Endovascular stimulation within the left pulmonary artery to induce slowing of heart rate and paroxysmal atrial fibrillation

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Abstract

Objective: In recent years there have been many reports dealing with basic models for sustained atrial fibrillation (AF), however few animal models exist for paroxysmal AF which closely simulate that seen clinically. Methods: In 12 dogs, anesthetized with sodium pentobarbital, a right thoracotomy was performed. We stabilized a basket electrode catheter within the left pulmonary artery (LPA) through a purse string suture in the right ventricle. Electrode catheters were sutured to multiple atrial sites including the four pulmonary veins and the right and left atrial appendages, along Bachman’s bundle and the coronary sinus. Results: Continuous pulses of electrical stimulation (20 Hz square wave stimuli, each 0.1 ms in duration, voltage range 1–40 V) across adjacent splines of the five arms of the basket induced slow heart rates (at lower voltages) and then initiated atrial premature depolarizations (APDs), atrial tachycardia (AT) and AF (at higher voltages). To avoid possible direct activation of atrial myocardium, we also applied a train (50–100 ms duration) of high frequency stimuli (200 Hz) coupled to each atrial paced beat so that the train fell within the atrial refractory period. Stimulation in the LPA at an average of 14±7 V induced heart rate slowing, APDs were seen followed by AT /AF at a voltage of 20±6 V, \( P = 0.002 \). Stimulation in the LPA resulted in APDs arising from a variety of sites including the left pulmonary veins (superior or inferior) and the left atrial appendage. After \( \beta \)-blockade (intravenous esmolol or propranolol, 1 mg / kg) the voltage threshold for induction of AF rose from 14±7 to 25±10 V, \( P = 0.02 \). Upon the addition of intravenous atropine (1–2 mg) the arrhythmic response (AF) to stimulation was completely abolished. Atrial pacing threshold was unchanged after autonomic blockade. Local application of radiofrequency energy (average number \( 5±3 \) ) across the metallic splines of the basket catheter in the LPA (70–80 V for 60 s) caused abolition of both the slowing and the arrhythmic response to LPA stimulation. Conclusion: These data suggest that stimulation of autonomic nerves in the LPA causes slowing of the heart rate followed by paroxysmal APD/AT /AF simulating the spontaneously occurring paroxysmal AF syndrome, associated with bradycardia, reported in patients. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Ablation; Adrenergic (ant)agonists; Arrhythmia (mechanisms); Autonomic nervous system; Bradycardia; Muscarinic (ant)agonists

1. Introduction

Atrial fibrillation (AF) has been recognized as the most common supraventricular arrhythmia found clinically. Its prevalence is mainly in the elderly, i.e. in those aged 50–80 and particularly affects men in that age group [1]. There are suggestions in the literature that sustained, chronic AF begins with episodic AF and that more frequent episodes lead to an electrophysiological remodeling of the atria, i.e. chronic shortening of the atrial refractory period, eventually leading to establishment of chronic AF. This process has been termed “AF begets AF” [2].

Recently we have developed a new experimental model for induction of the PAF syndrome, i.e. atrial premature depolarizations (APDs), atrial tachycardia (AT) and AF.
via endovascular stimulation of autonomic nerves in the superior vena cava [3]. These preliminary findings not only suggest that activation of both parasympathetic and sympathetic nerves to the atria can induce PAF in structurally normal hearts but also provides: (1) insight into a neural–electrophysiologic mechanism for induction of PAF, (2) may provide a diagnostic test for determining those at risk for developing PAF and (3) may allow for the determination of key neural sites involved in the development of PAF and therefore particularly susceptible for radiofrequency ablation and prevention of PAF occurrences. In the present study, we have found that endovascular stimulation within the LPA, presumably of the autonomic neural elements overlying this vessel can initially induce slowing of the heart rate. Then, with higher voltages, APDs, AT and AF can be induced.

2. Methods

Twelve adult mongrel dogs (weighing 18–30 kg) were anesthetized with sodium pentobarbital (30 mg/kg) administered intravenously. A 50–100-mg amount was injected hourly in order to maintain a surgical plane of anesthesia. The animals were intubated and ventilated with room air. A catheter was inserted into the left external jugular vein for drug delivery. Blood pressure was monitored via a sheath inserted in the left common carotid artery. A quadripolar electrode catheter with 2 mm inter-electrode spacing was introduced into the left common carotid artery. A quadrupolar electrode catheter with 2 mm inter-electrode spacing was introduced into the left common carotid artery and advanced to the aortic root to record His bundle electrograms. Two standard ECG leads were monitored continuously.

Using a right lateral thoracotomy at the 4th intercostal space, a pericardiotomy allowed access to the atria and base of the ventricles. Several octapolar electrode catheters (2 mm interelectrode spacing) were attached by sutures to contact the four pulmonary veins, Bachman’s bundle, the coronary sinus and the right and left atrial appendages. All tracings were amplified and digitally recorded on a computer-based Bard Labsystem. ECG filter settings ranged between 0.1 and 250 Hz, whereas bipolar electrograms were filtered at 30–250 Hz.

2.1. Stimulation within the left pulmonary artery (LPA)

A purse string suture was placed in the right ventricular outflow tract. A basket electrode catheter (Biosense-Webster, Diamond Bar, CA, USA) (Fig. 1) was inserted through the purse-string and advanced into the left pulmonary artery. The five splines of the basket were specially formed of uninsulated metal so that adjacent splines could be used for bipolar stimulation and individual splines used for radiofrequency ablation in conjunction with a skin patch. The impedance of the naked spline was in the range of 180–270 Ω. Stimulation of presumed autonomic neural elements was achieved by continuous delivery of high frequency square waves at 20 Hz, with each stimulus 0.05–0.1 ms in duration. The appropriate site of stimulation was indicated by a marked slowing of the atrial rate at voltages between 1 and 40 V. The features of the PAF syndrome appeared in the higher voltage range and consisted of APDs/AT leading to runs of AF.

2.2. Administration of autonomic blocking agents

In order to assess the involvement of either or both arms of the autonomic nervous system in the pacing induced PAF syndrome, β-blockade was induced by the administration of either esmolol 1 mg/kg or propranolol 1 mg/kg intravenously. For muscarinic receptor blockade atropine, 1–2 mg, was given by the same route.

All animal studies were reviewed by the local Animal Studies Subcommittee and approved by the Research and Development Committee of the Department of Veterans Affairs Medical Center, Oklahoma City, Oklahoma. The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US Nationals Institutes of Health (NIH Publication No. 85-23, revised 1996).

3. Results

The PAF syndrome could be induced by electrical stimulation within the LPA. At an appropriate site stimulation resulted in marked slowing of the atrial rate prior to the induction of APD/AT/AF. Fig. 2 shows a typical example, in which continuous pulsed stimulation was applied across a pair of splines of the expanded basket catheter in the LPA. At a stimulation intensity of 8 V the sinus cycle length of 420 ms (heart rate 143/min) was
prolonged to 496 ms (heart rate 121/min) initially, Fig. 2A). When the voltage was raised to 26 V the atrial cycle length increased from 448 (heart rate 134/min) to 1072 ms (heart rate 56/min) but then was followed by single and multiple APDs and AT (Fig. 2B). In Fig. 2C, at a voltage level of 30 V, APDs leading to AT then AF occurred in quick succession.

Atrial ectopy leading to AF could also be induced by coupling trains of high frequency (200 Hz) stimuli to atrial paced beats. Fig. 3 shows two separate arrays of electrogram recordings from the multiple electrode catheters sutured to various sites in the right and left atria and pulmonary veins. The two beats shown in right panel and left panel are the same atrial paced beats viewed from different multiple electrode arrays. Note that the earliest electrical ectopic activation after the end of the high frequency pulse (duration 100 ms) arises from the electrodes at the left atrial appendage (LAA, asterisks) even though the highest voltage was applied closest to the left superior pulmonary vein (LSPV, arrow) in the left pulmonary artery. Of the four dogs in whom the high frequency trains were delivered during atrial pacing, two showed the site of earliest ectopic activation at the left atrial appendage; one near the left superior pulmonary vein and one which arose earliest from the left inferior pulmonary vein.

Ten of the twelve dogs showed inducible APD/AT/AF which was still inducible after intravenous administration of β-blockers but the voltage required to induce AF increased significantly from 14±7 to 25±10 V, P<0.05 (Table 1). However, after administration of atropine, none of the dogs were inducible (0/10, Table 1), moreover, atrial pacing thresholds were unchanged from the control state. In eight of ten inducible dogs, radiofrequency current (75 V) applied for 60 s at the splines, at which stimulation induced slowing and AF, abolished both slowing of the heart rate and AF inducibility even when continuous pulsed stimulation was increased to the highest voltage (40 V). The average number of radiofrequency application was 3±2.

4. Discussion

These experiments provide evidence suggesting that autonomic nerve stimulation close to the heart can induce the electrophysiologic manifestation seen clinically as the paroxysmal atrial fibrillation (PAF) syndrome. The latter is characterized by frequent atrial premature beats, followed by runs of atrial tachycardia eventually degenerating, episodically, to AF. In those patients with no structural heart disease, the syndrome has been defined as lone AF.

In the present study continuous pulsed electrical stimula-
tion in the left pulmonary artery in the normal dog heart induced slowing of the heart rate. This finding provides strong evidence that parasympathetic stimulation of preganglionic fibers from the left vagosympathetic trunk is part of the mechanism underlying this effect. Randall and Armour in 1977 [4] provided meticulous studies tracing the para- and sympathetic fibers which course over the pulmonary artery in the dog, the baboon and in man. Interestingly, they alluded to “stimulation of a small branch arising immediately below the caudal cervical ganglion. During or immediately following cessation of stimulation, atrial fibrillation occurred and persisted for periods varying from a few seconds to several minutes.” They also state that “Identical stimulation of comparably sized branches rostral or caudal to it did not produce the response, although stimulation of the vagal trunk did.”

Furthermore, they go on to state that this response “was not sufficiently consistent to identify any specific nerve as an ‘atrial fibrillation nerve,’ but the concept of such a morphological–functional entity is of such importance as to merit much additional research.” [4]

The stimulation site mentioned by Randall and Armour is found in the plexus of fibers forming the vagosympathetic input to the heart which runs over the left pulmonary artery [4]. Thus, it appears that stimulation of these nerves via endovascular stimulation would activate both para- and sympathetic efferents to the heart. The former being responsible for the heart rate slowing and the latter for triggering the ectopic beats. These ectopic beats, in turn, could serve as the initiators of AT/AF in the context of the markedly shortened atrial refractory period caused by autonomic nerve stimulation, mainly the response to parasympathetic stimulation [5].

Some question can be raised as to whether the induction of atrial ectopy is mediated by autonomic nerve stimulation or direct stimulation of underlying left atrial tissues or both. Even the use of the trains of stimuli, coupled to atrial pacing, and falling in the refractory period can be chal-

Table 1

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<th></th>
<th>Baseline</th>
<th>After β-blockade</th>
<th>After atropine (2 mg)</th>
<th>RFC ablation (75 V, 60/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD and AF inducibility/tested animals</td>
<td>AF</td>
<td>AF</td>
<td>0/10</td>
<td>0/8</td>
</tr>
<tr>
<td>Intensity (V)</td>
<td>14±7</td>
<td>25±10</td>
<td>–</td>
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Values are mean±S.D.; *P<0.05 compared to baseline; APD, atrial premature depolarization; AF, atrial fibrillation; RFC, radiofrequency ablation.
lenged. For, if autonomic stimulation, particularly parasympathetic stimulation, shortens atrial refractoriness therefore, even a short duration, 50 ms, train can become a depolarizing stimulus albeit falling during the relative refractory period and perhaps inducing EADs or closely coupled stimulation in the atrial vulnerable period. Perhaps, more convincing evidence that there is a predominant autonomic bases for the atrial ectopy, is the response seen after β-blockers or after atropine administration. First, there was a significant increase in the voltage required to induce AF suggesting that β-stimulation contributed to the induction of the atrial ectopy. Secondly, the complete abolition of inducible APD, AT/AF by atropine, even at the highest applied voltages, indicated the critical role of the parasympathetic influence in the induction of PAF. Of importance, there was no change in the atrial pacing threshold before and after autonomic blockade.

4.1. Clinical implications

Experimental animal studies over several decades have shown that increased parasympathetic tone can predispose to AF [6–8]. The role of the autonomic nervous system in relation to paroxysmal atrial fibrillation has not been precisely defined but several suggestive clinical studies have been forthcoming. Specifically, recent studies have shown that the sympathovagal balance, as indicated by altered values of heart rate variability, are significantly different in those patients with recurrence of AF after cardioversion than in those without early recurrences [9,10]. Both these studies indicated that an increased sympathetic tone was associated with the enhanced chances of AF recurrence. In patients with paroxysmal focal AF originating in the pulmonary veins and superior vena cava, β-adrenergic stimulation (isoproterenol infusion) could initiate AF [11,12] whereas increasing parasympathetic tone (phenylephrine infusion) suppressed focal activity mainly in the pulmonary veins [13]. The latter authors explained the apparent contradiction by hypothesizing that accentuated antagonism caused by increased parasympathetic tone could decrease automaticity and suppress focal firing [13].

Coumel described two forms of autonomically based paroxysmal atrial fibrillation [14]. The adrenergic form was associated with exercise or emotional stress occurred during the daytime and occurred at sinus rates around a heart rate of 90 beats/min—β-blockade was an effective treatment. In contrast, the PAF of vagal origin occurred mostly at night, particularly during sleep and was associated with bradycardia. β-Blockade was contraindicated since it tended to increases PAF episodes presumably by enhancing the parasympathetically induced bradycardia during sleep.

The form of PAF induced in the present study appears to be an experimental counterpart of clinical patients described by Coumel with bradycardia induced PAF. Admittedly, this is an uncommon form of PAF but there might be a possible use of this experimental means for AF induction, clinically. In some patients, brought to the electrophysiology laboratory for ablation of PAF, the arrhythmia is difficult to induce, many times requiring the infusion of isoproterenol in order to activate episodes of PAF [11,12]. The use of endovascular stimulation within the LPA, particularly during atrial pacing, could be an adjunctive means for inducing PAF.

Also, the possibility that ablation of localized neural elements by applying radiofrequency energy to the successful stimulation sites in the LPA may actually decrease or eliminate the PAF syndrome in those susceptible patients. Of course, studies are needed to ascertain the safety and efficacy of such ablation procedures.

Acknowledgements

We thank Mrs. Andrea K. Moseley for her technical assistance and her dedicated efforts in the preparation of the manuscript.

Supported by a research grant from the Helen and William Webster Fund of the Oklahoma University Foundation and Biosense-Webster, Diamond Bar, CA, USA

References

