Atrial remodeling due to atrial tachycardia and heart failure
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Chapter 2

Electrical Remodeling and Atrial Dilation During Atrial Tachycardia are Influenced by Ventricular Rate

Role of Developing Tachycardiomyopathy

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ABSTRACT

Background Atrial fibrillation (AF) and chronic heart failure (CHF) are two clinical entities that often coincide. Our aim was to establish the influence of a concomitant high ventricular rate and the consequent development of CHF on electrical remodeling and dilation during atrial tachycardia.

Methods and Results A total of 14 goats was studied. Five goats were subjected to 3:1 atrioventricular (AV) pacing (A-paced group, atrial rate 240 bpm, ventricular rate 80 bpm). Nine goats were subjected to rapid 1:1 AV pacing (AV-paced group, atrial and ventricular rate 240 bpm). During 4 weeks, right atrial (RA) and left ventricular (LV) diameters were measured during sinus rhythm. Atrial effective refractory periods (AERP) and inducibility of AF were assessed at three basic cycle lengths (BCL). After 4 weeks of rapid AV pacing RA and LV diameters had increased to 151% and 113% of baseline, while after rapid atrial pacing alone these parameters were unchanged. Right AERP (157±10 ms vs. 144±16 ms, at baseline at a BCL of 400 ms in the A-paced and AV-paced group, respectively) initially decreased in both groups, reaching minimum values within one week. However, subsequently, AERP partially recovered in AV-paced goats, while AERP remained short in A-paced goats (79±7 ms vs. 102±12 ms after 4 weeks, p<0.05). Left AERP demonstrated a similar time course. Inducibility of AF increased in both groups, and reached a maximum during the first week in both groups being 20% and 48% in the A-paced and AV-paced group, respectively.

Conclusions Nature and time course of atrial electrical remodeling and dilation during atrial tachycardia are influenced by a concurrent high ventricular rate and the consequent development of CHF.
INTRODUCTION

During the last years the electrophysiologic changes caused by atrial fibrillation (AF) have been subject of increasing interest. It has been comprehensively demonstrated that both chronic AF and chronic atrial tachycardia cause shortening of the atrial effective refractory period (AERP) and a loss or even reversal of the physiological rate adaptation of the AERP in both animals\(^1\)-\(^5\) and in patients.\(^6\)-\(^9\) These changes are known as atrial electrical remodeling and are considered to play an important role in the progressive nature of AF.

However, in a setting of experimental heart failure caused by chronic rapid ventricular pacing it has been demonstrated that atrial refractoriness prolongs.\(^10\)-\(^12\) Despite this prolongation, the atria are vulnerable to the development of AF, which complies with the clinical experience that heart failure is often complicated by AF. Conversely, AF may be complicated by heart failure caused by rapid, irregular ventricular rates, a shortened diastole and the loss of atrial contraction.\(^13\) In addition, an intrinsic tachycardia induced cardiomyopathy may develop. This so-called tachycardiomyopathy (TCMP) contributes to the impaired ventricular function.

Considering the above, in TCMP, tachycardia related shortening of the AERP possibly competes with heart failure related prolongation of the AERP. TCMP is not uncommon and may be present to a certain degree in most patients with AF.\(^14\) The aim of the present study was to investigate atrial electrical remodeling and dilation during atrial tachycardia both in the presence and absence of a simultaneously developing TCMP due to a high ventricular rate.

METHODS

Animal preparation
All experiments were performed in accordance with the Guidelines for Animal Research and approved by the Ethics Committee on Animal Research of the University of Groningen. We used 14 female goats. Under isoflurane anesthesia, a right intercostal thoracotomy was performed and the pericardium opened. Four custom made felt electrode arrays (3.0 x 1.0 cm) each containing 4 platinum electrodes (electrode diameter, 1.5 mm; interelectrode distance, 8 mm) were sutured on the right and left atrial appendage and the right and left ventricular lateral wall. Two pairs of piezoelectric transducers (2mm-xtal-36S, Sonometrics Inc., London, Ontario) were placed on the right atrium (RA) and the left ventricle (LV), respectively, for measurement of RA and LV diameters. The RA transducers were sutured to the epicardial surface, using a D acron
patch. One was attached to the RA anterolateral wall, the other one to the RA wall next to the aorta. The LV transducers were placed in the LV wall, one in the anterior mid portion, the other in the opposite part of the posterior wall. Additionally, in five goats, a DDDR pacemaker in VDD mode (DiamondII, Vitatron Medical, Dieren, the Netherlands) was implanted with epicardial pacemaker leads (Type 4965, Medtronic Inc.) on the RA and right ventricle (RV) after which total AV block was created by radiofrequency catheter ablation via the external jugular vein. The animals received ampicillin 1000mg prophylactically and once daily for 3 days after surgery. After a recovery period of two weeks, the goats were placed in a cage (1.5 x 0.7m), with free access to food and water. The electrode wires were connected to a cardiac stimulator and multi-channel recording unit (bandwidth, 50 to 400Hz). The piezoelectric transducer wires were connected to a sonomicrometry unit, consisting of a sonomicrometer (Triton 120, Triton Technology Inc. San Diego, CA), an AD converter (sample frequency 100Hz) and a personal computer for acquisition, storage and analysis of the signals.

Experimental protocol
During sinus rhythm, mean RR interval was calculated by averaging 500 consecutive RR intervals, recorded from the RA electrodes.
RA and LV diameters were measured simultaneously during sinus rhythm over a period of 10 seconds. In order to eliminate fluctuations by respiration, endexpiratory maximum (“end-diastolic”) values were taken.

AERP was measured from one pair of electrodes on each atrium at three different basic cycle lengths (BCL) of 400, 300 and 200 ms. At 4 times diastolic threshold, eight basic drive stimuli (S₁) were followed by one single premature stimulus (S₂). The S₁S₂ coupling interval was increased in steps of 5 ms, starting from well within the refractory period. The longest S₁S₂ coupling interval that failed to result in a propagated response was taken as the local ERP. Inadvertent induction of at least 1 second of AF during AERP measurements was scored. In case AF was induced which did not spontaneously convert to sinus rhythm within 30 minutes, flecainide (1 mg/kg) was given intravenously during 10 minutes through a catheter in the right external jugular vein in order to restore sinus rhythm. After administration of flecainide rapid pacing was resumed and measurements were postponed for at least 24 hours because of possible influence of flecainide on the investigated parameters. Basically this protocol precluded the development of chronic AF during the course of the experiments.

Pacing protocol
After a baseline study, the goats were subjected to AV pacing during 4 weeks. Pacing was performed at the RA and the RV, using a biphasic pulse of 2 ms duration at twice diastolic threshold. The goats were divided in two groups. The five goats with AV block (A-paced group) were subjected to 3:1 AV pacing with a rapid atrial pacing cycle length
of 250 ms (240 bpm) and a ventricular pacing cycle length of 750 ms (80 bpm), which resembles the physiological heart rate of a goat during sinus rhythm (Figure 1, top panel). The other nine animals (AV-paced group) were subjected to rapid 1:1 AV pacing with an atrial and ventricular pacing cycle length of 250 ms (240 bpm) (Figure 1, bottom panel). In both groups the AV delay was 100 ms.

Pacing was only interrupted for measurement of the above-mentioned parameters at t=4, 8, 12, 24, 30, 36, 48, 60 hours and 3, 7, 10, 14, 17, 21, 24, 28 days (4 weeks). Continuous capture during pacing was confirmed by randomly performed 24-hour Holter registrations.

Statistical analysis

All data are reported as mean±SD and were assessed on predefined time points. To analyze time series a repeated measurements analysis was performed, using a 2-way ANOVA model with main effects group and time, and their interaction. Contrasts were defined to obtain a subanalysis within groups between time points and between groups. If data were not normally distributed, logarithmic transformation was performed. If this did not normalize the data a Wilcoxon test was used. All p-values are two-sided. A p-value<0.05 was considered statistically significant. SAS version 6.12 (Cary, NC) was used for all statistical evaluations.

RESULTS

Two goats in the AV-paced group died suddenly after developing end stage congestive heart failure. One goat died after 23 days, the other after 25 days. Ventricular fibrillation was documented by Holter registration as the cause of death in one goat.

Heart rate

Cessation of pacing always resulted in immediate restoration of sinus rhythm (with VDD pacing in the A-paced group). In the A-paced group, the spontaneous heart rate did not change significantly. In contrast, in the AV-paced group, the mean heart rate increased progressively, due to increasing heart failure (Table 1).

Right atrial and left ventricular dimensions

To correct for differences in baseline diameters between individual goats mean diameters are calculated as a percentage of baseline values. In the A-paced group, mean RA diameter did not change during 4 weeks of 3:1 AV pacing. However, in the AV-paced group, the mean RA diameter increased progressively, reaching 151% of baseline after 4 weeks (Figure 2, top panel).
Figure 1. Tracings of the pacing protocol recorded at the left atrium (LA) and left ventricle (LV) in the A-paced group (top panel) and the AV-paced group (bottom panel). In both groups, the RA was paced with a pacing cycle length of 250 ms. In the A-paced group, the RV was paced with a pacing cycle length of 750 ms while in the AV-paced group the ventricular pacing cycle length was 250 ms.

Figure 2. Time course of mean RA (top panel) and LV (bottom panel) diameters represented as a percentage of baseline in the A-paced group (open dots) and the AV-paced group (solid dots). *p<0.05 vs. baseline; †p<0.05 vs. A-paced group.
Table 1. Condensed Time Course of Mean RR Interval During Sinus Rhythm and Mean Left and Right Atrial Effective Refractory Periods

<table>
<thead>
<tr>
<th></th>
<th>Mean RR interval</th>
<th>RAERP 400</th>
<th>RAERP 300</th>
<th>RAERP 200</th>
<th>LAERP 400</th>
<th>LAERP 300</th>
<th>LAERP 200</th>
</tr>
</thead>
<tbody>
<tr>
<td>t=0</td>
<td>632±247</td>
<td>562±91</td>
<td>157±10</td>
<td>144±16</td>
<td>156±10</td>
<td>153±15</td>
<td>139±11</td>
</tr>
<tr>
<td>t=1 week</td>
<td>500±68</td>
<td>448±44*</td>
<td>89±12*</td>
<td>94±16*</td>
<td>98±12*</td>
<td>100±14*</td>
<td>102±11*</td>
</tr>
<tr>
<td>t=2 weeks</td>
<td>519±79</td>
<td>426±33†</td>
<td>83±14*</td>
<td>118±29†</td>
<td>99±13*</td>
<td>126±21*</td>
<td>102±12*</td>
</tr>
<tr>
<td>t=3 weeks</td>
<td>510±53</td>
<td>423±40†</td>
<td>81±10*</td>
<td>111±26†</td>
<td>96±14*</td>
<td>119±18†</td>
<td>99±10*</td>
</tr>
<tr>
<td>t=4 weeks</td>
<td>586±197</td>
<td>418±43†</td>
<td>79±7*</td>
<td>102±12†</td>
<td>95±9*</td>
<td>109±11*</td>
<td>99±12*</td>
</tr>
</tbody>
</table>

RAERP and LAERP indicate left and right atrial effective refractory period, respectively; A-paced, rapid atrial pacing only; AV-paced, rapid atrioventricular pacing. *p<0.05 vs. baseline; †p<0.05 vs. A-paced group.
In the A-paced group, mean LV diameter did not change. However, in all goats subjected to rapid 1:1 AV pacing (AV-paced), LV diameter increased progressively and reached 113% of baseline after 4 weeks. (Figure 2, bottom panel)

Atrial effective refractory periods
Right and left AERP decreased rapidly at all BCL. This shortening was more pronounced in the right atrium than in the left atrium. Furthermore, there was a trend towards a greater shortening of AERP in the A-paced group when compared to the AV-paced group (Figure 3 and Table 1). Additionally, in both groups a reversal of the physiological rate adaptation of right and left AERP developed, characterized by shorter AERP at long BCL and vice versa (Table 1). AERP reached minimum values during the first week. Subsequently, AERP remained short in the A-paced group. However, in the AV-paced group, right and left AERP increased again but remained shorter than during baseline. This ‘rebound of atrial refractoriness’ was not paralleled by restoration of the physiological rate adaptation. The point of rebound, defined as the point in time after which all subsequent AERPs were higher, was 3 days in one goat, 1 week in five goats, 10 days in two goats and 14 days in one goat.

The relation between right atrial dilation and electrophysiologic changes in the AV paced group
Figure 4 demonstrates the relation between mean right atrial diameter and mean AERP in the AV-paced group. During the first 3 days, right AERP shortened at all BCLs without a significant concurrent change in RA diameter. Subsequently, between 3 days and one week, RA diameter started to increase while right AERP did not change. After 1 week of rapid ventricular pacing right atrial refractoriness started to prolong, along with a further progressive increase in RA diameter. After two weeks, the rebound of atrial refractoriness was complete although RA diameters continued to increase until the end of the experiment.

Inducibility of atrial fibrillation
Inducibility of short-lived AF was assessed in seven goats of the AV-paced group and all five goats of the A-paced group. Inducibility was not always measured at both atrial sites at all three BCLs due to sustained AF requiring flecainide or a sinus cycle length <400 ms. Table 2 shows the percentage of AERP measurements as well as the number of goats showing at least 1 second of AF during the course of the protocol.

There was no qualitative difference in the time course of inducibility of short-lived AF in both experimental groups. Initially, atrial as well as AV pacing resulted in an increase in inducibility of AF. In both groups, inducibility of AF was highest in the first week. The inducibility of AF in the AV-paced group reached higher values than in the A-paced goats. After 1 week, in the AV-paced goats, AF was induced in all 7 goats
during almost half of the AERP measurements, whereas in the A-paced goats, AF was induced in 4 of 5 goats albeit in only 20% of AERP measurements. However, after the first week, inducibility of AF decreased in both groups and remained constant thereafter.

Figure 3. Time course of mean right and left AERP measured at a BCL of 400 ms (□ top panels), 300 ms (○, middle panels) and 200 ms (Δ, bottom panels) in the A-paced group (open dots) and the AV-paced group (solid dots). Note the rebound of AERP and the trend towards less pronounced shortening in the AV-paced goats.
Figure 4. Relation between mean RA diameter and right AERP during four weeks of 1:1 AV pacing (AV-paced group) at t=0, 3 days and 1, 2, 3, 4 weeks, respectively, measured at BCL of 400 ms (top panel), 300 ms (middle panel) and 200 ms (bottom panel).
DISCUSSION

Main findings
In the present study we investigated the processes of atrial electrical remodeling and atrial dilation during atrial tachycardia in the presence and absence of a simultaneously developing ventricular tachycardiomyopathy. First, it demonstrates that during the development of pacing induced heart failure AERP shows a dynamic behavior. Initially, the AERP decreased in both A-paced goats and AV-paced goats. However, in the AV-paced group, during the development of heart failure the AERP prolonged, resulting in a rebound of atrial refractoriness. This rebound occurred only after the atria started to

Table 2. Condensed Time Course of Inducibility of AF (>1 second) by a Single Extrastimulus.

<table>
<thead>
<tr>
<th></th>
<th>A-paced goats</th>
<th>AV-paced goats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Goats (n)</td>
<td>AERP measurements (n)</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>1 day</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>1 week</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>2 weeks</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>3 weeks</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>4 weeks</td>
<td>5</td>
<td>50</td>
</tr>
</tbody>
</table>

A-paced, rapid atrial pacing only; AV-paced, rapid atrioventricular pacing.
dilate. Second, pacing induced heart failure results in a pronounced increase of atrial diameters whereas rapid atrial pacing without a high ventricular rate did not have any effect on the diameters of the atria or ventricles. This suggests that, at least in this model, atrial dilation during atrial tachycardia is not caused by the high atrial rate itself but mainly by a rapid ventricular response and the consequent development of heart failure. Thus, in tachycardiomyopathy electrophysiologic changes and dilation in the atria follow a different time course. This indicates that the processes underlying these changes are not identical.

Atrial electrophysiologic changes during atrial tachycardia and the role of concurrent heart failure
The effects of AF or rapid atrial pacing on atrial electrophysiology have been elaborately investigated. These phenomena are known as electrical remodeling and comprise shortening of the AERP, loss or even reversal of adaptation of the AERP to rate, a decreased atrial conduction velocity, an increased dispersion of atrial refractoriness and depression of sinus node function. However, it is not well known if and to what extent atrial electrical remodeling is modified by an underlying heart disease. In the present study in both groups the AERP decreases rapidly and a reversal of the adaptation of the AERP to rate develops. These processes are probably related to the high atrial rate and are in accordance with earlier studies.

At a later stage, however, in animals developing tachycardiomyopathy, the AERP partly recovers, without a restoration of the physiological adaptation of the AERP to rate. Previous studies evaluated the influence of altered hemodynamic conditions on atrial electrophysiology. An acute rise in atrial pressure due to (near) simultaneous atrial and ventricular pacing or long term AV dissociation due to VVI pacing in patients with sinus rhythm results in an increase of the AERP. Similarly, the AERP is prolonged in patients with mitral valve regurgitation when compared to patients without this condition. Power et al also demonstrated a progressive prolongation of the AERP in a sheep model of pacing induced heart failure. Furthermore, Li et al demonstrated a prolongation of the AERP at shorter BCL in dogs with congestive heart failure.

The time course of changes in the AERP in the AV-paced goats in this study seems to be a combination of the two above-mentioned processes. First there is shortening of the AERP, which is complete within one week and relates to the high atrial rate. Subsequently, the AERP recovers and this rebound is exclusively present in the goats with pacing induced heart failure.

The effects of chronic atrial tachycardia on atrial function and structure
Chronic rapid atrial rates may lead to changes in atrial function and structure. Morillo et al. demonstrated that rapid atrial pacing (400 bpm) during 6 weeks in dogs results in marked atrial dilation. Also in humans, AF may result in progressive atrial dilation,
even in the absence of underlying cardiovascular disease. After restoration of SR, atrial dilation may diminish. In the present study we found an increase in the right atrial diameters during 4 weeks of rapid 1:1 AV pacing. However, no change in atrial diameters occurred in goats of the A-paced group which is in contrast with the study by Morillo et al. This discrepancy is probably related to a concurrent high irregular ventricular rate with possible development of TCM P in the latter study. Unfortunately, they neither reported the ventricular rate nor the presence of ventricular dilation or CHF. Another difference relates to the relatively low atrial rate in our experiments which resulted in a relatively long atrial diastole. This may allow recovery of cellular processes thus putting a smaller metabolic burden on the atrial myocytes. In this way, the atrial cellular integrity may be preserved and dilation prevented. Of note, the atrial rate in the present study was sufficiently high to produce AERP shortening comparable to that found in experimental AF.

Inducibility of AF and the role of concurrent heart failure during atrial tachycardia This study demonstrates a dynamic time course of inducibility of AF during atrial tachycardia, both in the presence and absence of the development of pacing induced heart failure. Of note, we studied inducibility of short-lived AF and not the development of sustained AF. Initially, inducibility of AF was low, increased rapidly after initiation of rapid pacing and was highest in the first week. Subsequently, however, inducibility decreased and was comparable to the baseline situation after 4 weeks. Similar results were obtained in an ovine model of pacing induced heart failure. Six weeks of ventricular pacing at a rate of 190 bpm resulted in an initial increase but a subsequent decrease of inducibility of shortlasting AF along with a progressive increase of left AERP. However, in the present study, since the atria were also paced, AERP shortened. Furthermore, after reaching a maximum, inducibility of AF decreased when AERP still was markedly shortened with a reversed rate adaptation. One would expect that inducibility of AF would have remained high since AERP, although longer than minimum values, was still short resulting in shorter wavelengths. Additionally, in the goats subjected to rapid atrial pacing only, inducibility of AF was less prominent when compared to the goats subjected to rapid AV pacing, although AERP shortened more markedly. Apparently, other factors which we did not determine such as conduction velocity, dispersion of refractoriness and/or conduction or neurohormonal changes may play a role in the dynamic behavior of inducibility of AF.

The present findings seem in contrast with previous rapid pacing and sustained AF models. Probably, chronic AF did not occur probably due to the lower and regular atrial rate in the present study. Additionally, the irregular ventricular rhythm during AF may have influenced atrial vulnerability to AF in previous studies. Aboveall, our methodology virtually excluded the development of chronic AF since episodes of sustained AF were terminated with flecainide to allow for subsequent AERP measurements.
Clinical relevance

Heart failure is often encountered in the setting of atrial fibrillation either as a cause or consequence. The prevalence of tachycardiomyopathy in patients with AF is unknown and may often be not overt. However, a certain degree of tachycardiomyopathy may be present in many patients suffering from AF. The present study demonstrates that concurrent development of heart failure during atrial tachycardia may modulate atrial electrophysiology in a way that, theoretically, initiation and perpetuation of AF are eventually attenuated. The clinical implications are as yet unknown but the findings should be taken into consideration when contemplating the role of atrial electrical remodeling in clinical AF. Furthermore, recent experimental data have indicated that the efficacy of antiarrhythmic drug therapy depends on the substrate underlying AF. In a dog model it was demonstrated that the class III antiarrhythmic drug dofetilide was most efficacious in terminating AF and preventing induction of AF by burst pacing in dogs with ventricular pacing induced CHF compared to dogs subjected to rapid atrial pacing. The importance of these findings in treating patients with “classical tachycardiomyopathy” (i.e. AF preceding CHF) remains to be established.

Limitations

In the A-paced group, AV node ablation was performed which was not done in the AV-paced group. Although unlikely, this may have influenced the results. It remains uncertain whether the data of animal studies can be extrapolated to human physiology. In the present study the goats were subjected to a rapid atrial rhythm during 4 weeks while in patients atrial arrhythmia may be present for many months. The development of heart failure was assumed based on progressive left ventricular dilation, the progressive increase of heart rate during sinus rhythm and the two premature deaths both with end stage heart failure in the AV-paced group. Additionally, many previous animal studies have demonstrated the development of heart failure during rapid ventricular pacing with a similar rate during an identical period of time. In this study we did not include a group of animals which were paced rapidly in the ventricle only in order to determine the effects of 1:3 AV pacing in this model.

ACKNOWLEDGEMENTS

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Atrial Electrical Remodeling and Dilation During TachycardioMyopathy

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