Effects of inhibiting Na\(^+\)/H\(^+\)-exchange or angiotensin converting enzyme on atrial tachycardia-induced remodeling

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Abstract

Background: Inhibitors of the Na\(^+\)/H\(^+\)-exchanger (NHE1) and of angiotensin-converting enzyme (ACE) have been shown to reduce short-term (<6 h) tachycardia-induced atrial electrical remodeling. The role of NHE1 and ACE in longer-term electrical remodeling, as might occur with persistent AF, has not been studied. Methods: Dogs were subjected to atrial-tachypacing (400 bpm) for 7 days during treatment with 240 mg/day (standard clinical dose) of the NHE1 inhibitor cariporide (CariL, n=6), 1000 mg/day cariporide (CariH, n=6), 2 mg/kg/day of the ACE inhibitor enalapril (E, n=6), or no-drug controls (n=7). To ensure steady state concentrations at the onset of pacing, treatment began 3 days before the initiation of atrial tachypacing. Results were compared to those of unpaced dogs (n=9). Results: Atrial tachypacing reduced atrial effective refractory period (ERP), e.g. at a basic cycle length of 300 ms from 126±6 ms (unpaced, mean±S.E.) to 79±6 ms (no-drug controls, P<0.001). ERP abbreviation was unchanged by CariL (83±8 ms), CariH (80±7 ms), or E (76±5 ms). Atrial tachypacing increased mean duration of the longest AF episode in each dog (DAF) from 130±60 s (unpaced) similarly in all groups: 864±364 s, no-drug controls; 609±376 s, CariL; 709±353 s, CariH; 645±365 s, E (P=NS for differences among groups). Sustained AF requiring cardioversion for termination was induced in 0% of unpaced dogs vs. 33% of CariL, 33% of CariH, 33% of E, and 43% of control dogs. AF inducibility by single extrastimuli increased from 4±2% in unpaced dogs vs. 33% of CariL, 33% of CariH, 33% of E, and 43% of control dogs. AF inducibility by single extrastimuli increased from 4±2% in unpaced dogs to 48±13% (P<0.01) in no-drug control dogs, an effect not changed by CariL (33±14%), CariH (35±17%) or E (48±16%). Conclusions: In contrast to short-term (several-hour) atrial tachycardia-induced remodeling, remodeling by 7-day tachycardia is not affected by NHE1 or ACE inhibition. These results support the notion that short-term atrial tachycardia remodeling involves different mechanisms from longer-term remodeling, and urges caution in extrapolating results from studies of short-term remodeling to effects in longer-term remodeling as often occurs clinically. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Atrial fibrillation (AF) is currently the most common sustained arrhythmia in clinical practice. It has been shown that AF alters atrial electrophysiology to promote its own maintenance, a process often referred to as electrophysiological remodeling [1]. Sustained atrial tachycardia causes a variety of electrophysiological alterations, including atrial effective refractory period (ERP) abbreviation, that promote AF inducibility and maintenance [1–5]. There is evidence for Ca\(^{2+}\) overload as an initiating signal for tachycardia-induced remodeling [6–9].

Because of the limitations of presently available therapy, there has been an interest in developing novel approaches to AF therapy. One potentially interesting possibility is the use of drugs to prevent atrial electrical remodeling. The T-type Ca\(^{2+}\)-channel blocker mibefradil strongly inhibits...
atrial tachycardia-induced remodeling [10,11], but has been withdrawn from the market because of adverse drug reactions. Although L-type Ca$^{2+}$-channel blockers reduce short-term atrial tachycardia remodeling (<24 h), they are ineffective for remodeling by longer-lasting atrial tachycardias [11,12].

Recent work has focused on the potential role of two important systems, the Na$^+$/H$^+$ exchanger (NHE1) [13] and the renin–angiotensin system [14]. There are similarities between the histological appearance of tissue from atria that have been kept in AF for prolonged periods and chronically-ischemic ventricular myocardium [15]. In addition, preliminary data have been presented that pointed to reduced atrial blood flow in chronic AF [16]. Strong activation of NHE1 results from the intracellular acidosis during acute ischemia [17], and NHE1 stimulation plays an important role in arrhythmias associated with acute ischemia [18,19], possibly by promoting Ca$^{2+}$-loading [20,21]. These observations led Jayachandran et al. [13] to evaluate the ability of cariporide, an NHE1 inhibitor previously known as HOE642, to prevent atrial tachycardia-induced remodeling. They found that cariporide prevented effective refractory period (ERP) abbreviation occurring within 30 min of atrial pacing at 600 bpm, and concluded that NHE1 might be involved in short-term tachycardia-induced remodeling.

Pedersen et al. [22] have shown that the angiotensin-converting enzyme (ACE) inhibitor trandolapril reduces the prevalence of AF after acute myocardial infarction in patients with left ventricular dysfunction. The mechanism of this benefit is unknown. Based on their own unpublished observations that the non-ACE angiotensin-II forming enzyme chymase is more strongly expressed in the left atrium than in other cardiac chambers, Nakashima et al. [14] evaluated the effects on atrial tachycardia-remodeling of blocking angiotensin-I (AT$_1$) receptors and inhibiting ACE. They found that atrial tachypacing at 800 bpm decreased atrial ERP over 120 min, an effect that could be mimicked by angiotensin-II infusion and could be blocked by the AT$_1$-receptor antagonist candesartan as well as the ACE inhibitor captopril.

These observations suggest that either NHE1 or ACE inhibition can prevent short-term (<2 h) tachycardia-induced atrial electrical remodeling. Since NHE1 and ACE inhibitors are available for clinical development, they could be used for AF therapy if they effectively prevented remodeling; however, the efficacy of NHE1 and ACE inhibitors in longer-term electrical remodeling, as might occur with persistent AF, has not been studied. In order to address this issue, we examined the effects of the NHE1 inhibitor cariporide and the ACE inhibitor enalapril on atrial electrophysiological remodeling caused by 7 days of rapid atrial pacing in the dog. A 7-day pacing period was chosen because L-type Ca$^{2+}$ current ($I_{CaL}$) downregulation is quite significant after 7 days, with only small additional decreases noted after 42 days of rapid pacing [23].

2. Methods

2.1. Animal preparation

All animal-handling procedures were approved by the animal research ethics committee of the Montreal Heart Institute and followed the guidelines of the Canadian Council on Animal Care. Twenty-five mongrel dogs (weight, 23–40 kg) were initially anesthetized with ketamine (5.3 mg/kg, i.v.), diazepam (0.25 mg/kg, i.v.) and halothane (1–2%). Unipolar pacing leads were inserted in the right ventricular (RV) apex and the right atrial (RA) appendage under fluoroscopic guidance. The leads were connected to a ventricular pacemaker (model 8084 or 8086, Medtronic) and a custom-modified atrial tachypacemaker implanted in a subcutaneous pocket in the neck. AV block was created by radiofrequency catheter ablation to avoid excessively rapid ventricular responses during atrial tachypacing, and the RV pacemaker was programmed to capture the ventricles at 80 bpm. The right atrium was stimulated at 400 bpm for 1 week.

Rapidly-paced dogs were treated with 240 mg/day of cariporide, an NHE1 inhibitor (CariL, n=6), 1000 mg/day cariporide (CariH, n=6), 2 mg/kg/day enalapril, an ACE inhibitor (E, n=6), or no drug (ND, n=7), beginning 3 days before atrial pacemaker activation and continuing until the morning of the electrophysiological study. The 240 mg/day dose of cariporide was selected because it is the highest dose in clinical use. When our initial data suggested a lack of cariporide effect at this dose, we decided to study an additional series of dogs (CariH) exposed to higher doses. To ensure therapeutic concentrations in the high-dose cariporide group, blood samples were obtained for subsequent measurement of plasma cariporide concentration at 0, 30, 60 and 90 min after the morning dose on the day before electrophysiological study, prior to the second dose on that day, and at the time of the electrophysiological study. Cariporide concentrations were measured by Aventis Pharma, Frankfurt, Germany. The enalapril dose was based on a previous study we conducted in which 2 mg/kg of enalapril produced highly-significant reductions in CHF-induced atrial remodeling [24]. Nine dogs were used as an unpaced control group, three of which were instrumented and monitored like atrial tachypacing dogs but without pacemaker activation. The results in these sham dogs were the same as in six acute control animals; therefore the results of all nine unpaced control dogs were grouped together for analysis purposes.

On study days, dogs were anesthetized with morphine (2 mg/kg, s.c.) and α-chloralose (120 mg/kg, i.v., followed by 29.25 mg/kg/h) and ventilated to maintain physiological arterial blood gases (pH 7.38–7.45, $\text{SaO}_2 >95\%$). In atrial tachypacing dogs, the surface ECG was recorded to confirm maintained atrial and ventricular pacing and AV block. The atrial pacemaker was then deactivated. Body temperature was maintained at 37°C, and the left femoral
artery and both femoral veins were cannulated for pressure monitoring and drug administration. A median sternotomy was performed, and bipolar, Teflon-coated stainless steel electrodes were inserted into the RA and left atrial (LA) appendages for recording and stimulation. A programmable stimulator (Digital Cardiovascular Instruments) was used to deliver 2-ms pulses at twice-threshold current. Five thin silicon plaques containing 240 bipolar electrodes were sewn into position to cover the atrial epicardial surface, and stimulation and recording were performed as previously described [25].

2.2. Electrophysiological study

The ERP was measured at the LA and the RA appendages with 15 basic (S1) stimuli at basic cycle lengths (BCLs) of 150, 200, 250, 300 and 360 ms, followed by a premature (S2) stimulus, with the ERP defined as the longest S1S2 interval failing to produce a response. The mean of three ERP values at each BCL was used for data analysis. In the case of a ±10-ms difference between each measurement, one or two additional ERP measurements were obtained, and the mean of all determinations was used. To evaluate regional ERP properties, ERPs were measured at a BCL of 300 ms at seven sites: RA appendage, RA posterior wall, RA inferior wall, LA appendage, LA posterior wall, LA inferior wall, and Bachmann’s bundle.

AF was induced by stimulating the atrium with up to three consecutive extrastimuli at a BCL of 150 ms and then atrial burst pacing (10 Hz, 2-ms stimuli at four times threshold current for 1–10 s). To obtain an index of AF duration, AF was induced ten times if AF duration was ≤20 min and five times if AF lasted between 20 and 30 min. AF that lasted >30 min, which was considered persistent, was terminated by DC electrical cardioversion, and 30 min was allowed before the experiment was continued. If persistent AF was induced on two occasions, no further AF inductions were performed. We found that the longest AF period in each dog was the most consistent index of AF duration for each group. The mean duration of longest AF episodes per dog was therefore used as the index of AF duration to characterize each group. Atrial vulnerability was defined as the percentage of sites in each dog at which AF could be induced by single extrastimuli.

2.3. Data analysis

Conduction velocity (CV) was determined by analyzing activation at four electrode sites in the direction of rapid propagation. Distance from the proximal site was plotted against activation time, and CV was determined from the slope of the best-fit regression line [4,24], with a clear linear relation (r>0.99) required for analysis. The local wavelength was calculated as the product of local CV and local ERP [26].

Statistical comparisons of multiple group means were obtained by analysis of variance (ANOVA). A t-test with Bonferroni correction was used to evaluate the significance of differences between individual mean values. Average results are given as the mean±S.E.M., and a two-tailed P<0.05 was considered statistically significant.

3. Results

3.1. Changes in properties of AF

Dogs subjected to 7 days of rapid atrial pacing without drug therapy had significantly increased AF duration (864±364 s, P<0.05) compared to unpaced dogs (129±80 s). AF duration of enalapril-treated dogs (645±365 s), low-dose cariporide dogs (609±376 s) and high-dose cariporide-treated dogs (709±352 s) were not significantly different from no-drug atrial tachypacing dogs. Persistent AF was noted in three of seven (43%) no-drug dogs, two of six (33%) enalapril dogs, two of six (33%) low-dose cariporide dogs and two of six (33%) high-dose cariporide dogs vs. none (0%) of unpaced dogs.

Fig. 1 shows vulnerability to AF induction by single atrial premature extrastimuli. A single premature extrastimulus was able to induce AF at 47.9% of sites in no-drug tachypaced dogs, 47.9% in enalapril dogs, 33.3% in low-dose and 35.4% in high-dose cariporide dogs, with each
value in atrial tachypaced dogs significantly greater than in unpaced dogs (4.2%, \( P < 0.01 \) for no-drug and enalapril dogs, \( P < 0.05 \) for each cariporide group; \( P = \text{NS} \) among all tachypaced groups).

### 3.2. Changes in electrophysiological variables

Fig. 2A shows ERP values at various BCLs in the RA appendage (left) and LA appendage (right) for all groups. Atrial tachypaced no-drug dogs, enalapril-treated tachypaced dogs, and cariporide-treated tachypaced dogs had significantly reduced ERP at all BCLs at either site compared to unpaced dogs (\( P < 0.01 \) for each). All groups of tachypaced dogs had the ERP changes characteristic of atrial tachycardia-induced remodeling in normal hearts as described previously [1–5]: decreased ERP and loss of ERP rate-adaptation. Fig. 2B shows mean CV values in RA (left) and LA (right). These were unaltered in any atrial tachypaced group and were consistent with the results of previous studies in the 7-day atrial tachycardia remodeling setting [4]. Wavelength changes in the RA (Fig. 2C, left) and LA (Fig. 2C, right) largely reflected ERP alterations, with wavelength significantly decreased in all tachypaced groups and with no significant differences among groups treated with different drugs.

Fig. 3A displays an analysis of atrial ERP values at a single BCL (300 ms) in seven different atrial regions. Although the degree of remodeling varied among regions, atrial tachypacing significantly reduced atrial ERP compared to unpaced controls at all sites in each tachypaced group. Results were not significant among tachypaced groups. Fig. 3B displays the regional distribution of CV at a BCL of 300 ms. There were small but inconsistent differences among groups and CV was not affected overall. Fig. 3C provides mean data for wavelength in the four areas for which CV was obtained in each group. Wavelength significantly decreased in all zones in all tachypaced dogs. The changes in Bachmann’s bundle were quantitatively smaller in low-dose cariporide treated dogs, but the value at this site in this group remained statistically significantly different compared to unpaced dogs.

### 3.3. Plasma cariporide concentrations

Mean plasma cariporide levels in high-dose cariporide treated dogs averaged 1.6±0.3, 2.3±0.9, 4.6±1.4, and 5.9±1.6 μg/ml at 0, 30, 60 and 90 min after the morning dose on the day before electrophysiological study, 4.8±0.7 μg/ml prior to the second dose on that day, and 1.5±0.4 μg/ml at the time of the electrophysiological study, respectively. All of these concentrations were greater than the concentration (0.55 μg/ml) required for complete NHE1 blockade (Aventis Pharma, unpublished data). Therefore, the lack of important effects of cariporide on atrial tachycardia-induced remodeling were not due to inadequate plasma concentrations.

### 4. Discussion

In the present study, we have evaluated the effects of inhibiting NHE1 and ACE by oral therapy with enalapril and cariporide on the atrial remodeling induced by 7 days of atrial tachypacing. We found that, despite evidence for benefit from these drugs against short-term remodeling, they have no significant protective effects against the ERP reduction, abolition of rate-adaptation, and increases in AF duration and atrial vulnerability produced by a week of atrial tachycardia.

#### 4.1. Relationship to previous observations regarding atrial tachycardia-induced remodeling

Recent studies in animal models and humans have shown that atrial tachycardia (whether as a result of rapid 1:1 pacing or maintained AF) produces shortening of the atrial ERP and loss of physiological ERP rate adaptation [1–5,10,11]. Changes in CV with long-term (several-week) atrial pacing have been variable, however, no studies have shown that atrial tachycardia slows conduction in normal hearts significantly over a 1-week period. In this study, we found shortening of atrial ERP and loss of ERP rate adaptation produced by rapid pacing that parallels previous reports in animal models of AF as well as human experiments.

Although the mechanisms underlying atrial tachycardia-induced remodeling in normal hearts are incompletely understood, decreases in \( I_{\text{cat}} \) density resulting from sustained rapid activation likely contribute importantly to changes in atrial ERP and ERP rate-adaptation [23]. Intracellular \( \text{Ca}^{2+} \) overload is thought to contribute to this phenomenon [6–8,19,27,28]. The \( I_{\text{cat}} \) blocker verapamil prevents atrial ERP shortening and AF promotion caused by short-term AF (5–15 min) in man [7,8]; however, despite reducing ERP abbreviation caused by 24 h of atrial tachypacing, verapamil does not substantially alter the attendant increase in vulnerability to AF induction [28]. Verapamil has no effect on ERP or AF vulnerability changes induced by 1 and 6 weeks of atrial tachycardia [12]. Whereas the selective T-type \( \text{Ca}^{2+} \) channel blocker mibefradil protects against atrial remodeling caused by 7-day atrial tachycardia, the L-type \( \text{Ca}^{2+} \) channel blocker diltiazem is not effective [10,11]. These reports indicate that the efficacy of an intervention for remodeling by short-term atrial tachycardia (minutes or hours) does not necessarily imply efficacy against remodeling induced by longer durations (>24 h) of atrial tachyarrhythmia. This observation is consistent with evidence that the mecha-
Fig. 2. Mean±S.E.M. electrophysiological data as a function of BCL in RA (left) and LA (right) appendages. Tachypaced dogs receiving no drug, enalapril (E), low (Cari L) and high (CariH) dose cariporide had significantly reduced ERP (A) and ERP rate-adaptation at all BCLs at either site compared to unpaced controls. CV values were not significantly different among groups (B). Like ERP, wavelength (C) was significantly decreased in no-drug, enalapril, and cariporide dogs compared to unpaced controls.
4.2. Effects of ACE and NHE1 inhibition on atrial electrical remodeling and AF

The ACE inhibitor trandolapril has been shown to reduce the occurrence rate of AF in post-myocardial infarction patients with left ventricular dysfunction [22]. The mechanism of AF prevention by this ACE inhibitor is unknown; however, there is evidence for a role of the renin–angiotensin system in clinical AF. Goette et al. [30] have observed increased ACE expression and alterations in angiotensin II receptor expression [31] in atrial tissues of patients with AF. Recently, Nakashima et al. [14] reported that intravenous administration of the ACE inhibitor captopril or the angiotensin II type 1 receptor (AT1) antagonist candesartan prevents the shortening of atrial ERP and loss of ERP rate adaptation caused by 180 min of atrial tachypacing. The results of Nakashima’s study suggest that inhibition of atrial tachycardia-induced remodeling could have contributed to the clinical benefits against AF observed with trandolapril. The results of the present study argue that beneficial effects against tachycardia-remodeling are unlikely to be the principal mechanism of ACE inhibitor efficacy in AF. Li et al. [32] have shown that oral enalapril reduces mitogen activated protein kinase activation, atrial fibrosis and AF promotion in a dog model of CHF. This observation provides an alternative explanation for the therapeutic benefits of ACE inhibition in AF: the prevention of atrial structural remodeling.

NHE1 plays a key role in a variety of cardiac injury states, particularly those associated with myocardial ischemia and reperfusion [33]. NHE1 inhibition has been shown to have beneficial effects on myocardial remodeling and CHF after myocardial infarction [34] and to promote conversion of VF in a rat model [35]. Jayachandran et al. [13] showed that the atrial ERP abbreviation and loss of ERP rate adaptation produced by atrial pacing at 600 bpm for 5 h in dogs were prevented by the NHE1 inhibitor HOE642 (cariporide). In addition, acute atrial ischemia produced by right coronary artery occlusion produced shortening of the right atrial ERP and loss of ERP rate adaptation, which were also prevented by NHE1 blockade. These findings were interpreted as pointing to a potential role for NHE1 activation by ischemia in atrial electrical remodeling caused by 5 h of atrial tachypacing. Similarly, cariporide was found to attenuate atrial contractile dysfunction caused by short-term atrial tachycardia [36]. Cariporide is well-tolerated in man and has been studied in a large multicenter trial of patients with acute coronary syndromes [37]. Therefore, if cariporide were beneficial in preventing atrial tachycardia remodeling, it would be potentially quite useful in AF. Unfortunately, the results of the present study were disappointing in this regard — no benefit against atrial remodeling was observed from cariporide in dogs exposed to 7 days of atrial tachycardia, even at a dose demonstrated by plasma concentration.

Fig. 3. Regional distribution of ERP (A), CV (B) and wavelength (C) in various groups. RAA, LAA=RA, LA appendage; RAPW, LAPW=RA, LA posterior wall; RAIW, LAIW=RA, LA inferior wall; BB= Bachmann’s bundle.
measurements to maintain effective concentrations of the drug at all times.

4.3. Novel findings and potential significance

This is the first study of which we are aware to evaluate the effects of inhibiting NHE1 and ACE on long-term atrial tachycardia-induced remodeling. The results suggest that neither NHE1 inhibition nor ACE inhibition alone is sufficient to prevent remodeling caused by 7 days of atrial tachycardia. Although this result is disappointing, the study was rigorously performed and it is in many ways just as important to know when interventions do not work as when they do.

Short-term studies of atrial tachycardia-remodeling are much easier to perform than longer-term studies. There is no need for sterile surgery to implant chronic pacemakers, AV block may be unnecessary because the ventricular response can be observed directly, and drugs can be given by intravenous infusion rather than orally. On the other hand, there are important limitations to short-term studies. The administration of bolus intravenous doses of drugs can result in plasma concentrations much higher than those achieved clinically, with a significant risk of non-specific effects. Short-term atrial tachycardia remodeling (<12 h duration) has quite limited AF-promoting action [1,4]; therefore, the clinical relevance of preventing short-term remodeling is much less than that of preventing longer-term tachycardia remodeling. The autonomic state of dogs during the remodeling process is quite abnormal in a short-term open chest model, which may interfere with signal transduction mechanisms normally involved in atrial tachycardia remodeling. In addition, short-term remodeling primarily involves functional changes such as $\text{Ca}^{2+}$- and voltage-dependent $I_{\text{CaL}}$ inactivation [38,39], whereas longer-term remodeling likely involves changes in ion channel expression due to reduced levels of messenger RNA encoding ion channel subunits [40–42] and possibly post-transcriptional mechanisms as well [43]. These considerations may explain why so many agents, including verapamil [7–9], capropide [13,38], renin–angiotensin system inhibitors [14] and even flecainide [44] inhibit short-term electrical remodeling, but so few agents are effective in models of long-term atrial tachycardia-induced remodeling. It is therefore very important that studies of agents to prevent atrial tachycardia remodeling not be limited to short-term observations.

The reasons to believe that NHE1 inhibition might be useful in preventing atrial tachycardia-remodeling relate to similarities in histological appearance of fibrillating atrial tissue and chronically ischemic ventricles [15], preliminary data suggesting reduced atrial blood flow in AF [16], and evidence for a role of NHE1 in ventricular arrhythmias associated with acute myocardial ischemia [18,19]. More recent studies have shown that adenine nucleotides, their degradation products, and the activity of mitochondrial oxidative enzymes are not altered by AF lasting 1 week or greater [45], arguing against a role for atrial ischemia in mediating the effects of long-term atrial tachycardia-induced remodeling. The concentrations of tissue phosphocreatine decreased by 60% over the first week and normalized by 8 weeks [45]. It is therefore conceivable that ischemia could play a role in short-term atrial tachycardia-remodeling, with adaptive changes occurring subsequently. Such a scenario might explain why NHE1 blockade seems to prevent short-term atrial tachycardia-remodeling but to have no effect on longer-term remodeling.

The rationale for expecting ACE or AT$_1$ receptor inhibition to antagonize atrial tachycardia remodeling is based on the efficacy of ACE inhibition in preventing AF in patients with left ventricular dysfunction post-myocardial infarction. The studies of Li et al. [32] provide an alternative explanation, the inhibition of structural remodeling. The basis for benefit in short-term atrial tachycardia remodeling seen by Nakashima et al. [14] is unclear and merits further study.

4.4. Potential limitations

The present study evaluated electrical remodeling induced by 7 days of atrial tachycardia. This tachypacing duration was selected because ionic remodeling is near steady state after 7 days of tachycardia [23]. Although we cannot exclude the possibility that results might have been different for a different tachypacing duration, the absence of any clear effect in the present study suggests that the process of ionic remodeling underlying longer-term atrial tachycardia remodeling was not significantly altered.

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