Rate-dependence of atrial tachycardia effects on atrial refractoriness and atrial fibrillation maintenance

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Aims Although atrial-tachycardia remodelling is a significant atrial fibrillation (AF) promoting factor, little information is available about how atrial-tachycardia rate determines remodelling effects. This study assessed the effects of atrial tachypacing (ATP) over a range of clinically relevant rates on atrial electrophysiology and AF.

Methods and results Chronically instrumented dogs underwent sequential 7 day ATP at 400, 300, 200, and 160 bpm in random order with 2 day recovery intervals between periods of ATP. ATP at 400, 300, and 200 bpm significantly decreased atrial effective refractory period (ERP) by 41 ± 2, 37 ± 3, and 7 ± 1 ms, respectively, with no significant effects at 160 bpm. Mean duration of induced AF was increased by 400 and 300 bpm ATP (404 ± 284 and 410 ± 283 s on day 4, respectively, vs. 12 ± 4 s at baseline, P < 0.01), but not by 200 or 160 bpm ATP. ATP effects developed slowly with 200 bpm pacing, so we studied 5 week ATP at 200 and 160 bpm in additional dogs. ERP shortened gradually over 3 weeks at 200 bpm (131 ± 5 ms baseline vs. 112 ± 4 and 105 ± 4 ms at 2 and 3 weeks, respectively), but no decrease occurred thereafter (5-week value: 104 ± 3 ms) and AF duration was not significantly affected. No change in ERP or AF duration occurred at 160 bpm. Because of the limited effects of 200 bpm ATP on AF duration despite significant effects on ERP, we tested 200 bpm ATP effects in the presence of AF substrates. When 200 bpm ATP was induced in the presence of a fibrotic AF substrate induced by 2 weeks of ventricular tachypacing followed by 1 week recovery, no change in AF duration or atrial vulnerability occurred. However, when 200 bpm ATP was followed by 400 bpm ATP, the onset of remodelling and AF duration increases was accelerated.

Conclusion There is a non-linear relationship between atrial rate and the extent of atrial electrical remodelling. Remodelling at rates equivalent to paroxysmal supraventricular tachycardias in man is insufficient to promote AF alone or in the presence of an atrial fibrotic substrate, but can accelerate the remodelling and stabilization of AF when followed by faster atrial tachyarrhythmias.

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice. AF alters atrial electrophysiology to promote its own occurrence and maintenance, a phenomenon that is often referred to as ‘electrical remodelling’.1–4 Atrial flutter causes similar electrical remodelling to AF in humans.5,6 AF often coexists with paroxysmal supraventricular tachycardias (PSVTs),7–10 and it has been suggested that electrical remodelling related to the rapid rates of PSVT may contribute to AF occurrence.11 Although it is recognized that atrial tachycardia causes atrial electrophysiological remodelling, we were unable to identify any information in the literature about the relationship between atrial rate on one hand and the degree of associated remodelling and AF promotion on the other. This study was accordingly designed: (i) to investigate the relationship between the rate of atrial tachyarrhythmia and the degree of atrial electrical remodelling and (ii) to assess the effects of atrial tachypacing (ATP) at rates corresponding to those typical of clinical PSVTs (140–180 bpm) on atrial electrophysiology and AF promotion in the absence and presence of AF substrates.

2. Methods

2.1 Animal preparation

This investigation conforms 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). All animal-handling procedures were approved by the Animal Research Ethics Committee of the Montreal Heart Institute. Forty-one mongrel dogs (weight 21–38 kg) were studied. Dogs were anesthetized with ketamine (5.3 mg/kg IV), diazepam (0.25 mg/kg IV), and halothane (1.5%) and mechanically ventilated. Unipolar pacing leads were inserted into the right-ventricular (RV) apex and the right-atrial (RA) appendage (RAA) and connected to pacemakers in subcutaneous pockets in the neck. A bipolar-electrode lead was inserted into the RAA for stimulation/record during serial electrophysiological studies (EPSs). Atrialventricular block was created by radiofrequency catheter ablation to control the atrial response during ATP. For ATP-dogs, the RV pacemaker was programmed to 80 bpm. For dogs subjected to ventricular tachypacing (VTP), the RV pacemaker was set to 240 bpm. The ATP pacemaker was programmed as required to pace the RA at 160, 200, 300, or 400 bpm.

2.2 Groups and study design

Dogs were divided into the following groups (schematic in Figure 1): (i) sequential 7 day ATP at 400, 300, 200, and 160 bpm in random order, with each ATP-interval followed by a 2 day recovery period (n = 6), (ii) 5 week ATP at 200 and 160 bpm (n = 5 and 4, respectively), (iii) non-paced controls (n = 6), (iv) 7 day ATP at 400 bpm (ATP only, n = 5), (v) 3 week ATP at 200 bpm in the presence of an atrial fibrotic substrate produced by 2 week VTP to induce heart failure and a 1 week recovery interval (n = 8), and (vi) 3 week ATP at 200 bpm followed by 1 week ATP at 400 bpm (n = 7). The 2 day recovery period in Group 1 was based on evidence that 2 days of sinus rhythm allow for recovery from the effects of 5 day AF in goats. In the present studies, we noted full recovery of atrial effective refractory period (ERP) changes from 7 day ATP by the beginning of the next tachypacing interval.

2.3 Serial closed-chest electrophysiological study

On each closed-chest EPS day, dogs were anesthetized with ketamine (5.3 mg/kg IV), diazepam (0.25 mg/kg IV), and isoflurane (1.5%). Atrial pacemakers were deactivated for RAA ERP measurement at basic cycle lengths (BCLs) of 150, 200, 250, 300, and 360 ms (10 basic stimuli (S1) followed by premature S2 stimuli with 5 ms decrements). All stimuli were twice-threshold, 2 ms pulses. The longest S1–S2 interval failing to capture the atria defined the ERP. ERP rate-adaptation was determined as the difference between ERPs at a BCL of 360 vs. 150 ms. We also assessed the duration of AF induced by atrial burst pacing at 10 Hz and four times threshold current for 1–10 s. To estimate the mean AF duration (DAF) in each dog, AF was induced 10 times for AF < 20 min, and five times for AF lasting 20–30 min. When AF > 30 min was induced, AF was terminated by direct-current electrical cardioversion and a 20 min rest period was allowed before continuing measurements. If prolonged AF was induced twice during the experiment, no further AF induction was performed.

2.4 Open-chest electrophysiological study

The open-chest EPS was performed at the final study in non-paced controls, 7 day ATP-only, and 5 week ATP study groups. Dogs were anesthetized with morphine (2 mg/kg SC) and a-chloralose (120 mg/kg IV, followed by 29.25 mg/kg/h), and ventilated mechanically. Body temperature was maintained at 37°C, and a femoral artery and both femoral veins were cannulated for pressure monitoring and drug administration. A median sternotomy was performed, and bipolar electrodes were hooked into the RA and left-atrial (LA) appendage. Five silicon sheets containing 240 bipolar electrodes were sutured onto the atrial surfaces as previously described for electrophysiological mapping with the Cardiomap® system (Research Center, Sacré-Coeur Hospital and Biomedical Engineering Institute, École Polytechnique and Université de Montréal, Montreal, Canada). Atrial ERPs were measured at multiple BCLs in the RAA and at a BCL of 300 ms at seven additional sites (LA appendage, RA and LA posterior wall, RA and LA inferior wall, RA and LA sides of Bachmann’s bundle) to evaluate atrial vulnerability (percentage of sites at which AF (>1 s) was induced by single extrastimuli).

2.5 Data analysis

Data are presented as mean ± SEM. Time-dependent comparisons within groups were obtained by one-way or two-way ANOVA with repeated measures. One-way ANOVA was performed for the comparison of AF duration and AF vulnerability during open-chest EPS among groups. DAF data were normalized by log-transformation. Bonferroni-corrected t-tests were used to evaluate individual mean difference when ANOVA revealed significant group effects. A two-tailed P < 0.05 defined statistical significance.

Figure 1 Groups and study designs. ATP, atrial tachypacing; VTP, ventricular tachypacing; EPS, electrophysiologic study.
3. Results

3.1 Changes caused by 7 day atrial tachypacing at various pacing rates

We first performed a preliminary study to identify the changes produced by ATP at various rates, with repeated ATP periods in each dog to control for inter-animal variability in the response to ATP (Group 1 dogs). Figure 2 shows ERP–BCL relations over 7 day ATP at various pacing rates. ATP at 400 (Figure 2A) and 300 bpm (Figure 2B) decreased ERPs and ERP rate-adaptation, with changes apparent by day 2. At 200 bpm, ERP changes were much smaller, with significant decreases seen only after 7 days (Figure 2C). No significant ERP changes were seen with 160 bpm ATP (Figure 2D).

AF > 30 min requiring cardioversion was induced in 50% of dogs after 4 days of 300 and 400 bpm ATP, but in no dogs tachypaced at 160 or 200 bpm. DAF was significantly increased after day 4 by 400 bpm ATP (from 13 ± 4 s at baseline to 404 ± 284 s, \( P < 0.01 \)) and remained increased at day 7 (427 ± 278 s, \( P < 0.001 \)). DAF was similarly increased by 300 bpm ATP (from 8 ± 3 s at baseline to 410 ± 282 s at day 4, \( P < 0.01 \) and 421 ± 280 at day 7, \( P < 0.001 \)). No AF promotion was seen over 7 days with either 200 bpm (DAF 8 ± 4 s on day 7) or 160 bpm ATP (DAF 4 ± 1 s on day 7).

3.2 Effects on electrophysiological parameters caused by longer term atrial tachypacing at 200 or 160 bpm

Figure 3 shows an analysis of the time course of ERP changes during ATP at the four rates studied. The results at 400 and 300 bpm are consistent with previous findings suggesting near-maximal ERP changes within 1 week of ATP onset.\(^1,4\) However, the changes at 200 bpm suggested a much slower time-course. We therefore performed a 5 week study in additional dogs (Group 2 dogs) with separate groups subjected to serial EPS during ATP at 200 (\( n = 5 \)) and 160 bpm (\( n = 4 \)) to evaluate longer term effects. ERPs shortened gradually over 5 weeks in dogs paced at 200 bpm (Figure 4), and reached near-steady-state values by 3 weeks. On the other hand, pacing at 160 bpm ATP did not significantly change ERPs at any BCL over the full 5 week study period.

ERP rate adaptation was also significantly decreased by 200 bpm pacing in the 5 week ATP study. Figure 5 shows a detailed analysis of ERP rate-adaptation changes in dogs subjected to ATP at 400 or 300 bpm in the 7 day study (Figure 5A and B) compared to changes at 200 or 160 bpm in the 5 week study (Figure 5C and D). At the faster pacing-rates (top panels), ERP rate adaptation virtually disappeared by the 7th day of tachypacing. In contrast, in 160 bpm ATP dogs, there was no appreciable change in ERP rate-adaptation over 5 weeks (Figure 5D). In 200 bpm ATP dogs (Figure 5C), ATP rate-adaptation decreased significantly but remained present even after 5 weeks.

The above results show that 200 bpm ATP causes significant functional atrial electrical remodelling, albeit more slowly than 300 or 400 bpm ATP. Whether these changes translate into the creation of a substrate able to support AF maintenance is addressed by the results shown in Figure 6. Figure 6A and B shows changes in DAF that occurred during 7-day ATP at 400 and 300 bpm. DAF increased, with statistically significant changes occurring by day 4 of ATP.

**Figure 2** Time-dependent ERP changes in Group 1 dogs at each basic cycle length (BCL) during 7-day atrial tachypacing at 400 (A), 300 (B), 200 (C), and 160 bpm (D). Each dog served as their own control, with each pacing frequency applied in random order for a 7 day period followed by a 2 day rest interval. P0, P2, P4, P7 indicate baseline, 2, 4, and 7 days after ATP onset. **\( P < 0.01 \)** vs. P0. Abbreviations are as Figure 1.

**Figure 3** Changes in ERP measured at BCL 360 ms in Group 1 dogs as a function of time at four different ATP rates. **\( P < 0.01 \)** vs. day 0. Abbreviations are as Figure 1.

**Figure 4** Time-dependent ERP changes at three different BCLs in Group 2 dogs subjected to 5 week atrial tachypacing at 200 (A) or 160 bpm (B). *\( P < 0.05 \), **\( P < 0.01 \)** vs. day 0. W, week.
lower in 200 and 160 bpm dogs (13 ± 8 and 3 ± 3%, respectively) compared to ATP-only (60 ± 11%, \( P < 0.01 \)), and not significantly different from values in non-paced dogs (13 ± 6%).

### 3.3 Effects of 200 bpm pacing on dogs with an atrial fibrotic substrate for atrial fibrillation maintenance

Atrial pacing at 200 bpm produced atrial electrical remodelling (decreased ERPs and ERP rate-adaptation), but did not induce AF promotion in otherwise normal dogs. We wondered whether this moderate degree of remodelling would promote AF in the presence of a vulnerable substrate. We therefore studied the effects of 200 bpm ATP in a series of dogs with an atrial fibrotic substrate induced by prior congestive heart failure (CHF) (Group 5). Dogs were subjected to 2 weeks of VTP, sufficient to induce atrial structural remodelling,\(^1\), followed by a 1 week recovery period to allow CHF to reverse, followed by 3 weeks of ATP at 200 bpm, sufficient to produce steady-state effects on ERP and ERP rate-adaptation (Figures 4 and 5). The results are summarized in Figure 7. ERPs increased slightly during VTP and then decreased back to baseline values during the recovery period, but these ERP changes were not statistically significant. With subsequent 200 bpm ATP, ERPs decreased gradually, with statistically significant changes appearing 4 days after ATP onset and reaching a maximum at 3 weeks (Figure 7A). ERP rate adaptation was not changed during VTP and recovery periods, but decreased gradually during ATP, reaching statistically significant changes after 3 weeks of 200 bpm ATP (Figure 7B). The mean duration of induced AF increased significantly after 1 week of VTP and remained elevated through the whole subsequent study period, with no statistically significant changes from the 1 week VTP value (Figure 7C). Atrial vulnerability at the final open-chest

**Results during 5 weeks of ATP at 200 bpm are shown in Figure 6C, and indicate that despite the significant ERP abbreviation and decreases in ERP rate-adaptation produced by 200 bpm ATP (Figures 4 and 5), 200 bpm ATP did not significantly increase AF duration. Not surprisingly, 160 bpm ATP, which failed to alter ERP or ERP rate adaptation, similarly failed to produce a substrate for AF maintenance.**

In order to have comparison groups for the open-chest EPS in 160 and 200 bpm dogs, we performed open-chest EPSs in non-paced dogs (Group 3) and a series of dogs subjected to 7 day ATP at 400 bpm followed directly by open-chest study (Group 4). DAF during the open-chest study in 160 and 200 bpm ATP dogs (41 ± 10 and 11 ± 4 s, respectively) was not significantly different from values in non-paced dogs (24 ± 8 s), and all three groups had significantly smaller DAF values compared to ATP-only dogs (703 ± 348 s, \( P < 0.01 \)) vs. each of non-paced, 160, and 200 bpm groups. Atrial vulnerability to AF induction was also significantly

**Figure 5** The time-dependent changes in ERP rate adaptation during 7 day ATP at 400 (A) and 300 bpm (B), and 5 week ATP at 200 (C) and 160 bpm (D). ERP rate adaptation is determined as differences between ERPs at 360 and 150 ms. P0, P2, P4, P7, 1W, 2W, 3W, 4W, 5W indicate baseline, 2, 4, and 7 days and 1, 2, 3, 4, and 5 weeks after ATP onset. *\( P < 0.05 \), **\( P < 0.01 \), ***\( P < 0.001 \) vs. P0.

**Figure 6** Time-dependent changes in AF during 7 day ATP at 400 (A) and 300 bpm (B), and 5 week ATP at 200 (C) and 160 bpm (D). The duration of induced AF (DAF) increased significantly by 4 days of ATP at 400 and 300 bpm, whereas no DAF increases were seen with up to 5 weeks of ATP at 200 and 160 bpm. P0, P2, P4, P7, 1W, 2W, 3W, 4W, 5W indicate baseline, 2, 4, and 7 days and 1, 2, 3, 4, and 5 weeks after ATP onset. *\( P < 0.05 \), **\( P < 0.01 \), ***\( P < 0.001 \) vs. P0.

**Figure 7** Time-dependent electrophysiological changes during VTP, recovery (Rec), and subsequent 200 bpm ATP periods. (A) ERP was not significantly changed during VTP/Rec periods, but shortened clearly with subsequent ATP. (B) ERP rate adaptation was not significantly changed during VTP/Rec periods, but decreased significantly within 3 weeks of ATP onset. (C) DAF was significantly increased after 1 week of VTP and remained elevated during VTP/Rec/ATP periods. P0 = baseline, V1W, V2W = 1 and 2 weeks after VTP onset, Rec1W = 1 week after no-pacing period onset, A4D, A1W, A2W, A3W = 4 days, 1, 2, 3 weeks after onset of 200 bpm ATP. *\( P < 0.05 \), **\( P < 0.01 \), ***\( P < 0.001 \) vs. P0. Vertical dotted line = ATP-onset time.
EPS was not significantly different in these dogs (averaging 17 ± 7%) compared to non-paced controls (13 ± 6%).

3.4 Effects of 200 bpm atrial tachypacing on subsequent rapid atrial-tachycardia remodelling

The studies in VTP dogs indicated that ATP at 200 bpm does not promote AF (based on both measures of AF duration and atrial vulnerability) in the presence of an atrial fibrotic substrate. To determine whether atrial tachycardia remodelling at 200 bpm can modify changes resulting from subsequent atrial tachycardia at rates comparable to those of AF, another seven dogs were subjected to 3 week ATP at 200 bpm prior to 1 week of ATP at 400 bpm (Group 6). The results were compared to changes during 400 bpm ATP without a prior period of 200 bpm ATP, as shown in Figure 8. Figure 8A shows the ERP changes in the 200 bpm ATP dogs at BCLs of 360, 200, and 150 ms during serial closed-chest EPSs at various times during the study. ATP at 200 bpm produced a moderate degree of ERP shortening after 3 weeks. With the onset of 400 bpm ATP, the ERP abbreviated rapidly and substantial further ERP shortening was observed by day 7 of 400 bpm pacing. Figure 8B compares ERP values as a function of time during ATP at 400 bpm in dogs subjected to prior ATP at 200 bpm (ATP 400 post ATP 200) and dogs with no prior tachypacing (ATP 400 bpm-only). The ERP began at a significantly lower value in the dogs with prior tachycardia (121 ± 5 vs. 138 ± 5 ms, P < 0.05) and remained significantly lower throughout 7 day tachypacing at 400 bpm. Figure 8C shows the changes in ERP rate adaptation over time in the two groups. ATP at 200 bpm alone produced modest reductions in rate adaptation. However, when ATP at 400 bpm was then instituted, ERP rate adaptation decreased rapidly, much more rapidly than when ATP at 400 bpm was instituted without prior 200 bpm ATP. Figure 8D shows AF duration changes in the two groups. As observed in the two prior series of 200 bpm ATP dogs, no statistically significant AF promotion was noted during 3 weeks of ATP at 200 bpm. However, when 400 bpm ATP was subsequently begun, AF duration increased rapidly, becoming highly significant within 24 h. In contrast, dogs subjected to ATP at 400 bpm only achieved statistically significant AF increases 4 days after ATP onset. These results suggest that slower atrial tachycardias, such as those induced by 200 bpm pacing, may sensitize the atria to AF promotion upon the onset of a more rapid atrial rhythm like AF.

4. Discussion

4.1 Main findings

In the present study, we investigated the relationship between the rates of atrial tachyarrhythmias and the resulting atrial electrical remodelling. We found a steeply non-linear response, with atrial tachycardia at 300 and 400 bpm causing substantial and similar remodelling, 200 bpm atrial tachycardia causing slowly developing moderate ERP changes and no AF promotion, and 160 bpm causing no measurable atrial electrical remodelling.

Figure 8 Time-dependent electrophysiological changes during ATP at 400 bpm with or without a preceding 3 week period of 200 bpm ATP. (A) 200 bpm ATP for 3 weeks gradually and modestly shortened ERP, which then shortened rapidly within 1 day of 400 bpm ATP onset (vertical dashed line). *P < 0.05, **P < 0.01, ***P < 0.001 vs. P0. (B) ERP changes during ATP at 400 bpm in dogs subjected to prior 3 week 200 bpm ATP compared to dogs subjected to 400 bpm ATP without prior 200 bpm ATP (**P < 0.001 for inter-group difference). (C) ERP rate adaptation gradually and modestly decreased with 200 bpm ATP, and decreased markedly after 1 day of subsequent 400 bpm ATP (filled bars). ERP rate adaptation shortened more slowly after the onset of 400 bpm ATP without a preceding tachypacing interval (open bars). (D) DAF was increased significantly after 4 days in 400 bpm ATP-only group dogs (open bars); however, DAF increased substantially within 1 day after beginning 400 bpm ATP in dogs subjected to prior 200 bpm ATP (filled bars). P0 = baseline; P2, P4, P1W, P2W, P3W = 2, 4 days, 1, 2 and 3-weeks of 200 bpm ATP; A1D, A2D, A4D, A7D = 1, 2, 4, and 7 days of 400 bpm ATP. Vertical dotted line = ATP-onset time.
4.2 Rate dependence of electrical remodelling caused by atrial tachycardia

Despite the widespread recognition of the importance of atrial tachycardia-induced remodelling and the many studies that have examined it, we were unable to find any study in the literature that addresses the relationship between atrial tachycardia rate and resulting remodelling. In the original study reporting atrial remodelling by electrically maintained AF, the median AF cycle length was initially 149 ms and decreased to 91 ms when AF became sustained after 2 weeks, corresponding to atrial rates of about 400–600 bpm. Most studies of atrial remodelling with 1:1 ATP in large animal models have used rates of the order of 400 bpm. Schoonderwoerd et al. found that 240 bpm atrial pacing reduced ERP significantly in the goat, but did not evaluate effects on the AF substrate. We found that atrial-tachycardia remodelling effects had a very non-linear relationship with heart rate: after 7 days of ATP in the cross-over study, atrial ERP at a cycle length of 360 ms decreased by averages of 41, 37, 7, and 1 ms at 400, 300, 200, and 160 bpm pacing rates, respectively. When 200 bpm tachypacing was extended for several weeks, ERP decreased by ~25 ms at 3 weeks, whereas prolonged 160 bpm tachypacing continued to show no significant effects. AF promotion effects were even more non-linear, with clear and substantial AF promotion at 300 and 400 bpm, but no significant promotion at either 200 or 160 bpm for up to 5 weeks. The lack of AF promotion with 160 bpm pacing is not surprising in view of the absence of other significant electrophysiological changes. However, 200 bpm tachypacing produced significant reductions in both ERP and ERP rate adaptation, yet failed to increase AF duration or vulnerability even in the presence of an atrial fibrotic substrate.

4.3 Supraventricular tachyarrhythmias and atrial fibrillation

An increased risk of AF is known to be associated with various forms of supraventricular tachyarrhythmia. The relationship between atrial flutter and AF is well-established, and is consistent with our observation of extensive AF promoting remodelling with 300 bpm ATP. There is also a well-recognized enhancement of AF risk in patients with AV node re-entrant tachycardia (AVNRT) and AV-re-entrant tachycardias (AVRT) involving accessory pathways. Premature atrial complexes initiate AF during re-entrant supraventricular tachycardias, and slow-pathway or accessory-pathway ablation alone can prevent AF recurrence in patients referred for AF ablation that are found to have AVNRT or AVRT at electrophysiologic study.

A variety of mechanisms have been suggested to underlie the association between supraventricular arrhythmias and AF, including autonomic factors, refractoriness abbreviation, underlying cardiac pathologies, haemodynamic effects of tachycardia, and atrial remodelling. Electrical remodelling could contribute to the association between AF and supraventricular arrhythmias by promoting AF occurrence in the tachycardia-remodelled atria. The results of the present study bear on the potential contribution of tachycardia-induced remodelling to the clinical association between PSVT and AF. The only indication we were able to find of AF promotion at rates comparable to human PSVT was an acceleration of AF duration increases when prolonged ATP at 200 bpm preceded the onset of 400 bpm ATP. Accelerated onset of AF promotion may help stabilize AF induced by premature atrial complexes in the presence of an ongoing PSVT that has persisted for long enough to induce remodelling. It is difficult to compare tachycardia rates across species, but the 160–200 bpm range of rates we studied in the dog approximates the range of PSVT rates in man. The resting heart rate of the dog is 70–120 bpm, slightly greater than that of man, suggesting that somewhat higher rates in the dog would be needed to approximate the typical average PSVT rate of about 140–180 bpm in man. A recent study of dogs symptomatic with EPS-proven AVRT reported an average rate of 229 bpm, compared to about 175 bpm for orthodromic re-entrant tachycardias in man, confirming this expectation.

4.4 Potential significance

The present study characterizes for the first time the effects of ATP over a range of frequencies on atrial ERP, ERP rate adaptation, AF duration, and AF vulnerability. We were surprised by the lack of AF promoting effects at an ATP rate of 200 bpm, despite significant reductions in ERP and ERP rate adaptation, and therefore pursued the possibility that 200 bpm ATP might promote AF in the presence of a pre-existing AF substrate. Dogs with prior CHF have a fibrotic atrial substrate that supports prolonged AF, and we expected that 3 weeks of 200 bpm ATP, which significantly shortens atrial ERP, would promote AF maintenance or inducibility in the presence of such a substrate, but this proved not to be the case. These findings indicate that moderate ERP abbreviation does not necessarily facilitate AF, which in itself is an interesting observation, and reinforces the notion that AF promotion by electrical remodelling is more than a question of ERP changes alone. A range of factors other than ERP abbreviation that may contribute to the tachycardia-induced AF substrate have been identified, often referred to as ‘second factors’. Such factors may include cell-ultrastructure remodelling, contractile impairment, atrial dilation, connexin changes, conduction slowing related to connexin-abnormalities and/or Na⁺-channel dysfunction, tissue-structure changes like fibrosis, and the development of ectopic-impulse formation related to altered Ca²⁺-homeostasis. Although the importance of factors other than ERP is clear based on results in the present and previous studies, the specific factor(s) involved in different pathophysiological contexts remains uncertain and an appropriate issue for further investigation.

Our results bear on the mechanisms underlying the association between PSVT and AF in man. They argue against rate-related remodelling as a major underlying mechanism, leaving such alternative possibilities as common underlying atrial pathology, haemodynamic consequences of atrial tachycardia, a potential role of changed atrial activation sequence, and autonomic changes as alternative potential factors. Further assessment of these mechanisms and of electrical remodelling with PSVT in man would be of interest. In addition, our data suggest that other forms of supraventricular tachyarrhythmias with rates below 160 bpm (e.g. sinus tachycardia and multifocal atrial tachycardias) are unlikely to produce sufficient atrial remodelling to promote AF.
Our findings argue for caution when considering the role of atrial-tachycardia remodelling in clinical arrhythmogenesis. They indicate that the results of studies of remodelling caused by very rapid atrial tachycardias (such as atrial flutter and AF in man or 400 bpm tachypacing in animal models) should not be extrapolated directly to the effects of slower tachycardias, such as those associated with PSVT in man.

4.5 Limitations of the study

Because of practical considerations, we were limited by the number of ATP frequencies that we could study. It would perhaps be interesting to examine in more detail the effects of other ATP rates over the critical range between 200 and 300 bpm to clarify further the rate-remodelling relationship. One limitation to such a study may be the large intrinsic variability in AF duration between animals and even between AF inductions in the same animal, which could make it difficult to establish fine differences at different rates. The significantly prolonged AF duration prior to 200 bpm ATP in CHF-recovery dogs (Figure 7) could have made it difficult to show a further increase with ATP; however, this concern does not apply to AF vulnerability, which was low in CHF-recovery dogs (13%) and which was not significantly altered by 200 bpm ATP. Although we required a return to baseline ERP prior to the next ATP interval in the repeated 7 day ATP study (Group 1) and we randomized the order of ATP frequencies, we cannot completely exclude carry-over effects from one ATP-interval to the next. However, this concern does not apply to the dogs subjected to ATP at only one frequency, such as Group 4 dogs (400 bpm ATP for 7 days) or Group 2 dogs (160 or 200 bpm ATP for 5 weeks). We used regular-rate ATP, which may differ in some ways from the rapid but irregular activation in clinical AF and the goat-AF model. However, this limitation does not apply to the relationship between our observations of 160 and 200 bpm ATP and clinical PSVT, which is generally quite regular.

5. Conclusions

Atrial-tachycardia remodelling in the dog at rates comparable to PSVTs in man produces (at most) moderate ERP reductions and no detectable AF promotion, even in the presence of an AF promoting atrial fibrotic substrate. The onset of AF promotion by more rapid atrial tachycardias is accelerated by an earlier period of prolonged atrial tachycardia at rates equivalent to clinical PSVT, and this may contribute to AF promotion in the setting of a pre-existing atrial tachycardia. Atrial-tachycardia remodelling shows a strongly non-linear relationship to tachycardia rate, which has significant implications for understanding its mechanisms and role in clinical arrhythmogenesis.

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