The pharmacological response of ischemia-related atrial fibrillation in dogs: Evidence for substrate-specific efficacy

Lena Rivard a, Hani Sinno a, Akiko Shiroshita-Takeshita a, Gernot Schram a, Tack-Ki Leung b, Stanley Nattel a,⁎

a Research Center and Departments of Medicine, Montreal Heart Institute and Université de Montréal, Montreal, Canada
b Research Center and Department of Pathology, Montreal Heart Institute and Université de Montréal, Montreal, Canada

Abstract

Objective: Acute atrial ischemia produces a substrate for atrial fibrillation (AF) maintenance, but the response of this substrate to antiarrhythmic-drugs has not been defined. The present study assessed the effects of class 1–4 antiarrhythmic-drugs on the electrophysiological consequences of acute atrial ischemia, and compared effects in ischemic AF with those in vagal AF.

Methods and results: Isolated atrial ischemia was created by ligating a right coronary artery branch perfusing the right atrial free wall. Experiments were performed in dogs treated with loading and maintenance doses of flecainide (class 1; n=5), nadolol (class 2, n=7), dofetilide (class 3, n=5), or diltiazem (class 4, n=7) prior to coronary artery occlusion. Dogs subjected to coronary occlusion without pre-treatment (n=10) served as controls. Coronary artery occlusion substantially increased AF duration, e.g. from 7±4 s (pre-ischemic baseline) to 876±245 s at 3 h of ischemia, and caused substantial ischemic zone conduction slowing. Diltiazem and nadolol prevented AF promotion (AF durations 12±8 s and 4±1 s at 3 h of ischemia respectively; each p<0.001 vs control) and suppressed ischemic conduction slowing. Flecainide and dofetilide failed to prevent ischemia-induced AF promotion (e.g. AF durations at 3-hour ischemia 779±417 and 801±414 respectively, p=NS vs control) and failed to alter ischemia-induced conduction slowing. A different pattern of response occurred with vagal AF: flecainide was highly effective in reducing vagal AF duration; dofetilide, diltiazem, and nadolol were ineffective.

Conclusions: Beta-blockade and Ca2+ antagonism suppress the arrhythmic consequences of acute atrial ischemia, whereas Na+ channel or K+-channel block are ineffective. These results are relevant to understanding the effects of different classes of antiarrhythmic-drugs on AF occurring in coronary disease patients.

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Keywords: Arrhythmia; Antiarrhythmic agents; Conduction (block); Ischemia

1. Introduction

Atrial fibrillation (AF) is an extremely common cardiac arrhythmia, for which therapy remains problematic. It has been suggested that drug-efficacy in AF may be related to underlying mechanisms [1]. In experimental models, class 3 antiarrhythmic-drug-efficacy is greater in AF associated with structural remodeling than in atria remodeled by sustained atrial tachycardia [2].

Beta-adrenoceptor antagonists and Ca2+-channel blockers are considered to be poorly effective for sinus-rhythm maintenance and pharmacological conversion in AF. There is, however, evidence for efficacy of β-blockers (class 2 antiarrhythmic-drugs) [3,4] and diltiazem (a class 4 agent) [5,6] for sinus-rhythm maintenance post-cardiothoracic surgery.
Sustained-release metoprolol has weak but statistically-significant sinus-rhythm maintenance properties post-AF cardioversion [7]. β-Blockers and Ca²⁺-antagonists may thus be effective for certain forms of AF, with a lack of overall efficacy in AF because of our inability to identify patients likely to respond favorably to these compounds.

Isolated atrial ischemia produces a substrate for AF maintenance [8]. AF is a relatively-common complication of acute myocardial infarction, and chronic coronary artery disease is an important predisposing factor for AF [9]. Ca²⁺-antagonists and β-blockers suppress the electrophysiological consequences of acute ventricular ischemia [10,11]; however, their actions on atrial ischemia and associated arrhythmias are unknown. We hypothesized that β-adrenoceptor blockers (class 2 drugs) and Ca²⁺-antagonists (class 4) might have beneficial actions on the AF substrate caused by acute atrial ischemia, and that antiarrhythmic-drug actions on the atrial ischemic substrate might be class-specific. This study addressed this issue in a canine model, with flecainide, a class 1 agent widely used to treat AF [12], and dofetilide (a class 3 agent) as comparators. We then performed additional experiments with the same compounds in vagotonic AF [13] to assess the model-specificity of AF-suppressing drug properties.

2. Methods

2.1. General

Fifty-one adult mongrel dogs (both sexes, 20–35 kg) were anesthetized with morphine (2 mg/kg SC) and α-chloralose (120 mg/kg IV, followed by 29.25 mg/kg/h), and ventilated mechanically. A median sternotomy was performed to access the coronary arteries for acute-ischemia studies. Body temperature was maintained at 37.5± 1 °C. Bipolar Teflon-coated stainless-steel plunge electrodes were inserted into the atrial appendages for recording and stimulation. Arterial blood pressure was monitored via a femoral-artery catheter. Femoral-vein catheters were used for drug and fluid administration. Animal-handling procedures conformed 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).

2.2. Ischemic model

Isolated right atrial ischemia was created by double ligation of the right intermediate atrial artery (RIAA), which supplies only the RA free wall (RAFW, Fig. 1A). To delineate the area of hypoperfusion and exclude ischemia in the left atrium (LA) and right ventricle (RV), 6% thioflavin-S in 0.9% NaCl was injected into the femoral-artery at the end of each experiment. Subsequently, the atria and RV were removed and hypoperfused regions (non-fluorescing under ultraviolet light) were traced. Ischemic zone area was quantified by computerized image-analysis algorithms.

Fig. 1. A. Site of occlusion on right intermediate atrial artery (R.i.a.a.), along with ischemic zone location. R.V. indicates right ventricle; S.N.A., sinoatrial nodal artery; and R.C.A., right coronary artery. B. Electrode arrays covering atrial surface. Electrode sites are indicated by dots. AVR indicates atrioventricular ring; SVC, superior vena cava; IVC, inferior vena cava; PV, pulmonary vein; BB, Bachmann’s bundle; PW, posterior wall; and IW, inferior wall. Asterisks indicate pacing sites for ERP measurements. The RA free wall electrode array (white, dashed border) was used for detailed conduction analyses in the ischemic zone.

2.3. Electrophysiological measurements and experimental groups

Atrial effective refractory period (ERP) was measured in the right atrial appendage (RAA), the RAFW and the right atrial inferior wall (RAIW, Fig. 1B). A single atrial extrastimulus (S₂) was introduced after every 10 basic S₁s (2-ms twice-threshold pulses), with 5-ms S₁–S₂ decrements until capture failed. Results were obtained in duplicate, with ERP defined as the longest S₁–S₂ failing to capture. Global epicardial mapping was performed with 5 arrays containing 240 bipolar electrodes. Mapping was conducted with the Cardiomap system (Research Center, Sacre-Coeur Hospital and Biomedical Engineering Institute, Ecole Polytechnique and Université de Montreal).
To evaluate conduction slowing and spatial conduction inhomogeneities, phase maps were constructed for the RAFW electrode array (white plaque with dashed border in Fig. 1B) as previously reported [14,15]. For each electrode, activation time differences to neighbouring points were normalized to interelectrode distances. The largest local phase difference at each site was used to create a phase map and obtain a phase-delay histogram. The median (P50) and the 95th percentile (P95) of the phase-delay histogram reflect average conduction speed and regions of slowest local conduction, respectively. The variation coefficient (P5–95/P50) is a heterogeneity index that assesses conduction heterogeneity independently of overall conduction velocity changes. Results were obtained at basic cycle lengths (BCLs) of 360, 300, 250, 200 and 150 ms. AF was defined as a rapid (>400 bpm) atrial arrhythmia with irregular atrial electrograms. We aimed for 10 AF inductions in each dog; however, AF inductions were stopped if 5 episodes lasted between 5 and 30 min, or 2 episodes >30 min. AF was induced by burst pacing at the RAA (10 Hz, 4× threshold current). AF >30 min was terminated by QRS-synchronised DC cardioversion. Dogs subjected to atrial ischaemia without pre-treatment (No-drug, n=10) were compared to dogs receiving diltiazem (0.8 mg/kg over 15 min followed by a continuous infusion at 15 μg/kg/min; n=7), nadolol (0.5 mg/kg over 15 min followed by repeated doses of 0.25 mg/kg every 2 h, n=7), flecainide (1 mg/kg followed by a continuous infusion of 1.33 mg/kg/h for 60 min and then 0.66 mg/kg/h, n=5) or dofetilide (0.04 mg/kg followed by a continuous infusion of 0.008 mg/kg/h, n=5). Drug infusion was initiated after obtaining initial basic electrophysiological measurements. Measurements obtained after drug injection but before coronary artery occlusion were used as the baseline for results following occlusion.

2.4. Histology

After each experiment, the atria and the right ventricle were immersed in 10% neutral buffered formalin for >24 h. Right atrial myocardial necrosis and its dimensions were identified by examination of sections stained with hematoxin-phloxin-saffron and Gomori trichrome by a trained pathologist. In addition, the LV and the RV were examined to ensure the absence of ventricular ischemia.

2.5. Vagal model

Bipolar stainless-steel stimulating electrodes, coated with Teflon except for the distal 1 cm, were inserted within and parallel to cervical vagal nerves of closed-chest dogs. Bipolar vagal nerve stimulation (0.2-second stimuli, 10 Hz) was applied continuously during AF measurements. The amplitude of stimulation was adjusted in each dog to two thirds of the threshold producing severe bradycardia (<40 bpm). AF was induced by a brief burst of 10-Hz atrial pacing during continuous vagal stimulation. Mean AF duration during vagal stimulation was quantified in each dog as described above. After the duration of vagotonic AF was quantified under control conditions, nadolol (n=4 dogs), diltiazem (n=4), flecainide (n=4) or dofetilide (n=5) were given and the measurements repeated.

2.6. Statistical analysis

Two-way repeated measures analysis of variance (ANOVA) was performed using mixed model methodology with group and time as main effects. Time was used as the repeated measures variable in each dog. If appropriate, heterogeneous variance–covariance matrices were used for groups. The repeated measures ANOVA were applied to determine if there was interaction between the two main effects. Global conclusions were drawn based on the main TIME and GROUP effects of the model. If the interaction term (TIME×GROUP) was significant for at least the 0.05 level, groups were compared at specific times with a range test. The assumptions of normality and variance homogeneity were verified for all indices. For one variable, AF duration, the data were found to be highly non-normal. Logarithmic transformation was found to normalize AF duration data and was therefore applied prior to statistical comparisons of AF duration. Event prevalences were compared with Fischer’s exact test. Statistical analysis was performed with SAS software (SAS Institute Inc.). P<0.05 was considered statistically-significant.

3. Results

3.1. Histology

Ischemic zones showed typical necrotic changes with pyknotic nuclei, acidophilic staining and contraction bands (Fig. 2). Ischemic changes were often nearly transmural, with surviving subendocardial tissues. Arterial ischemic changes were also present, as assessed by vascular-wall invasion of polymorphonuclear leukocytes. The ischemic zone size as a function of right atrial area was not different among groups (30 ± 13% in CTL, 34± 4% in flecainide, 36±4% in nadolol, 35±5% in dofetilide, and 30±5% in diltiazem, p=NS). There was no evidence of ventricular ischemia or atrial ischemia outside the zones perfused by occluded arteries.

3.2. AF duration

Ischemia-related changes in AF duration, AF cycle length and ERP are summarized in Table 1. Isolated right atrial ischemia increased AF duration in control animals and in those receiving flecainide or dofetilide. However, nadolol and diltiazem prevented the AF-promoting effect of acute atrial ischemia: ischemia did not significantly affect AF duration in animals receiving these compounds prior to coronary artery occlusion. Prolonged AF (>20 min) could
not be induced before ischemia, but occurred in the presence of ischemia in 7/10 (70%) of control dogs, 3/5 (60%) flecainide dogs and 3/5 dofetilide dogs (60%) (\(p=NS\) vs control for each). No instances of prolonged AF could be induced following coronary artery occlusion in dogs pretreated with nadolol or diltiazem (\(p<0.001\) vs control for each). AF cycle length was not significantly altered by ischemia. Both flecainide and dofetilide significantly increased AF cycle lengths, reflecting class 1 and class 3 actions respectively. There were no significant ischemia-induced ERP changes. Dofetilide and (to a lesser extent) nadolol significantly increased ERPs.

3.3. Conduction measurements

Ischemia strongly changed atrial conduction in no-drug control, flecainide and dofetilide groups, but not in nadolol and diltiazem groups. Fig. 3 shows representative RA free wall activation maps from one dog of each group before and after 3 h of ischemia at a basic cycle length of 150 ms. The hypoperfused zone is represented by the shaded areas. Without any pre-treatment (Control), a zone of clear conduction slowing appeared as the propagating impulse reached the border of the ischemic zone (upper left panels). Ischemia-induced atrial conduction slowing was not observed in dogs pretreated with nadolol (upper right) or diltiazem (lower right) prior to coronary artery occlusion. Prior to coronary artery occlusion, flecainide caused mild, homogeneous conduction slowing compared to pre-drug control. Following occlusion, flecainide-treated dogs manifested conduction slowing that was not significantly different from dogs subjected to ischemia without the drug. Dofetilide did not alter conduction prior to ischemia and showed similar ischemia-induced conduction slowing to control dogs.

To obtain a quantitative and objective index of ischemia-induced conduction changes, we analyzed phase-delay histograms at all RA sites with the use of previously described methods [8,14]. For any activation map, the activation time difference between each electrode and all adjacent sites was first determined. This time difference was then divided by the corresponding inter-site distance, and the maximum time delay/distance value at each of the RA sites was taken to represent the local phase-delay. All phase-delays were then used to create a histogram of phase-delay values at all 104 electrodes in the RA array. We then calculated the P5, P50 and P95, representing respectively the

Table 1
Effects of ischemia and antiarrhythmic-drugs on AF properties and ERP

<table>
<thead>
<tr>
<th></th>
<th>AF duration (s)</th>
<th>AF CL (ms)</th>
<th>ERP RAFW</th>
<th>ERP RAA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No-drug (n = 10)</strong></td>
<td></td>
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<tr>
<td>0 h</td>
<td>8 ± 3</td>
<td>109 ± 9</td>
<td>106 ± 5</td>
<td>117 ± 3</td>
</tr>
<tr>
<td>0.5 h</td>
<td>489 ± 243 **</td>
<td>109 ± 8</td>
<td>98 ± 3</td>
<td>116 ± 4</td>
</tr>
<tr>
<td>3 h</td>
<td>876 ± 245 ***</td>
<td>122 ± 9</td>
<td>103 ± 5</td>
<td>122 ± 6</td>
</tr>
<tr>
<td>5 h</td>
<td>697 ± 280 **</td>
<td>121 ± 10</td>
<td>101 ± 3</td>
<td>114 ± 4</td>
</tr>
<tr>
<td><strong>Flecainide (n = 5)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0 h</td>
<td>10 ± 16</td>
<td>140 ± 17</td>
<td>103 ± 9</td>
<td>112 ± 8</td>
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<tr>
<td>0.5 h</td>
<td>255 ± 114</td>
<td>143 ± 11</td>
<td>107 ± 3</td>
<td>116 ± 8</td>
</tr>
<tr>
<td>3 h</td>
<td>779 ± 417 ***</td>
<td>132 ± 7</td>
<td>111 ± 5</td>
<td>116 ± 9</td>
</tr>
<tr>
<td>5 h</td>
<td>494 ± 245</td>
<td>133 ± 18</td>
<td>110 ± 7</td>
<td>116 ± 9</td>
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<td><strong>Nadolol (n = 7)</strong></td>
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<td></td>
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<tr>
<td>0 h</td>
<td>3 ± 1</td>
<td>99 ± 7</td>
<td>123 ± 4</td>
<td>121 ± 5</td>
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<tr>
<td>0.5 h</td>
<td>5 ± 1</td>
<td>113 ± 3</td>
<td>116 ± 5</td>
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<tr>
<td>3 h</td>
<td>4 ± 1</td>
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<tr>
<td>5 h</td>
<td>7 ± 4</td>
<td>113 ± 2</td>
<td>122 ± 6</td>
<td>120 ± 2</td>
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<td><strong>Dofetilide (n = 5)</strong></td>
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<tr>
<td>0 h</td>
<td>2 ± 0.5</td>
<td>123 ± 8</td>
<td>128 ± 10</td>
<td>130 ± 13</td>
</tr>
<tr>
<td>0.5 h</td>
<td>832 ± 407 ***</td>
<td>130 ± 18</td>
<td>112 ± 10</td>
<td>130 ± 15</td>
</tr>
<tr>
<td>3 h</td>
<td>801 ± 414 ***</td>
<td>177 ± 23</td>
<td>124 ± 15</td>
<td>140 ± 5</td>
</tr>
<tr>
<td>5 h</td>
<td>669 ± 568 *</td>
<td>156 ± 16</td>
<td>133 ± 3</td>
<td>140 ± 10</td>
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<tr>
<td><strong>Diltiazem (n = 7)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>0 h</td>
<td>20 ± 7</td>
<td>93 ± 5</td>
<td>104 ± 5</td>
<td>113 ± 4</td>
</tr>
<tr>
<td>0.5 h</td>
<td>29 ± 20</td>
<td>106 ± 7</td>
<td>113 ± 3</td>
<td>105 ± 7</td>
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<td>3 h</td>
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<td>113 ± 10</td>
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<td>112 ± 6</td>
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</tbody>
</table>

AFCL: AF cycle length (ms); ERP RAFW, ERP RAA: RA free wall (ischemic zone), RA appendage ERP at BCL 250 ms. *\( p<0.05\); **\( p<0.01\); ***\( p<0.001\) vs 0 h. \( p<0.05\), \( ^{*} p<0.01\); \( ^{**} p<0.001\) vs No-drug at the corresponding time point.
values (in ms/mm) containing the smallest 5%, 50% and 95% of the phase-delay results.

Fig. 4 illustrates the results for P50, representing overall average conduction speed, in each group. Although there was a tendency for the values to increase, particularly in the flecainide and dofetilide groups, the changes were not statistically-significant. On the other hand, the P95 (reflecting the longest local phase-delays) increased substantially and significantly at 3 and 5 h after coronary artery occlusion in dogs without drug pre-treatment (Fig. 5, upper left). For

Fig. 3. Representative RAFW epicardial activation maps obtained at a BCL of 150 ms are shown for dogs subjected to acute atrial ischemia without drug pre-treatment (Control) or following pre-treatment with flecainide, nadolol, dofetilide or diltiazem. Data shown were obtained before occlusion and after 3 h of atrial ischemia. Hypoperfused zones are shown by the shaded areas. Isochronal activation times are indicated.

Fig. 4. Mean±SEM data for median conduction delays (P50) as obtained from the phase-delay histogram at each time point in each dog in flecainide, nadolol, dofetilide and diltiazem, pretreated groups, as well as in non-pretreated (No-Drug) controls. Results are shown under baseline conditions (control) as well as at varying times following coronary artery occlusion. There were no statistically-significant differences among groups.
example, the P95 averaged 2.42±0.12 ms/mm pre-occlusion and increased to 5.74±0.61 and 6.19±0.92 ms/mm respectively (p<0.001 vs pre-occlusion for each) after 3 and 5 h of ischemia at a basic cycle length of 150 ms. This significant increase, despite the lack of significant changes in overall conduction as reflected by the P50, is due to localized areas of severe conduction slowing in the ischemic zone. Both nadolol (upper right) and diltiazem (lower right) prevented significant ischemia-induced P95 increases. In the presence of diltiazem, the P95 averaged 2.72±0.26 ms/mm at a basic cycle length of 150 ms pre-occlusion, vs 3.21±0.40 and 2.80±0.43 ms/mm (p=NS for each) respectively after 3 and 5 h of ischemia. For nadolol, the corresponding values were 3.21±0.52 ms/mm pre-occlusion vs 3.38±0.43 and 3.22±0.66 ms/mm respectively at 3 and 5 h post-occlusion (p=NS for each). The P95 increased substantially with ischemia in flecainide- and dofetilide-treated dogs (lower right). For flecainide dogs, mean values at a basic cycle length of 150 ms increased from 3.36±0.13 ms/mm pre-occlusion to 8.38±2.28 ms/mm (p<0.001) at 3 h and

Fig. 5. Mean±SEM data for 95th percentile of phase-delays (P95) as obtained from the phase-delay histogram at each time point in each dog in flecainide, nadolol, dofetilide and diltiazem pretreated groups, as well as in non-pretreated (No-Drug) controls. Results are shown under baseline conditions (control) as well as at varying times following coronary artery occlusion. ††p<0.01, †††p<0.001 vs pre-occlusion, at 3 h of ischemia. ***p<0.001 vs pre-occlusion, at 5 h of ischemia.

Fig. 6. Mean±SEM data for phase-delay heterogeneity index (P5–P95/P50) as obtained from the phase-delay histogram at each time point in each dog in flecainide, nadolol, dofetilide and diltiazem pretreated groups, as well as in non-pretreated (No-Drug) controls. Results are shown under baseline conditions (control) as well as at varying times following coronary artery occlusion. †p<0.05, ††p<0.01, †††p<0.001 vs pre-occlusion, at 3 h of ischemia. *p<0.05, **p<0.01, ***p<0.001 vs pre-occlusion, at 5 h of ischemia.
7.45±2.39 at 5 h (p<0.001 vs pre-occlusion). For dofetilide dogs, corresponding values were 2.94±0.20 ms/mm pre-occlusion to 6.77±1.89 ms/mm (p<0.001) at 3 h and 7.22±2.00 at 5 h (p<0.001 vs pre-occlusion). The conduction heterogeneity index (P95–P5)/P50 increased significantly after 3 h and 5 h of ischemia in dogs not pretreated with antiarrhythmic-drugs and in flecainide or dofetilide pre-treated dogs (Fig. 6). The ischemia-induced increase in (P95–P5)/P50 was prevented in dogs pretreated with diltiazem or nadolol.

3.4. Atrial activation during AF

Atrial activation maps were performed during 2 consecutive cycles of AF. With both ischemia alone and ischemia plus flecainide or dofetilide, we consistently saw zones of marked activation delay within the RA ischemic region during AF. These activation delays occupied a significant portion of the AF cycle but complete cycles of epicardial reentry were rarely observed. During AF induced in the presence of ischemia in diltiazem and nadolol treated dogs (which was always short-lived), zones of conduction delay were less frequent and varied in location from cycle to cycle, implying functional delays related to interacting wavefronts. These observations are consistent with the notion that ischemic zone conduction abnormalities played a significant role in ischemia-induced AF promotion, and that attenuation of ischemic conduction abnormalities by diltiazem and nadolol was an important factor in the lack of ischemia-induced AF promotion in dogs receiving these agents. The absence of complete epicardial reentry circuits during ischemic AF (possibly due to insufficient spatial resolution of mapping arrays or to reentry involving non-epicardial, e.g.

transmural, components) limited the value of mapping in defining underlying mechanisms.

3.5. Efficacy of diltiazem, nadolol, flecainide and dofetilide in vagal AF

Fig. 7 contrasts the drug responses in the acute ischemic model with those in the vagotonic model of AF. The left panel shows mean AF duration under baseline conditions, which was extremely brief for all groups. The middle panel shows AF duration after 3 h of atrial ischemia, with clear and striking increases from baseline in the absence of drug pre-treatment and also following pre-treatment with flecainide or dofetilide. These increases contrasted with the relatively short AF durations induced at 3-hour ischemia in the presence of diltiazem or nadolol. The right panel shows the AF duration increase resulting from vagal stimulation. Nadolol, dofetilide and diltiazem did not affect AF duration in the presence of vagal nerve stimulation, but flecainide substantially reduced vagal AF duration. Thus, the pattern of relative antiarrhythmic-drug-efficacy in the vagal model was different from the drug-efficacy pattern in AF associated with acute myocardial ischemia.

4. Discussion

We have shown that the class 2 antiarrhythmic β-adrenoceptor blocker nadolol and the class 4 L-type Ca²⁺-channel blocker diltiazem prevent the atrial conduction changes and AF maintenance-enhancing consequences of acute atrial ischemia. In contrast, the class 1 Na⁺-channel blocker flecainide and class 3 K⁺-channel blocker dofetilide provided no AF-preventing benefit in acute atrial ischemia. These results contrasted with effects on AF induced in the presence of vagal activation, for which flecainide was quite effective but diltiazem, dofetilide and nadolol were totally ineffective.

4.1. Relation to previous drug studies in experimental AF and acute myocardial ischemia

A variety of animal models have been used to study the actions of antiarrhythmic agents in experimental AF [13]. Class 1 agents are effective in suppressing AF in several of these, including atrial tachycardia remodeling [16] and cholinergic AF [17,18]. β-Adrenoceptor antagonists are ineffective in cholinergic AF [19]. Ca²⁺-antagonists show varying effects in experimental AF. Verapamil tends to prolong AF induced in the presence of atrial tachycardia remodeling [20] or enhanced vagal tone [21], whereas diltiazem has neutral effects [21].

We were unable to identify any data in the literature about the effects of antiarrhythmic-drugs on AF associated with acute atrial ischemia. Verapamil and diltiazem suppress ventricular electrophysiological abnormalities and ventricular tachyarrhythmias associated with acute ventricular
myocardial infarction [10,22]. Metoprolol also suppresses conduction slowing and arrhythmias caused by acute ventricular ischemia [11]. In contrast, class 1 agents may worsen ischemic ventricular conduction slowing and arrhythmias [10,11,23]. In the present study, the Ca²⁺-channel blocker diltiazem and the β-adrenoceptor antagonist nadolol suppressed both atrial conduction slowing and AF promotion caused by acute atrial ischemia, whereas class 1 and 3 agents had no beneficial effects.

4.2. Potential importance of AF related to myocardial ischemia

A detailed review of the pathophysiology and prevention of AF came to the conclusion that myocardial infarction is one of the most frequent causes of AF and that ischemic heart disease is one of the most common clinical settings [9]. Acute atrial ischemia is a likely potential contributor to the pathophysiology of AF in such patients. Several studies have suggested that atrial infarction is relatively-common, evident at autopsy in up to 17% of cases of myocardial infarction [24,25]. Isolated atrial infarction is difficult to diagnose clinically and atrial tachyarrhythmia is a characteristic manifestation [26]. In a recent clinical trial, atrial flutter or fibrillation complicated ~ 20% of myocardial infarctions and was associated with significantly increased mortality [27]. AF is also a common complication of cardiac surgery (occurring in ~ 30–40% cases overall), increasing morbidity and hospital costs [28]. Stenoses of the right coronary and sinoatrial nodal arteries, which perfuse significant RA tissue, predispose patients to post-operative AF [29–32], pointing to an ischemic component. Thus, atrial ischemia is a potentially significant contributor to the pathophysiology of AF in many patients. The response to antiarrhythmic-drugs in such patients could be substantially influenced by drug effects on ischemia-related AF mechanisms, but to date there has been no information in the literature about the specific effects of antiarrhythmic-drugs on AF associated with acute atrial ischemia.

4.3. Relevance to understanding antiarrhythmic-drug action in AF

Whereas class 1 agents are much more effective in terminating recent-onset AF in settings not associated with evidence of myocardial ischemia than β-blockers (class 2 agents) or Ca²⁺-antagonists (class 4 drugs) [33], β-blockers [3,4] and diltiazem [5,6] have clear AF-preventing actions post-cardiothoracic surgery. A recent study reported that the β-blocker carvedilol effectively prevents AF after acute myocardial infarction [34]. Although sotalol is much less effective than amiodarone overall for sinus-rhythm maintenance in AF patients, both are equally effective in AF patients with ischemic heart disease [35]. The present study provides a potential mechanistic basis for the differential efficacy of class 1–4 antiarrhythmic agents in two different clinical settings. The efficacy that we observed for the class 2 and 4 drugs nadolol and diltiazem in preventing AF promotion caused by acute atrial ischemia suggests that a similar action may contribute to the anti-AF properties of β-blockers and Ca²⁺-antagonists in patients with active coronary artery disease and post-cardiac surgery. Furthermore, our observations suggest that such compounds may be more effective than class 1 or 3 drugs for the prevention and treatment of AF in acute myocardial infarction patients. On the other hand, the superior efficacy of flecainide that we noted in vagal AF, a model that corresponds in antiarrhythmic response to recent-onset persistent AF [13], agrees with the clinical observation that class 1 agents have superior efficacy in patients with recent-onset AF compared to β-blockers or Ca²⁺-antagonists. Dofetilide lacked efficacy in both models. Class 3 antiarrhythmic agents are relatively ineffective in terminating recent-onset AF [36], consistent with their relative inefficacy in suppressing AF in the vagotonic model.

4.4. Potential limitations

In this study, we sought to assess the effects of various antiarrhythmic agents on atrial electrophysiological abnormalities and arrhythmias resulting from atrial ischemia per se. For this reason, we occluded a coronary artery branch that perfuses only the right atrium. In the clinical context, acute myocardial infarction that involves the atria often also involves the left ventricle and the clinical picture is rendered more complex by potential changes in atrial pressures secondary to ventricular dysfunction, by autonomic nervous system responses and by concomitant drug therapy. Therefore, extrapolation to the clinical arena should be cautious.

Our observations were restricted to the first 5 h after the onset of acute atrial ischemia. The electrophysiological and arrhythmic changes caused by chronic atrial ischemia and/or a prior atrial infarction may well be different and respond differently to antiarrhythmic-drugs.

Our doses were selected based on prior canine studies which showed that they produce effective and sustained β-blockade for nadolol [37] and clinically-relevant effects and/or plasma concentrations for flecainide [17], dofetilide [36] and diltiazem [38]. We cannot exclude the possibility that larger doses might have had different effects.

5. Conclusions

Atrial ischemia promotes AF maintenance and this effect is prevented by both β-blockers and Ca²⁺-antagonists, but not by a class 1 or 3 antiarrhythmic-drug. This efficacy pattern is different from what is seen for vagotonic AF. Thus, the response of the AF substrate to antiarrhythmic-drugs may differ qualitatively depending on the underlying mechanism, and the present findings may account for some of the variability in AF-suppressing effectiveness of antiarrhythmic compounds, particularly β-blockers and Ca²⁺-antagonists, noted in the clinical literature.
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References


