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Differential effects of cervical vagosympathetic and mediastinal nerve activation on atrial arrhythmia formation in dogs

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Abstract

To investigate the influence of the thoracic autonomic neuronal hierarchy on atrial arrhythmia formation, we compared the characteristics of atrial tachyarrhythmias induced by electrical stimulation of 1) the right vagosympathetic nerve complex at the cervical level and 2) the more caudal juxta-cardiac mediastinal nerves located on the anterior surface of the superior vena cava. Unipolar electrograms were recorded from 191 sites on the entire epicardial atrial surface and, in some experiments, from 63 right atrial endocardial sites. The sites of origin of initial beats at the onset of atrial tachyarrhythmias so induced were investigated analysing atrial activation maps. Neural effects on repolarization were determined by computing the integral surface subtended by unipolar recordings under basal conditions and at maximum neurally induced bradycardia, and calculating differences at each recording site. The mean area affected by nerve stimulation in all animals was significantly greater in response to vagosympathetic than mediastinal nerve stimulation. Atrial cycle length prolongation prior to tachyarrhythmia onset was more pronounced in response to vagosympathetic than mediastinal nerve stimulation. The earliest epicardial activations in early tachyarrhythmia beats were localized in the right atrial free wall and Bachmann bundle region in both cases, but with a higher incidence of double breakthroughs from septal sites of origin in response to vagosympathetic versus mediastinal nerve stimulation. Sites of early activation were associated with the areas of neurally induced repolarization changes. Thus, differential contributions are made to the electrophysiologic substrate of neurally induced atrial tachyarrhythmias depending on the pattern of engagement of neural elements within the autonomic neuronal hierarchy.

Keywords: Atrial tachyarrhythmias; Parasympathetic efferent neuron; Atrial mapping; Intrinsic cardiac nervous system; Vagally mediated atrial fibrillation

1. Introduction

Recently, ablative procedures for the treatment of atrial fibrillation (Hsieh et al., 1999; Pappone et al., 2004) have caused renewed interest for the role of the intrinsic cardiac nervous system in the pathophysiology of atrial arrhythmias (Olgin et al., 1998; Schauerte et al., 2001). It has been known for many years that atrial tachyarrhythmias (AT) can be induced in anaesthetized canines by electrical stimulation of the cervical vagosympathetic nerve complex (Lewis et al., 1914; Loomis and Krop, 1955; Wilber and Morton, 2002) or by localized electrical stimuli delivered to small mediastinal nerve branches of the thoracic vagosympathetic nerve complex (Armour et al., 1972; Hageman et al., 1973; Armour et al., 1975). The existence of specific "atrial fibrillatory nerves" adjacent to cardiac tissues has been postulated (Armour et al., 1975). Recently, we have reported

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that atrial tachyarrhythmia/fibrillation can be induced by delivery of electrical stimuli during the atrial refractory period to discrete mediastinal nerves that course over the extra- or intrapericardial portions on the ventral aspect of the superior vena cava (Armour et al., 2005). This consistently induced a sequence of events consisting of bradycardia followed by spontaneous atrial premature depolarization, atrial tachycardia and atrial fibrillation. An analogous sequence of events has been previously reported for arrhythmias that are induced, albeit less readily, when the cervical vagosympathetic nerve complex is subjected to continuous, intense electrical stimulation (Sharifov et al., 2000).

Dispersion of atrial refractory periods is of fundamental importance in the mechanism of atrial fibrillation (Wang et al., 1996; Liu and Nattel, 1997). We have previously reported preliminary data suggesting that local delivery of pharmacological agonists (nicotine) or electrical activation of discrete intrinsic cardiac nerves induce more localized changes in atrial repolarization than the more widespread biatrial effects induced by stimulating the vagosympathetic nerve complex at the cervical level (Pagé et al., 1995).

The objective of this study was to investigate the influence of the peripheral autonomic neuronal hierarchy on atrial tachyarrhythmia formation. The sites of origin of early atrial tachyarrhythmias and the spatial distribution of repolarization changes so induced were compared when cervical versus mediastinal neural elements were activated electrically.

2. Methods

2.1. Animal preparation

Thirteen adult mongrel canines (either sex), weighing 15–40 kg, were employed in this study. Animals were anaesthetized with Na thiopental (25 mg/kg IV, supplemented as required), intubated and maintained under positive-pressure ventilation. After induction, anaesthesia was changed to α-chloralose (25–50 mg/kg IV bolus supplemented with 25 mg/kg IV as required). Vagosympathetic trunks were isolated bilaterally in the cervical region and sectioned cephalad to the stimulation site for decentralization. A bilateral thoracotomy was performed and the pericardium was incised for exposure of the heart. Left ventricular and aortic pressures (Millar electronic pressure sensors) and a lead II ECG were recorded on a rectilinear pen recorder (Nihon Kohden, Tokyo, Japan). Atrio-ventricular block was induced by formaldehyde injection (37%, 0.1 ml) into the AV node to facilitate separation of atrial from ventricular electrical events at the time of data analysis. Right ventricular pacing (60 beats/min) was instituted to maintain ventricular contractile rates in order to assure adequate cardiac output and temporarily stopped during nerve stimulation and mapping trials. Experiments were performed in accordance with guidelines for animal experimentation (World Medical Association, 2002) and approved by an institutional animal care committee.

2.2. Electrical stimulation of cervical and mediastinal nerves

The right vagosympathetic nerve complex (RVSC) was stimulated supramaximally (pulse width: 1 ms, intensity: 1–4 mA, frequency: 15–30 Hz, maintained continuously) via bipolar stainless steel electrodes connected to a battery-driven current source controlled by a Grass SD9 square wave stimulator. RVSC stimulation was maintained continuously, throughout the induction of bradycardia, until 10 s after the initiation of atrial tachyarrhythmias (AT).

In separate trials, electrical stimuli were delivered to individual right-sided mediastinal nerves coursing over the ventral and ventrolateral surfaces of the superior vena cava (SVCN) either within, or 1–2 cm craniad to the pericardial reflection. These small-diameter nerves can be identified by their accompanying vessels (Armour et al., 2005). Five to seven active sites associated with these nerves were identified such that, when stimulated electrically, AT occurred shortly thereafter. Once identified, each active locus was marked with ink for repeat stimulation. Electrical stimuli were delivered focally via bipolar electrodes (1.5 mm spacing) mounted on a roving probe and connected to a battery-driven current source controlled by programmable stimulator (Bloom Associates, Philadelphia, Penn). Trains of 5 electrical stimuli (1–2 mA, 1 ms duration; 5 ms pulse interval) were delivered during the refractory period of the closest atrial regions (i.e. ~30 ms after excitation of a reference electrogram) to avoid direct atrial muscle capture. Neural stimulation was terminated once AT was induced. Support ventricular pacing was stopped during both neural stimulation protocols and resumed after the first 5 s of AT.

2.3. Atrial activation mapping

Five silicone plaques carrying 191 unipolar recording contacts (4.6–5.9 mm spacing) were positioned epicardially over the right atrial free wall, the postero-inferior wall of the left atrium and coronary sinus, the posterior aspect of the left atrium between the pulmonary vein ostia, the lateral left atrial free wall and the interatrial band (Fig. 1A). In addition, endocardial unipolar electrograms were obtained from 2 preparations by means of an inflatable balloon electrode array (63 recording contacts) introduced in the right atrium via an incision through the tip of the right atrial appendage (Fig. 1B). The balloon was slightly inflated during data acquisition, thus avoiding adverse effects on blood flow. The endocardial aspect of the right atrium is depicted as a polar representation.

The mapping electrodes and lead II ECG were connected to a multi-channel recording system (EDI 12/256, Institut de génie biomédical, École Polytechnique de Montréal) controlled by custom-made software (Cardiomap III: