Tachy-brady arrhythmias: The critical role of adenosine-induced sinoatrial conduction block in post-tachycardia pauses

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BACKGROUND In patients with sinoatrial nodal (SAN) dysfunction, atrial pauses lasting several seconds may follow rapid atrial pacing or paroxysmal tachycardia (tachy-brady arrhythmias). Clinical studies suggest that adenosine may play an important role in SAN dysfunction, but the mechanism remains unclear.

OBJECTIVE To define the mechanism of SAN dysfunction induced by the combination of adenosine and tachycardia.

METHODS We studied the mechanism of SAN dysfunction produced by a combination of adenosine and rapid atrial pacing in isolated coronary-perfused canine atrial preparations by using high-resolution optical mapping (n = 9). Sinus cycle length and sinoatrial conduction time (SACT) were measured during adenosine (1–100 μM) and DPCPX (1 μM; A1 receptor antagonist; n = 7) perfusion. Sinoatrial node recovery time was measured after 1 minute of "slow" pacing (3.3 Hz) or tachypacing (7–9 Hz).

RESULTS Adenosine significantly increased sinus cycle length (477 ± 62 ms vs 778 ± 114 ms; $P < .01$) and SACT during sinus rhythm (41 ± 11 ms vs 86 ± 16 ms; $P < .01$) in a dose-dependent manner. Adenosine dramatically affected SACT of the first SAN beat after tachypacing (41 ± 5 ms vs 221 ± 98 ms; $P < .01$). Moreover, at high concentrations of adenosine (10–100 μM), termination of tachypacing or atrial flutter/fibrillation produced atrial pauses of 4.2 ± 3.4 seconds (n = 5) owing to conduction block between the SAN and the atria, despite a stable SAN intrinsic rate. Conduction block was preferentially related to depressed excitability in SAN conduction pathways. Adenosine-induced changes were reversible on washout or DPCPX treatment.

CONCLUSIONS These data directly demonstrate that adenosine contributes to post-tachycardia atrial pauses through SAN exit block rather than slowed pacemaker automaticity. Thus, these data suggest an important modulatory role of adenosine in tachy-brady syndrome.

KEYWORDS Sinoatrial node; Optical mapping; Adenosine; Atrial flutter/fibrillation; Tachy-brady syndrome

ABBREVIATIONS **AF** = atrial fibrillation; **AFL** = atrial flutter; **AP** = action potential; **APD** = action potential duration; **APD80**% = APD at 80% repolarization; **cSNRT** = corrected sinoatrial node recovery time; **DF** = dominant frequency; **OAP** = optical action potential; **SACP** = sinoatrial node conduction pathway; **SACT** = sinoatrial conduction time; **SAN** = sinoatrial node; **SCL** = sinus cycle length; **SNRT** = sinoatrial node recovery time; **SNRT*i*** = indirect SNRT; **SNRT*d*** = direct SNRT; **SNRT*r*** = real SNRT; **SR** = sinus rhythm

Introduction

Sinoatrial node (SAN), the primary pacemaker of the human heart, is a specialized and complex structure.[1–3] Dysfunction of the SAN leads to more than 50% (>100,000) of the annual pacemaker implants in the United States.[4] One of the main manifestations of SAN dysfunction is tachy-brady syndrome, characterized as the heart rate alternating between too fast and too slow.[5] In patients with SAN dysfunction, termination of rapid pacing or paroxysmal tachycardia may be followed by long atrial pauses lasting several seconds,[6–8] which can provoke another tachyarrhythmia paroxysm. However, the cause of the post-tachycardia pause remains elusive.

One possible reason for the pause could be the effect of adenosine, an endogenous metabolite of the heart.[9] In 1929, Drury and Szent-Gyorgyi[10] demonstrated for the first time that adenosine significantly slowed sinus rhythm (SR), produced atrioventricular block, and facilitated both atrial flutter (AFL) and atrial fibrillation (AF) by shortening the refractory period. In 1985, Watt[11] hypothesized that increased endogenous production of adenosine and/or hypersensitivity to adenosine could result in SAN dysfunction, particularly tachy-brady syndrome. This is supported by the

This study was supported by Davis Heart and Lung Research Institute (to Dr Fedorov) and National Institutes of Health (grants R01 NHLBI/HL089836 [to Dr Carnes] and NHLBI/HL086700 [to Dr Billman]). **Address reprint requests and correspondence:** Dr Vadim V. Fedorov, PhD, Department of Physiology and Cell Biology, College of Medicine, The Ohio State University, 306 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210-1218. E-mail address: vadim.fedorov@osumc.edu; fedorov.2@osu.edu.

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clinical findings that (1) bolus injection of adenosine suppresses SAN function and produces pauses especially in patients with SAN dysfunction[12,13] and (2) orally administrated theophylline, a potent nonselective antagonist of adenosine receptors, reduces both the frequency and the duration of the pauses in patients with sick sinus syndrome.[14]

Despite abundant evidence of a suppressive effect of adenosine in the SAN, the causal relationship between adenosine and post-tachycardia pauses has not been experimentally demonstrated. Furthermore, owing to a lack of direct clinical mapping data from the SAN, the mechanism by which adenosine leads to atrial pauses has not been determined. The atrial pauses during tachy-brady syndrome could result from (1) poor function of the SAN as an impulse generator (reduced automaticity and sinus arrest) or (2) conduction block of the generated pulses from the SAN to the atria (SAN exit block). In the present study, we propose that adenosine induces post-tachycardia atrial pauses via suppression of SAN conduction rather than by slowing pacemaker automaticity. To test this hypothesis, we used high-resolution multistructural near-infrared fluorescence optical imaging to map functionally the coronary-perfused canine SAN preparation.

Methods

All animal procedures and protocols (n = 9 dogs; 9.9 ± 1.1 months of age; 4 males and 5 females) were approved by the Ohio State University's Institutional Animal Care and Use Committee. Detailed description of the heart isolation procedure, data analysis, histology, and immunohistochemistry can be found in the online supplemental materials.

Experimental protocol

The optical mapping of the canine SAN has been described previously.[15,16] The excitation-contraction uncoupler blebbistatin[17] (10–20 μM) and the near-infrared voltage-sensitive dye di-4-ANBDQBS[18] (10–40 μM) were added to the perfusate. Optical mapping was performed at a rate of 1000 frames/s with the MiCam Ultima-L CMOS camera (SciMedia, Costa Mesa, CA) with an optical field of view of 25 × 25 mm^2 (250 μm/pixel).

After control measurements, the preparations (n = 7) were perfused with 1, 10, and 100 μM adenosine for 10–30 minutes, followed by perfusion with the selective A1 antagonist DPCPX (1 μM; n = 5) for an additional 30 minutes and/or washout of all drugs (n = 7). Sinus cycle length (SCL), direct sinoatrial conduction time (SACT), and SAN recovery time (SNRT) were measured.[16] SNRT was measured after 1 minute of slow atrial pacing (3.3 Hz) or tachypacing (7–9 Hz). To assess the potential effects of endogenous adenosine, we conducted 2 experiments where DPCPX (1 μM) was applied before the perfusion of adenosine (100 μM) and no significant effects were observed (online supplemental results and online Table 1). Histology was performed, and anatomic structures of the canine SAN pacemaker complex were identified as previously described.[15,19,20]

Optical mapping data analysis and interpretations

Since canine SAN is surrounded by atrial tissue layers, the near-infrared optical recordings were weighted averages of signals from both atria and SAN structures. The analysis of these multicomponent intramural optical action potentials (OAPs) has been previously described.[15,16,21] To determine the SAN activities during pacing, we developed a new method to extract SAN signals (online Figure 1). The details of the method are described in online supplemental materials.

Three different methods were used to measure SNRT (see online Figure 1): indirect SNRT (SNRT*i*), direct SNRT (SNRT*d*), and real SNRT (SNRT*r*). SNRT*i* was calculated as the interval from the last atrial pacing to the first postpacing atrial beat, which is the traditional way of SNRT measurement in the clinical setting. SNRT*d* was calculated as the interval from the last atrial pacing to the first spontaneous SAN activation as described previously by Gomes et al[22] in 1984 (online Table 2). SNRT*r* was calculated as the interval from the last SAN beat during pacing and the first postpacing SAN beat. Corrected SNRT (cSNRT) was measured by subtracting preceding SCL from the measured SNRT.

Statistics

Quantitative data are shown as mean ± SD. Hypothesis testing was carried out by using an unpaired Student *t* test or repeated measurements analysis of variance (Minitab 16), where appropriate. Following analysis of variance, significance of the pairwise difference between SAN compartments (head, center, and tail) was determined by using a post hoc Tukey test. A value of P of $<.05$ was considered to be statistically significant.

Results

Experimental preparations and anatomy of the canine SAN pacemaker complex

Figure 1 illustrates that the functionally defined SAN correlates precisely with the SAN structure, which is defined by cell morphology, fiber organization, and a lack of connexin 43 expression in the head of the SAN, as previously reported.[15] It has been previously recognized that the SAN is insulated from the atria except at specialized SAN conduction pathways (SACPs), via which SAN activation exits to the atrial myocardium.[15,16,21]

Effect of adenosine on SAN complex during SR

Adenosine (1–100 μM) increased SCL and SACT in a dose-dependent manner (Table 1). Adenosine (10 μM) slows SR and sinoatrial conduction, as evident from increased SCL and SACT in Figure 2. This depression in conduction