Atrial remodeling due to atrial tachycardia and heart failure

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Chapter 6

Atrial Natriuretic Peptides During Experimental Atrial Tachycardia

Role of Developing Tachycardiomyopathy

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ABSTRACT

Introduction Atrial tachycardia and chronic heart failure (CHF) are associated with elevated levels of atrial natriuretic peptide (ANP) and its amino terminal part NT-ANP. Chronic high atrial rates may cause CHF due to a rapid ventricular response. The aim of this study was to establish the contribution of elevated atrial rate on one hand and high ventricular rate resulting in CHF on the other, on ANP and NT-ANP levels during chronic atrial tachycardia.

Methods and Results Thirteen goats (AV-paced group) were subjected to 4 weeks of rapid AV-pacing with an atrial *and* ventricular rate of 240 bpm. Another five goats (A-paced group) were subjected to 4 weeks of atrial pacing at 240 bpm while the ventricular rate was kept low and regular at 80 bpm. Pacing was only interrupted for measurement of right atrial (RA) and left ventricular (LV) diameter and sampling for ANP, NT-ANP and renin. In the AV-paced group, RA and LV diameter reached 152 % and 109% of baseline values, respectively. Both ANP and NT-ANP (8.3±9.2 pmol/l and 0.5±0.4 nmol/l at baseline, respectively) increased progressively (53.1±37.9 pmol/l and 2.0±0.9 nmol/l, respectively, after 4 weeks). There was a significant correlation between the magnitude of atrial dilatation and natriuretic peptide levels after 3 days. In A-paced goats, however, RA and LV diameters did not change. Furthermore, ANP and NT-ANP levels (9.1±6.0 pmol/l and 0.8±0.2 nmol/l at baseline, respectively) were unchanged after 4 weeks (5.3±3.4 pmol/l and 0.6±0.2 nmol/l, respectively).

Conclusions Elevated levels of atrial natriuretic peptides during chronic atrial tachycardia relate to a high ventricular rate rather than to a high atrial rate alone. Rather than atrial tachycardia, the atrial hemodynamic burden is an important determinant of the sustained ANP response.

INTRODUCTION

Natriuretic peptides play an important role in regulation of cardiovascular homeostasis and fluid volume. These peptides have several cardiac and non-cardiac effects and constitute a counter-regulatory mechanism in situations during which there is an increased hemodynamic burden on the heart. Atrial natriuretic peptide (ANP) is mainly produced in the cardiac atria and their appendages. After secretion in the circulation, ANP is split into two fragments, of which the amino- or N-terminal part (NT-ANP) may have similar biologic actions as ANP.[1] Possible triggers for excretion of ANP are considered to be atrial stretch and an increased atrial rate although there is disagreement in the literature which of these triggers is the most important.[2-6]

Atrial tachycardia and atrial fibrillation (AF) are associated with elevated levels of plasma natriuretic peptides in the acute phase[7] but also when the arrhythmia is chronic.[8] The latter may also partly be due to the development of congestive heart failure (CHF), a condition that is also accompanied by increased plasma natriuretic peptides. In the failing heart, ANP is also produced in the ventricles. Chronic atrial tachycardia or AF may result in CHF due to chronic high ventricular rates. In most patients with chronic AF a certain degree of this so-called tachycardiomyopathy (TCM) may be present.[9]

We sought to investigate the contribution of the high atrial rate on one hand and of the high ventricular rate, resulting in TCM on the other, to the activation of the natriuretic peptide system during atrial tachycardia. The aim of the present study therefore was to establish the nature and time course of changes in plasma ANP and NT-ANP during atrial tachycardia in the presence and absence of simultaneously developing CHF due to a concurrent high ventricular rate.

METHODS

Animal preparation

All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and approved by the Ethics Committee on Animal Research of the University of Groningen. Our experimental protocol has been described previously.[10] In short, in 18 female goats four custom-made felt electrode arrays each containing 4 platinum electrodes 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.

Additionally, in five of the 18 goats, a DDDR pacemaker in VDD mode (Diamond II, 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. The animals were allowed to recover for two weeks.

Experimental protocol
Right atrial and left ventricular diameters were measured simultaneously during sinus rhythm over a period of 10 seconds. In order to eliminate fluctuations by respiration, end-expiratory maximum (end-diastolic) values were taken. Samples for determination of plasma ANP, NT-ANP and Renin were obtained from a catheter in the right external jugular vein and subsequently centrifuged and stored at –20 °C.

Pacing protocol
After a baseline study, the goats were subjected to AV pacing during 4 weeks. Pacing was performed at the right atrium and the right ventricle, 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 short 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. The other thirteen 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). In both groups the AV delay was 100 ms.

Pacing was only interrupted for measurement of right atrial and left ventricular diameters and plasma sampling for ANP, NT-ANP and Renin 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.

Determination of plasma neurohormone concentrations
ANP was measured with a commercial IRMA kit from Shionoria (Osaka, Japan). NT-ANP was measured with a commercial RIA kit from Biotop (Oulu, Finland). Renin was measured by radio immunoassay of generated Angiotensin I (ng AngI/ml/h) as described previously.[11]

Statistical analysis
All data are reported as mean±SD unless stated otherwise 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 sub analysis within groups between time points and between groups. In case of premature deaths the last values were carried forward. Since

the data were not normally distributed a logarithmic transformation was performed. All p-values are two-sided. Correction for multiple comparisons was used. A p-value<0.05 was considered statistically significant. SAS version 6.12 (Cary, NC) was used for all statistical evaluations.

RESULTS

Six of thirteen goats in the AV-paced group died suddenly after developing signs of end stage CHF. One goat died after seven days, three after 15 days, one goat after 23 days, and another one after 25 days. Ventricular fibrillation was documented by Holter registration as the cause of death in one animal. None of the A-paced goats died during the course of the experiment.

Plasma renin

Figure 1 shows the time-course of plasma renin levels in the A-paced goats and the AV-paced goats. There was no difference in baseline renin between both groups. In A-paced goats, 4 weeks of rapid atrial pacing only did not result in a change of plasma renin (2.3±1.0 ng AngI/ml/h at baseline and 3.2±1.0 ng AngI/ml/h after 4 weeks, p=NS). In

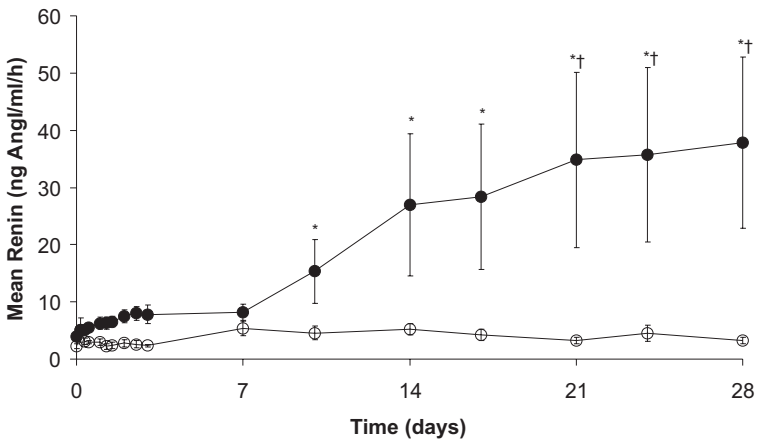

*Figure 1. Time course of plasma renin in goats of the A-paced group (open dots) and AV-paced group (solid dots). Error bars represent SEM. *p<0.05 vs. baseline; †p<0.05 vs. A-paced group.*

contrast, rapid AV pacing resulted in a progressive increase in circulating renin. During four weeks, mean plasma renin increased from 4.0±2.3 ng AngI/ml/h at baseline to 37.8±54.1 ng AngI/ml/h in these animals (p=0.0001).

Plasma atrial natriuretic peptide and N-terminal atrial natriuretic peptide
Figure 2 demonstrates the time-course of mean ANP (left panels) and NT-ANP (right panels) in the five A-paced goats and the thirteen AV-paced goats. Baseline plasma ANP levels were not statistically different between the A-paced and AV-paced group (9.1±6.0 vs. 8.3±9.2 pmol/l, respectively, p=NS). However, at baseline there were higher levels of NT-ANP in the A-paced group when compared to the AV-paced group (0.8±0.2 nmol/l vs. 0.5±0.4 nmol/l, respectively, p=0.0005). This was probably due to VDD pacing in the two-week recovery period in these goats after AV node ablation. After initiation of rapid AV pacing in the AV-paced goats, both ANP and NT-ANP increased rapidly until 10 days after initiation of pacing (45.3±43.0 pmol/l and 1.7±0.6 nmol/l, respectively, after 10 days. Both p=0.0001). Subsequently, however, both ANP and NT-ANP only slightly increased during the remaining 18 days of pacing (53.1±37.9 pmol/l and 2.0±0.9 nmol/l, respectively, after 4 weeks).

In contrast, in the goats that were paced with a high atrial rate only, ANP and NT-ANP levels only demonstrated a moderate acute but transient rise during the first hours of atrial pacing (14.6±7.5 pmol/l, p=0.02 and 1.2±0.4 nmol/l, p=0.05, respectively, after 4 hours, Figure 2 bottom panels). After one day, ANP (8.7±7.4 pmol/l) and NT-ANP (0.8±0.3 nmol/l) levels had returned to baseline values. Subsequently, there was a significant change in neither ANP nor NT-ANP levels during the further course of the experiment (5.3±3.4 pmol/l and 0.6±0.2 nmol/l, respectively, after 4 weeks. p=NS for both).

Atrial and ventricular diameters
In order to correct for differences at baseline between individual goats, diameters are reported as a percentage of baseline values. Rapid AV pacing resulted in progressive atrial and ventricular dilatation. After 4 weeks of rapid AV-pacing, RA and LV diameters reached 152% and 109% of baseline values, respectively (both $p<0.05$). In contrast, in the A-paced group, RA and LV diameters did not change, and reached 102% and 100% after four weeks, respectively (both p=NS).

The relation between atrial diameter and plasma ANP and NT-ANP
The time course of the relation between RA and plasma ANP (top panel) and NT-ANP (bottom panel) in AV-paced goats is demonstrated in figure 3. All goats demonstrated a progressive increase in natriuretic peptide levels parameters and RA diameter during the first two weeks. However, thereafter, RA diameters kept increasing while the levels of plasma natriuretic peptides did not increase along. Figure 4 demonstrates the individual

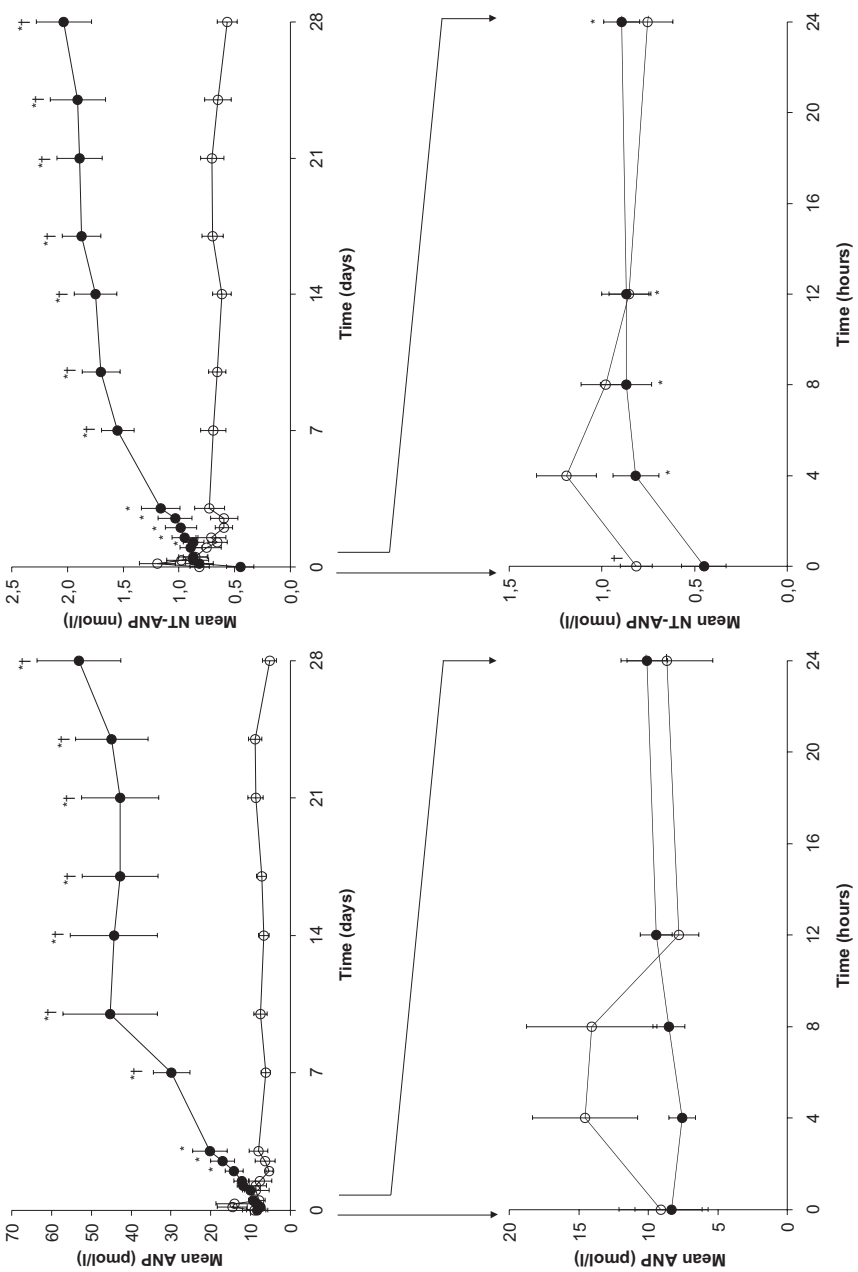

Figure 2. *Time course of mean ANP (left panels) and NT-ANP (right panels) in the A-paced group (open dots) and the AV-paced group (solid dots) during 4 weeks (upper panels) and the first day (bottom panels). Error bars represent SEM. *p<0.05 vs. baseline; †p<0.05 vs. A-paced group.*

relation between RA dilatation and circulating natriuretic peptides in the AV-paced goats. There was a significant correlation between these parameters (r^2=0.48, p=0.012 for ANP and r^2=0.48, p=0.013 for NT-ANP) after 3 days. However, during the further course of the experiment, the relationship between atrial diameters and circulating natriuretic peptides vanished due to ongoing RA dilatation in the absence of an equivalent increase in ANP and NT-ANP levels (Figures 3 and 4). Furthermore, both atrial dilatation and the increase of plasma natriuretic peptide levels were more prominent in goats that would eventually die during the experiment.

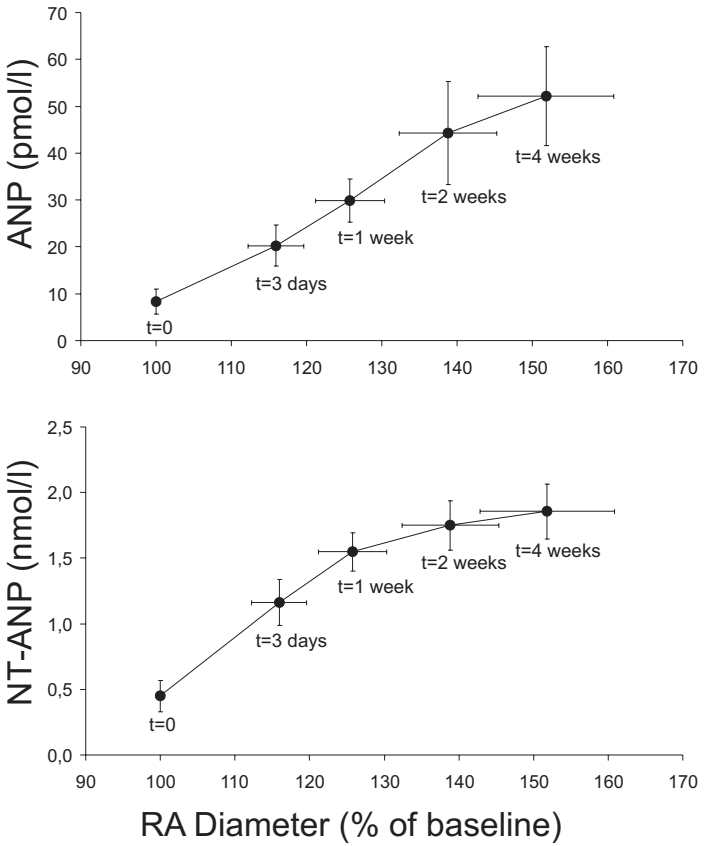

Figure 3. Relation between mean right atrial diameters and plasma natriuretic peptides during four weeks of rapid 1:1 AV pacing (AV-paced group) at t=0, 3 days and 1, 2, 4 weeks, respectively. Error bars represent SEM.

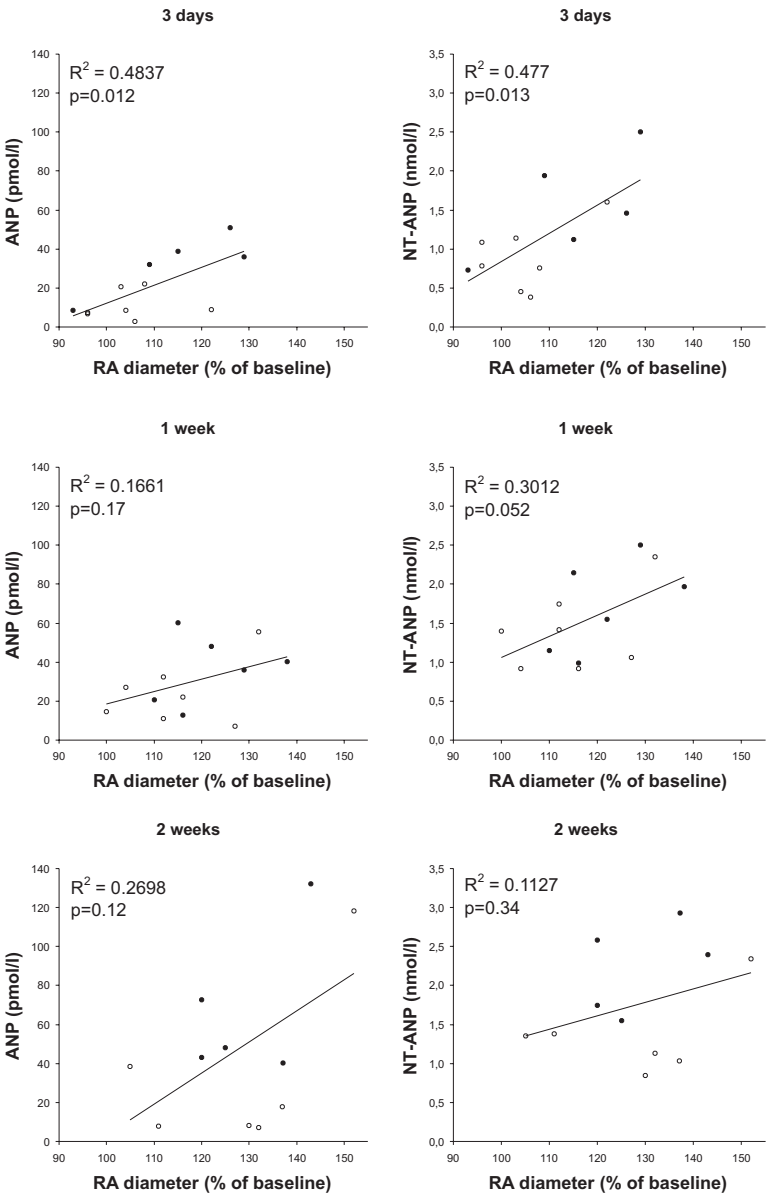

Figure 4. Relation between right atrial dilatation, as a percentage of baseline, and plasma natriuretic peptides after 3 days (top panels), 1 week (middle panels) and 2 weeks (bottom panels) of rapid 1:1 AV pacing (AV-paced group) in individual goats. Solid dots represent goats that died during the experiment from congestive heart failure. At three days, one data point is missing due to absent values of ANP and NT-ANP. At 2 weeks, two data points are missing due to one premature death and one absent value of RA diameter.

DISCUSSION

Main Findings

The present study demonstrates the time course of plasma atrial natriuretic peptides and renin during experimental atrial tachycardia in the presence and absence of simultaneously developing CHF due to a concurrent high ventricular rate. First, we show that during chronic atrial tachycardia, a concurrent high ventricular rate is responsible for elevated plasma atrial natriuretic peptide levels rather than the high atrial rate. Although both rapid atrial pacing and rapid atrioventricular pacing result in an acute rise of circulating natriuretic peptides, this increase is only transient in goats subjected to rapid atrial pacing.

Second, there is a relation between right atrial dilatation and circulating natriuretic peptides in the early stage of developing tachycardiomyopathy, indicating that either atrial stretch or increased atrial pressure is an important trigger for the release of ANP. Subsequently, however, further atrial dilatation is not accompanied by a similar rise in natriuretic peptide levels. If at that time point (or even before that time point) there is failure of ANP release to cope with developing fluid retention a progressive decline (characterized by increased ventricular and atrial diameters) follows, subsequently leading to death.

Finally, the increase in renin levels, along with progressive left ventricular dilatation indicate the development of tachycardia induced heart failure in the AV-paced goats.

Atrial arrhythmias and natriuretic peptides

Transient atrial tachycardia results in transient rise in circulating natriuretic peptides.[7] The mechanism of this increase has been attributed to a combination of an elevated atrial rate, a rise of intra atrial pressure resulting in stretch and an increased transmural pressure of the atrial wall.[2-6] Also other situations in which the hemodynamic burden on the atria is increased result in ANP rise such as loss of AV synchrony in patients with a pacemaker.[12] After cardioversion of long-lasting AF (weeks) ANP levels decrease.[13]

There is still discussion about the most prominent factor triggering release of ANP in patients with AF. In the present study we demonstrate that a chronic high atrial rate in the absence of a high ventricular rate does not result in an increase of circulating natriuretic peptides. Only during the first hours these levels rose but thereafter recovered within 24 hours. This indicates that the rise in ANP as occurring during clinical acute AF may be only transient. This may be especially true in case AF is not associated with hemodynamic compromise. In this respect it is noteworthy that in patients with persistent AF the expression of atrial mRNA of pro-ANP is only elevated in those patients who also have mitral valve disease.[14] In goats subjected to rapid AV-pacing, ANP and NT-ANP increased along with atrial dilatation indicating that atrial stretch is the principal

trigger for ANP release. At a later stage of the experiment, however, heart failure develops in these animals due to the chronic high ventricular rate.

Heart failure and natriuretic peptides

Chronic heart failure (CHF) results in neurohormonal activation, including an increase of circulating ANP and NT-ANP. The level of circulating natriuretic peptides is associated with the severity of CHF and the prognosis.[15] In CHF patients with AF, ANP is further elevated when compared to patients in sinus rhythm.[16] The results of the present study indicate that this difference in circulating natriuretic peptides may be attributed to a further deterioration of hemodynamics when AF develops during CHF since a high atrial rate itself does not result in elevated plasma levels of ANP. When AF has been present for many years however, ANP may decrease due to massive loss of functional atrial myocytes ("endocrinologic silence").[8,17,18]

In the present study the goats of the AV-paced group developed tachycardia induced heart failure characterized by progressive right atrial and left ventricular dilatation, activation of the neurohormonal system and premature death. In these goats, ANP and NT-ANP started elevating promptly after initiation of pacing and continued rising during the first ten days. Thereafter, however, both peptide levels only increased slightly until the end of the experiment and seem to reach a plateau. This may be due to an equilibrium of atrial ANP production, ANP depletion due to loss of atrial myocytes, and ventricular ANP production. At the equilibrium, the ANP production has reached its maximum. Also an altered renal ANP excretion may play a role. In this respect it is noteworthy that renin levels started increasing when ANP and NT-ANP curves started flattening. The flattening of the ANP response in combination with progression of CHF suggests that in tachycardiomyopathy the heart may escape the protective ANP mechanism, resulting in activation of the renin-angiotensin system and progression of heart failure.

Clinical Implications

These data support the concept that during supraventricular arrhythmias such as AF adequate control of the ventricular rate is essential, not only to prevent damage to the ventricles due to chronic rapid rates but also to inhibit "endocrinologic" deterioration. Furthermore, a sustained ANP release may be an early marker to identify those patients with AF prone to develop TCM.

Limitations

We did not measure (intra atrial) pressures. Furthermore, the duration of the present experiments was 4 weeks while in the clinical situation the arrhythmia and/or heart failure usually is present for many months. B-type natriuretic peptide is a very potent marker of CHF. However, it appeared to be impossible to measure this peptide in our goats, possibly due to interspecies differences.

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