore, the exact mechanisms by which CHF causes AF still remain to be fully unraveled.

V. ATRIAL ARRHYTHMIA COMPLICATING CHRONIC HEART FAILURE

Atrial arrhythmias, in particular AF are often encountered in patients with CHF. The prevalence of AF in the large CHF trials varies from 10% to 50% and increases with the severity of CHF.96-99 Also there is an increased incidence of AF in CHF patients. The presence of CHF increases the risk of developing AF by six times100 and even asymptomatic LV dysfunction is associated with an increased risk of developing AF.101 However, relatively little is known about the mechanisms by which CHF may cause AF. There may be an underlying cardiac disease that may cause CHF and AF independently. Secondly, CHF is associated with an altered neurohormonal status. The plasma level of circulating catecholamines is increased and there is an increased activity of the sympathetic neural system. Adrenergic stimulation is known to shorten atrial refractoriness which may form a substrate for the initiation of atrial arrhythmia. Finally, CHF leads to altered hemodynamic conditions which may result in atrial stretch. This atrial stretch in turn may cause direct changes in atrial electrophysiologic properties but in time also in structural changes such as atrial dilatation and fibrosis which favor the initiation and perpetuation of AF.

The impact of the development of AF in patients suffering from CHF on survival remains a subject of debate. Several studies did not show a independent prognostic significance of AF in CHF patients.102-105 Conversely, in other studies there was a significant association between the development of AF and mortality.106-108 Some authors
have suggested that the development of AF in patients with CHF, although associated with a higher mortality, does not independently increase mortality but is merely a reflection of general deterioration of the patients cardiac condition and rather is a consequence than a cause. Others suggest that the impact of the development of AF during CHF on mortality depends on the severity of CHF and is more significant when the degree of CHF is relatively low.\textsuperscript{109,110}

VI. HEART FAILURE CAUSED BY ATRIAL ARRHYTHMIA: TACHYCARDIOMYOPATHY

Chronic incessant supraventricular tachycardia or AF may result in CHF. On one hand, this is caused by the rapid irregular rhythm\textsuperscript{111,112} and the absence of the atrial contraction (“atrial kick”).\textsuperscript{113} On the other hand, a tachycardia induced cardiomyopathy may be induced during chronic fast atrial rhythms with a high concurrent ventricular rate. This so-called tachycardiomyopathy contributes to the impaired ventricular function. A case of a patient with AF who developed CHF suggesting a causal relationship was already reported in 1913.\textsuperscript{114} However, not until the 1940’s this relationship was established.\textsuperscript{115,116} It may be difficult to recognize this form of CHF. The diagnosis is made when underlying cardiac disease is absent and cardiac function improves after termination of the arrhythmia or control of the ventricular rate.\textsuperscript{117-120} However, still a subset of patients who are thought to have an idiopathic dilated cardiomyopathy in fact have tachycardiomyopathy. Left ventricular dysfunction due to AF has even been reported in patients with normal heart rates. A sustained improvement in LVEF from 30 to 39% after His bundle ablation has been reported in these patients.\textsuperscript{121}

VI.A. Experimental tachycardiomyopathy
The observation that chronic tachycardia may lead to CHF resulted in the development of the first experimentally pacing induced CHF model in 1962.\textsuperscript{122} Since then, numerous rapid atrial\textsuperscript{123-126} or ventricular\textsuperscript{127-136} pacing induced CHF models have been developed in order to study CHF in general and tachycardiomyopathy in particular.\textsuperscript{137} Chronic ventricular pacing or chronic atrial pacing with a high ventricular response results in a dilating cardiomyopathy characterized by elevated filling pressures, ventricular dilatation, a decreased ventricular end systolic pressure and a decreased left ventricular ejection fraction.\textsuperscript{138} Typically, the ventricular wall thickness reduces, which, together with ventricular dilatation results in an unchanged ventricular mass.\textsuperscript{125} On a microscopic level, ventricular tachycardiomyopathy is characterized by changes in ventricular myocyte shape and alignment, destruction of the myocardial collagen matrix and an altered orientation of contractile proteins.\textsuperscript{138} Termination of pacing results in a recovery of systolic function and changes in the extracellular matrix.\textsuperscript{139} However, diastolic function remains impaired and ventricular hypertrophy develops.
VII. ATRIAL FIBRILLATION AND CHF: A CHICKEN-EGG RELATIONSHIP

As mentioned at the beginning of this chapter, AF and CHF frequently coincide and have a reciprocal relationship which is schematically depicted in Figure 1.

In an individual patient, either CHF or AF may occur due to an underlying (cardiac) disease. Subsequently, there are different ways in which one of these conditions may result in the other. First, AF may cause CHF by an increased ventricular rate, eventually resulting in tachycardiomyopathy. Second, CHF may be complicated by the development of AF due to atrial remodeling depending on the altered hemodynamic and neurohormonal conditions during CHF (CHF dependent atrial remodeling). A vicious circle may thus develop. In addition, AF may stabilize due to atrial remodeling induced by the arrhythmia itself (Rate dependent atrial remodeling). Finally, both CHF and AF may be progressive due to deterioration of an underlying (heart) disease which may cause CHF and AF independently. Due to these interacting processes, it may be difficult to recognize which came first when a patient presents him/herself with both AF and CHF.

Figure 1.
VIII. CONCLUSION AND AIM OF THE PRESENT STUDY

Atrial arrhythmia, in particular AF and CHF are two frequently encountered conditions in clinical practice. Both lead to changes in atrial function and structure, an array of processes known as atrial remodeling. In the recent past, many studies have evaluated atrial remodeling due to either AF or CHF. However, AF and CHF often coexist in patients. Furthermore, in most of the above mentioned experimental AF/rapid atrial pacing studies, the ventricular rate was uncontrolled and therefore also high. This may have resulted in hemodynamic changes and/or the development of tachycardiomyopathy which could have influenced the results. In other words, apart of an increased atrial rate, AF will also have had hemodynamic consequences for the atria with consequent atrial remodeling in these experiments.

Therefore, the aim of the present study was to determine which processes in atrial remodeling during a chronic atrial tachycardia with developing tachycardiomyopathy are related to the high atrial rate ("rate dependent") on one hand and which are related to the high ventricular rate resulting in the development of tachycardiomyopathy ("CHF dependent") on the other.

For this purpose we developed an experimental animal model in which we could investigate the processes involved in atrial remodeling during chronic atrial tachycardia both in the presence and absence of a high ventricular rate, resulting in tachycardiomyopathy.

References


