

Cervical vagosympathetic and mediastinal nerves activation effects on atrial arrhythmia formation

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ABSTRACT

In anesthetized dogs both epi- and endocardial atrial activation maps and corresponding isointegral repolarization maps were created before and during right or left mediastinal nerve (RMN and LMN) and cervical vagus nerve (CVN) stimulation. Right mediastinal nerve stimulation typically caused sinus slowing, atrial tachycardia (AT), followed by atrial fibrillation (AF). Activation maps during AT showed epicardial breakthroughs from the right atrial free wall or Bachmann's bundle. Left mediastinal nerve stimulation (LMN) rarely caused sinus slowing and ATs originated mostly from Bachmann's bundle or from the pulmonary vein ostial region. Atrial repolarization changes induced by neural stimulation were measured by integrating the area subtended by 161 epicardial unipolar electrograms. Atrial tachycardia epicardial breakthrough sites were closely associated with the border zone where repolarization changes occurred. Both AT and AF were abolished by I.V. atropine, as were sinus bradycardia and atrial repolarization effects of nerve stimulation. Shortening of latency of onset and duration of AT by I.V. timolol suggest concurrent activation of adrenergic efferent neurons. In conclusion, juxta-cardiac mediastinal nerve stimulation can induce atrial fibrillation from multiple, discrete right and left atrial sites, which correspond to localized repolarization changes. Secondly, sinus bradycardia is not a necessary index of parasympathetic neurally induced atrial fibrillation. (*Anadolu Kardiyol Derg 2007; 7 Suppl 1; 34-6*)

Key words: atrial tachyarrhythmias, parasympathetic efferent neuron, atrial mapping, intrinsic cardiac nervous system, vagally mediated atrial fibrillation

Atrial fibrillation (AF) as a result of electrical stimulation of the vagosympathetic cervical trunk has been described nearly a century ago (1). Stimulation of selected mediastinal nerve branches of vagosympathetic origin close to the heart has been shown to consistently elicit atrial tachyarrhythmias (2).

Recently, the tachyarrhythmias, atrial tachycardia and AF following brief electrical stimulation of selected right-sided extra- and intrapericardial juxta cardiac nerve fibers were studied in detail (3). The main objective of such a study was to characterize the dynamics of atrial tachyarrhythmias so induced and to observe the effects of muscarinic and adrenergic blockade. Subsequently, the responses to stimulation of the right cervical vagosympathetic complex versus the right juxta cardiac nerves were compared (4). It was possible to relate the site of origin of the atrial tachyarrhythmias to the spatial distribution of repolarization changes caused by innervation patterns.

Subsequently, atrial tachyarrhythmias were also induced by electrical stimulation of left-sided mediastinal nerve fibres coursing over the ventrolateral and lateral surfaces of the left atrium (preliminary). Left atrial tachyarrhythmias were identified and it was observed that sinus slowing was not a prerequisite for the initiation of AF autonomic nerve stimulation.

These experiments were carried out in anaesthetized, mechanically ventilated mongrel dogs. Procedures were carried out in accordance with World Medical Association guidelines and approved by our institutional animal care committee. Under conti-

nuous anaesthesia with IV chloralose alpha, the heart was exposed and AV block followed intraseptal formaldehyde injection. The right ventricle was paced at 60 beats/min. In separate experiments, right and left mediastinal nerves were identified and stimulated using a hand held bipolar electrode probe, while marking the sites of successful stimulation. Trains of 5 stimuli (1-2 MA, 1 ms, 5 ms pulse interval) were delivered during the atrial refractory period (i.e. <30 ms after a corresponding atrial reference electrogram). Stimuli were derived from a battery driven current source controlled by a programmable stimulator (Bloom Ass Phil Penn, USA).

In a limited series, the cervical vagosympathetic trunks were sectioned and the right distal stump was stimulated with bipolar stainless steel electrodes supra (1 ms, 1 to 4 mA, 15 to 30 Hz) until sinus bradycardia, sinus arrest and then the initiation of AF was obtained. Right mediastinal nerve stimulation was also carried out in these preparations.

For epicardial recordings, five silicone plaques with 191 recording electrodes (5 to 6 mm spacing) were sutured onto the right and left atrial epicardium. Left atrial endocardial recordings were obtained with an inflatable balloon with 63 contact electrodes. In some preparations, right atrial intra cavity potentials were recorded using a noncontact balloon catheter of the Ensite 300 mapping system. Epicardial and endocardial mapping electrodes, as well as limb leads, were connected to a multichannel recording system (EDI 12/256, Institut de génie biomédical, École Polytechnique de Montréal, Canada) controlled by a custom-

made software (Cardiomap III) using a PC computer. Unipolar electrograms referenced to Wilson's central terminal derived from standard limb leads were amplified by programmable gain analog amplifiers (0.05 to 450 Hz) and converted to digital format at 1,000 samples/s/channel. Data were stored on hard disk, from which files were subsequently retrieved for analysis. Isochronal maps were computed by linear interpolation. Sites of earliest activation were determined for basal sinus beats, for atrial escape beats and atrial tachycardia beats. Epicardial breakthrough sites were identified as the areas of earliest 10 ms activation. Other variables measured were latency of onset, duration, and beat-to-beat cycle length. Atrial tachycardia had mapping characteristics distinctly different from AF. During AF, despite disorganized and overlapping activation patterns areas of slow conduction and unilateral block could be delineated.

The spatial effects of nerve stimulation on atrial repolarization were determined by integrating the areas subtended by the activation and repolarization portions of each atrial electrogram (5). Isointegral distribution maps were then obtained and the differences between the prestimulation maps and those recorded during peak nerve stimulation effect were calculated.

Mediastinal nerve stimulations were of short duration, usually 6 trains. Stimulus application was interrupted at the onset of tachyarrhythmia. The tachyarrhythmias lasted, on average, less than 6 seconds terminating spontaneously. Cervical vagal stimulation required more intense and more prolonged stimulation; and AF appeared after longer pauses of sinus arrest.

Typically, during right mediastinal nerve stimulation there was an initial sinus bradycardia followed by atrial tachycardia within 3 seconds of stimulus application. Within 3 to 6 beats, AF followed during the bradycardic response the site of the earliest activation migrated towards the inferior right atrium along the right atrial subsidiary pacemaker complex (6). The sites of the earliest activation of atrial tachycardia were on the right atrial free wall or in the Bachmann bundle region. At the onset of AF irregular activation patterns appeared with regions of conduction slowing and block suggesting local reentry. With endocardial mapping, breakthroughs were found to originate along the crista terminalis or more dorsally on the right side of the interatrial septum close to the dorsal component of the overlying right atrial ganglionated plexus (RAGP). Such endocardial sites appeared slightly earlier than the corresponding epicardial breakthroughs. With left-sided nerve stimulation most breakthroughs were in the Bachmann's bundle region (2/3 of episodes) while the others appeared adjacent to the pulmonary venous ostia or on the ventral left atrial wall.

Mediastinal nerves contain both cholinergic and adrenergic efferent axons (7). Sympathetic and parasympathetic efferent axons are intermingled in these nerves and their interactions are complex. The vagal effects mediated by acetylcholine include sinus bradycardia, atrioventricular block, shortening of the action potentials and refractory periods of atrial myocardial cells. The sympathetic effects include enhancement of automaticity and the generation of atrial ectopics acting as triggers or drivers.

Both atrial tachycardia and AF following mediastinal nerve stimulations were completely abolished by atropine confirming the predominant role of a parasympathetic effect and both were significantly altered by beta blockade (timolol), being more difficult to induce, with longer latencies of onset, longer cycle lengths and shorter durations.

The induction of AF under autonomic nervous influence is usually attributed to inhomogeneities and dispersion of refractory periods, the occurrence of conduction blocks and the appearance of reentrant circuits (8). The isointegral maps derived during stimulation of the cervical vagosympathetic or complex mediastinal nerves afford high-resolution identification of the spatial distribution of the terminal parasympathetic efferent neuronal fibers. From epicardial maps, AF originated at the border of the most marked neurally induced repolarization changes.

Pappone (9) has emphasized the importance of vagal inputs as useful markers of ablative sites for AF. Despite apparent clinical success, targeting sites according to a bradycardic response is limited in scope (10), although the possibility of vagal reflexes have been proposed (11). However, induction of AF without concomitant sinus bradycardia frequently was observed during left mediastinal nerve stimulation. When only chronotropic and dromotropic effects are used as markers, the effects of fibers projecting on to atrial tissue remote from the sinus node or the AV node may be overlooked. By mapping repolarization changes, fibers from the RAGP were found to project to many more atrial sites than previously suggested, particularly the atrial septum (12). These data imply that neural effects on atrial tissue can occur without necessarily eliciting a sinus bradycardia. These results also suggest that individual nerve fibers emerging from the ganglionic plexus are discretely distributed over the atria and that they can have quite selective localized effects. Left-sided mediastinal fibers project mostly to the postero-inferior wall of the left atrium.

Coumel et al. (13) studied patients with normal hearts presenting frequent attacks of paroxysmal AF. Remarkably, these attacks occurred mostly at night and were often related to digestion periods or the absorption of alcohol. These arrhythmias were typically preceded by a brief period of bradycardia, followed by a period of atrial tachycardia or atrial flutter and a rapid fibrillation corresponding to shortening of the atrial refractory period, changes reminiscent of the data obtained during mediastinal nerve stimulation.

In summary

Given the current interest in neurocardiology with respect to atrial arrhythmia formation, these data indicate that such events are not necessarily preceded by bradycardia and that they appear to be dependent on discrete neural elements within the intrinsic cardiac nervous system.

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