Arrhythmias induced by local cardiac nerve stimulation

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MATERIALS AND METHODS

Thirty-four open-chest dogs, weighing 17-26 kg, were studied under phencyclidine hydrochloride (2 mg/kg im) and α-chloralose (60-80 mg/kg iv) anesthesia and positive pressure respiration. Walton-Brodie strain-gauge arches (for recordings of regional contractile force) and either unipolar or bipolar electrodes were sutured onto the atria and ventricles (Fig. 1). Selected thoracic cardiac nerves were stimulated via a Grass model S5 square-wave stimulator at parameters of 5 msec duration, 10 Hz, and voltages ranging from 0.5 to 6 V; in a few experiments stimulus duration and frequency were also varied. Both stellate ganglia, thoracic and pericardial portion of the ventrolateral cardiac nerve (VLCN), and its branches, as well as the nerves coursing with the anterior descending coronary artery (Fig. 1) were stimulated. Hexamethonium (1 mg/kg), atropine (1 mg/kg), reserpine (two doses of 0.3 mg/kg over 2 days), propranolol (1 mg/kg), phentolamine (1 mg/kg), lidocaine (0.5 mg/kg), and procaine (0.5 mg/kg) were employed in efforts to abolish the induction of the arrhythmias.

In an initial group of 16 animals, mechanical and electrical events were recorded from multiple epicardial surfaces during stimulation of the VLCN. In eight of these animals a standard ECG was utilized along with force recordings from the left atrium, right ventricular sinus and conus musculatures, and the left ventricular anterior, anterolateral, posterolateral, and posterior surfaces. In four experiments the posterolateral force recording was replaced by a measurement of internal mammary artery pressure. In a further eight experiments, a standard limb lead II ECG, either or both contractile force and unipolar electrograms were recorded from the conus and sinus of the right ventricle, as well as the anterior, lateral, and posterior left ventricular epicardial surfaces. Sometimes electrical and mechanical activity of either atrium were substituted for ventricular recordings. On two occasions the right atrium was paced in order to record the effect of pacing rate upon local contractile behavior.

In a second group of 10 animals, bipolar electrodes were sutured onto the sinoatrial (S-A) node, the interatrial pathway as it courses onto the left atrium, the epicardium over the coronary sinus, and the middle-posterior junction of the two atria, as well as the right ventricular conus and left ventricular anterior epicardial surfaces. Force gauges were sutured onto one atrium, the right ventricular conus, and the anterior left ventricular epicardium. In six of these animals, atrioventricular (A-V) nodal blockade was created by the injection of phenol into the A-V node region. In four animals that were placed on total cardiac bypass, bipolar electrodes were sutured over the S-A node, the valvular limbus of the coronary sinus, the atrioventricular node, the bundle of His, and the internodal conduction pathways. Contractile force was recorded from the left atrium and the right ventricular sinus. In this group A-V blockade was created via a small incision into the lower

AN UNDERSTANDING OF THE MECHANISMS creating cardiac arrhythmias is of great importance, and views concerning such mechanisms have been the subject of much recent investigation (12). Owing to the difficulty in creating paroxysmal tachycardias in the experimental animal, conclusions concerning their origin have been largely speculative. Hoffmann and Cranefield observed that by far the single most important cause of alterations in cardiac rate and rhythm is the action of autonomic mediators (13). The purpose of this investigation is to report a mechanism of genesis of both supraventricular and ventricular tachyarrhythmias and to attempt to discern whether the underlying mechanism is related to a rapidly firing ectopic pacemaker or to reentry involving the atrioventricular nodal region.

Arrhythmias induced by local cardiac nerve stimulation. Am. J. Physiol. 223(5): 1068-1073, 1972.—Electrical and mechanical activity were recorded from multiple regions of the canine heart during electrical stimulation of distal portions of individual cardiac nerves. Functional responses included generalized augmentation in contractile force, together with sinus or supraventricular tachycardia when the stimulus was applied to the stellate ganglion or to portions of the left sympathetic rostral to their projection onto the surface of the heart. Alterations in contractile force and the development of tachyarrhythmic states became more localized as the ventrolateral cervical cardiac nerve was stimulated more distally. Mechanical alternans accompanied progressive acceleration in heart rate, but was generated to varying degrees within highly localized portions of the cardiac musculature. Excitation of the ventrolateral nerve at the level of the superior pulmonary vein elicited both atrial and ventricular tachycardias, each at a different rate. Effective resection or local procainization eliminated the ability to elicit such tachyarrhythmias.

Regional cardiac nerves; catecholamine-dependent arrhythmia; ectopic pacemakers; atrial and ventricular tachyarrhythmia; neurally induced tachyarrhythmia
A-V node. Finally, a group of four animals, which had been effectively reserpinized, were studied with bipolar electrodes placed immediately over the sinoatrial node, the anterior internodal pathway, the coronary sinus (epicardial surface), the left atrial portion of the interatrial bundle, and the right ventricular sinus epicardium. Right atrial and ventricular forces were also recorded. The criteria for effective reserpinization were lack of rate and force augmentation during stimulation of the stellate ganglia. Two doses of 0.3 mg/kg over a 2- or 3-day period resulted in effective reserpinization although 50% of the dogs died with this dosage; lesser dosages abolished rate but not force augmentation. In one of the four dogs the neurally induced arrhythmia was completely abolished. In the remaining three it was initiated only with 4- to 6-v stimulation of the midpericardial VLCN, a voltage 5-10 times that required in control experiments: in those instances the injection of phentolamine (1 mg/kg) abolished the arrhythmia. Local phenolization of the A-V node was performed in these animals to create A-V blockade. All of the hearts from reserpinized dogs were analyzed for tissue catecholamines using the extraction method of Anton and Sayre (2) and the assay method of O’Hanlon, Campuzalo, and Horvath (18).

RESULTS

Figure 1 illustrates the course of the ventrolateral cardiac nerve (VLCN) as well as some of the nerves accompanying the anterior descending coronary artery. The VLCN is a large nerve that leaves the caudal cervical sympathetic ganglion and courses towards the heart laterally to the thoracic vagus and enters the pericardium above the left superior pulmonary vein. It divides into several branches coursing along the ventral surfaces of the aortic arch and the pulmonary artery to enter the pretracheal, aortic, and coronary plexuses. A large lateral branch descends to penetrate the pericardium and to supply the dorsal wall of the left atrium and the vestigial fold of the left precaval vein and coronary sinus. This branch also projects from base to apex over the dorsolateral surfaces of the left ventricular wall. Rich interconnections with adjacent sympathetic and parasympathetic nerves occur at all levels (17). The arbitrary designations of upper, mid, and lower pericardial nerve are used to demonstrate the location of the nerve stimulation utilized throughout this paper. The small semicircles around the anterior descending artery and its branches locate sites of stimulation of other cardiac nerves.

Figure 2 represents recordings of contractile force from seven different epicardial surfaces, together with a standard ECG limb lead II that was turned off during nerve stimulation (horizontal bar at top of each segment). Right (RSS) and left (LSS) stellate ganglion stimulation caused augmen-
FIG. 3. In the same experiment as in Fig. 2, with ECG channel deleted, effects of stimulation of middle pericardial region of VLCN (A), and lower pericardial region of VLCN (B) are shown to compare regional effects of VLCN stimulation in ventricular region.

FIG. 4. Stimulation of middle pericardial VLCN developed a tachyarrhythmia as recorded on ECG, left atrial force (LAF), conus electrical (conus elect) and force (conus force) behavior, sinus force, anterior left ventricular electrical (LVA elect) and force (LVA force) changes, as well as lateral left ventricular force (LVL force). Left panel demonstrates arrhythmia at a slow recording rate, and right group of panels shows arrhythmia at a faster recording speed. Note conus electrical excitation is double its mechanical behavior in middle of trace.

tation in force in all recorded regions, the right ventricular force being primarily augmented during right stellate stimulation. When the cranial segment of the VLCN (up thor VLCN) was stimulated, the contractile force was augmented only in the left ventricular posteriolateral and posterior areas; heart rate increased from 160/min to 200/min. Stimulation of the caudal thoracic portion of the VLCN (low thor VLCN) caused the same regional force augmentation without change in heart rate. Stimulation of the total cranial portion of the pericardial (upper) VLCN elicited bradycardia (heart rate of 125/min) with some depression in atrial contractile force. Minimal depression in contractility occurred in the right ventricular conus as well as the anterior and posteriolateral regions of the left ventricle. Stimulation of the lateral branch of the cranial pericardial VLCN (br up peri VLCN) elicited augmentation in force in the posteriolateral and posterior regions of the left ventricle with minimal atrial force depression and bradycardia (heart rate of 150/min).

Figure 3 illustrates the effect of stimulation of the midpericardial (left panel, A) and lower pericardial (right panel, B) VLCN upon force generation in the same preparation as illustrated in Fig. 2. Control heart rate was 155/min. During 1-volt stimulation of the midpericardial VLCN, atrial rate was increased to 320/min, whereas the left ventricular rate accelerated to 270/min. Note that atrial tachycardia was regular, whereas the ventricular rate was not; in the right ventricle and anterior and anteriolateral left ventricle every third contraction was greater than the other two—pulsus trigemini. When the lower pericardial VLCN was comparably stimulated, atrial tachycardia was irregular and the left ventricular rate was driven at 320/min, whereas the right ventricular conus contracted 160/min. Contractile alternans occurred in the right ventricular sinus (rate of 320/min). Augmentation in contractile force occurred in some segments but not in others.

Figure 4 demonstrates the effects of stimulation (1 v) of the middle pericardial VLCN upon both electrical and mechanical activities in another animal. The first panel on the left illustrates at slow recording speed (2.5 mm/sec) the tachyarrhythmia induced by VLCN stimulation and reveals the widely varying responses in contractile force upon the different myocardial segments. The second panel illustrates a fast control trace, followed by a brief recording at slow speed, before nerve stimulation was initiated.
NEURALLY INDUCED TACHYARRHYTHMIAS

Figure 5 illustrates the effects of atrial pacing rates upon electromechanical events within small epicardial segments of the heart. The left panel shows a control sequence with a heart rate of 138/min. In the five subsequent panels the pacing rates were 170, 185, 210, 280, and finally 310/min. As pacing rate was increased, there developed increasing mechanical alternans, particularly in the right ventricle, until the second contraction in the sinus almost disappeared.

At a pacing rate of 310/min the larger contraction of the mechanical alternans in the conus occurred when the smaller contraction occurred in the sinus.

Figure 6 illustrates the effects of l-v stimulation of the low-pericardial VLCN and the anterior descending coronary nerve before (two left panels) and after (two right panels) the creation of A-V block. Stimulation of the VLCN

![Figure 5](http://ajplegacy.physiology.org/)

![Figure 6](http://ajplegacy.physiology.org/)
caused arrhythmia at a heart rate of 170 (control rate 145/min) with a great depression in atrial force. Stimulation of the coronary artery nerve elicited atrial tachycardia (180/min) as well as ventricular arrhythmia with concomitant fall in systemic arterial pressure. After atioventricular nodal block the atrial rate was 180/min and ventricular rate 120/min. Stimulation of the low-pericardial VLCN (third panel) now did not change atrial contractility or rate, whereas the ventricular rate was increased to 190/min. Stimulation of the coronary nerve (last panel) elicited similar results.

Figure 7 illustrates the sequence of electrical events utilizing multiple bipolar recording, from the sinoatrial node (S-A node), the valvular limb of the coronary sinus, the atrioventricular node (A-V node), the interatrial conduction pathway on the left atrium (Bachmann's bundle), and the right bundle in the right ventricular septum. Contractile force of the left atrium (LAF) and the right ventricular sinus (RSF) were also recorded. In the control sequence (left panel) S-A nodal activity was followed in 20 msec by A-V nodal activation, in 26 msec by the coronary sinus region, in 30 msec by Bachmann's bundle, and in 140 msec by the right bundle branch. During 0.5-v stimulation of the midpericardial VLCN (arrow), there was tachycardia (control rate of 150/min, tachycardia of 210/min) in which the first recorded areas to be activated electrically were coronary sinus and Bachmann's bundle. This initial activation was followed in 28 msec by the A-V node, in 33 msec by the S-A node, and in 140 msec by the right bundle. Each atrial activation was associated with ventricular excitation and contraction. During 1.5-v stimulation of the VLCN (right-hand panel) the atrial sequence remained unaltered from the middle panel; however, the right ventricular tachycardia was independent of atrial
activation, the atrial rate being 350/min and the ventricular rate 309/min. Contractile alternans appeared in the atrium (LAF) and the ventricle was activated electrically only after every second atrial activation.

Figure 8 represents the effects of 1.5-v stimulation of the VLCN in the same preparation as in Fig. 7 after the creation of A-V block. Note that the control sequence of atrial activation in the left panel is the same as in Fig. 7, but ventricular electrical activity was dissociated from that in the atrium. The right panel demonstrates an atrial arrhythmia induced by VLCN stimulation and its cessation when the stimulus was terminated (arrow in right-hand panel). The coronary sinus region was the first to be electrically activated, followed in 25 msec by Bachmann’s bundle, in 35 msec by the A-V node, and in 45 msec by the S-A node area. The sequence of activation following cessation of stimulation in this experiment returned immediately to that observed during the control period. During A-V dissociation, A-V nodal activity was clearly discernible and could easily be related to the control state as shown in Fig. 7. The ventricular rate was not accelerated as the ventricular ectopic focus (shown in the third panel of Fig. 7) was not activated after the lower nodal and upper His incision.

Figure 9 demonstrates the results of stimulation of the middle pericardial VLCN by 6 v (arrows) after effective reserpinization. In the control (left) panel the S-A node was electrically excited first, followed 15 msec later by the anterior internodal pathway (AIN), next (25 msec) by the posterior internodal pathway (PIN), next (30 msec) by the left atrium (LAF), and finally (115 msec) by the right ventricular epicardial surface (RVE). Right atrial (RA force) and right ventricular (RV force) force generation capabilities are also shown. Stimulation (10 Hz, 5 msec, 6 v) of the lower VLCN caused no rate (middle panel) or rhythm (right panel) changes. It is emphasized that these stimulation parameters were invariably supramaximal in the absence of reserpine (Fig. 7).

DISCUSSION

Considerable effort has been expended to elucidate the mechanisms underlying cardiac tachyarrhythmias. The two prevalent concepts regarding such mechanisms are the presence of a rapidly firing ectopic pacemaker and the development of reentry phenomena involving the A-V node or other conductile tissue—a form of circus excitation (6, 9, 20). Progress in understanding cardiac arrhythmias has been impaired by difficulties in production of sustained tachyarrhythmias during experimental conditions (13); application of a premature electrical event in the atria, A-V node, or ventricles may in fact produce a markedly different response from those characteristic of sustained tachyarrhythmias in man.

Stimulation of the autonomic nerves has been demonstrated to effect rate and contractility of the atria and ventricles—the parasympathetic nerves generally depressing and the sympathetic nerves augmenting these parameters. Abildskov has discussed the role of the autonomic nerves in clinical arrhythmias and illustrates the frustrations encountered in definitively explaining cause and effect relationship (1). To date, few if any observations of the tachyarrhythmic effects of local cardiac nerve stimulation have been reported. Both the sympathetic and parasympathetic systems have been implicated in the genesis of cardiac arrhythmias (4, 10, 11, 13); however, experimental arrhythmias induced by nerve stimulation were associated with coronary artery occlusion or other conditions that predispose to cardiac arrhythmias. Mechanical stimulation of the autonomic nerves in association with the great vessels in baboons regularly cause tachyarrhythmias. Tachyarrhythmias were induced in the dog during stimulation of the small nerves accompanying the main pulmonary artery or along the major coronary arteries, and the ventrolateral cardiac nerve as it projects onto the left lateral wall of the ventricles. The midpericardial portion of the VLCN elicited both atrial and ventricular tachyarrhythmias; if the voltage was grossly supramaximal (i.e., 3 v) or the stimulation period lengthened (i.e., 10 sec or more) the tachyarrhythmia generally persisted for prolonged periods (many minutes). Ventricular fibrillation was rarely if ever induced by such local nerve stimulations, but atrial tachycardia often led to flutter and atrial fibrillation. Figure 2 demonstrates that the upper pericardial VLCN often contains both parasympathetic and sympathetic elements (panels E and F); also, upper pericardial VLCN stimulation rarely produced tachyarrhythmia.

Concern about stimulus current spread directly onto the heart led to a series of experiments in which chemical agents were employed. Local application of lidocaine or procaine reversibly blocked the arrhythmic response; systemic infusion of these agents as well as local nerve application of phenol prevented the tachyarrhythmia. Acute section of
either the cervical vagi or stellate ganglia had only minimal influences. Hexamethonium, atropine, and propranolol had little or no influence. Reserpitation, with or without the addition of phenotamine, abolished the tachyarrhythmic response. A dose less than 0.3 mg/kg administered on two different days blocked the heart rate response upon stimulation of either stellate ganglion, but not the augmentation in force of ventricular contraction; the dose of 0.3 mg/kg for 2 days, which was the LD₅₀ in our experiments, reduced or abolished the tachyarrhythmia. Further when the tachyarrhythmia could be induced a stimulating intensity of 4–6 V was required, a considerably higher voltage than was required in control states. Local cardiac catecholamines were absent from both atria, ventricular free walls, and the ventricular septum (below the sensitivity of the analytical technique (16), which is <5 ng/g norepinephrine and <10 ng/g epinephrine). In four effectively reserpinized hearts, creation of A-V block resulted in ventricular standstill without spontaneous activation; extraneous excitation (mechanical or electrical) generated weak ventricular systole. This observation substantiates the important role of the sympathetic nervous system in maintaining intrinsic viability of the ventricles and their associated specialized conductile tissue responsible for automatic activity.

Preliminary studies with chronic section of the VLCN (upper thoracic portion) also eliminated the tachyarrhythmia. It therefore seems reasonable to conclude that stimulation induced tachyarrhythmias only when functional neural elements were present. Microscopic examination of the epicardium overlying the anterior descending coronary artery and its branches containing the tissues in contact with the stimulating electrodes demonstrated the presence of nerve bundles. However, stimulation of fascial tissues between major vessels with the same parameters did not elicit tachyarrhythmias. Procaine blocked the effects of nerve stimulations. Antiarrhythmic effects of procaine or lidocaine have been considered to be related to alterations in the transmembrane potential events in cardiac tissue (3).

The evidence presented here implicates local autonomic nerves in the mechanism.

The quality of tachyarrhythmia induced is quite dependent upon the location of the terminal cardiac nerves (Fig. 3). The more caudal the site of stimulation, the less the influence upon atrial function, and ventricular epicardial augmentation became more localized as the stimulation site progressed distally along the VLCN (Fig. 2). When the most distal portion of the VLCN projecting onto the heart or the coronary nerves along the LAD were stimulated, tachyarrhythmia was confined to the ventricles (Figs. 3 and 6); this became particularly evident after the creation of A-V block. Stimulation of the middle segments of the VLCN caused atrial tachyarrhythmia that did not effect the ventricles after A-V block (Figs. 7 and 8). It is therefore likely that the major site of origin of the tachyarrhythmia is determined by the anatomical distribution of the stimulated nerves.

Local ventricular force generating capabilities became grossly altered at high-tachyarrhythmia rates. When ventricular electrical activation rates approached or exceeded 400 beats/min, some areas of the ventricles did not generate contractile force with each cycle (Figs. 3 and 4); the alterations in force occurred within and between individual ventricular segments. It is evident (Fig. 4) that local electrical activations were synchronous, whereas only alternate excitations in the right ventricle were followed by local contractions. It has been demonstrated by in vitro (19) as well as in vivo (8) methods that force of contraction is rate-dependent. Mechanical alternans were produced in four paced preparations (Fig. 5) in which the atria and ventricles were paced at increasing rates. Above 280/min the force of contraction, particularly in the right atrium and the right ventricular conus, developed mechanical alternans. The generation of alternans by rapid pacing (Fig. 5) separated the electrical and mechanical changes developed during the tachyarrhythmia. Thus, the mechanical alternans evidenced during the tachyarrhythmias is considered to be due to the development of rapid electrical excitation.

The tachyarrhythmia reported here appears to be primarily related to local sympathetic nerve effects upon atrial and ventricular electrical events. Parasympathetic as well as afferent components exerted only minor regulatory functions upon the tachyarrhythmia. The important question arises as to the origin of this neuronally induced tachyarrhythmia. Gross division of the A-V bundle differentiated clearly that the origin can be either atrial or ventricular, or both, depending upon the site of neural stimulation. When the stimulus was applied to the nerves accompanying the anterior coronary vessels and their branches, the site of ectopic foci was below the A-V node, for when A-V nodal block existed (Fig. 6) the tachyarrhythmia was confined to the ventricles. The same experiment (Fig. 6) demonstrates that when the lower pericardial VLCN was stimulated after A-V block, the focus of ectopic activity was also confined to regions below the A-V node. In the latter instance the atria were not affected (although they were affected during control states), suggesting that the ventricular tachyarrhythmia may influence the atria when the node is intact or that nerves passing to the atria were damaged by the nodal incision.

When the middle pericardial VLCN was stimulated, the pacemaker shifted from the S-A node to the coronary sinus zone and fired at an accelerated rate (Fig. 7). As the stimulation voltage was increased (right panel) the rate of discharge of this coronary sinus region pacemaker increased and another pacemaker became activated in the A-V node-His region, the ventricular accelerated rate differing from the atrial rate. After incision in the lower A-V node-His region only atrial tachycardia occurred; it is presumed that the ventricular ectopic pacemaker was destroyed and was located in the lower node or upper His-bundle regions. Although these preliminary investigations do not accurately place the site of origin of the tachyarrhythmias they implicate one focus to be near the coronary sinus and the other to be in the region of the A-V node or His-Purkinje system (12). Thus, it appears that stimulation of local autonomic nerves can initiate a focus of rapid firing within either the atrium or ventricles depending on the location of the neuronal elements being stimulated, and the atrial pacemaker can generate atrial flutter that may change into atrial fibrillation.
Two major hypotheses of the mechanisms underlying the cardiac tachyarrhythmias are in vogue: 1) the rapid firing of an ectopic pacemaker in the atrium, atrioventricular junction, or the ventricles; 2) atrial or ventricular reentry involving the A-V node in particular (9, 20). It has been postulated recently (6) that the mechanism of reentry may exist in a very localized region of cardiac tissue and reentry mechanisms can account for very rapid firing rates (15, 16). However, we were unable to demonstrate (local bipolar electrograms) a disorganized atrial electrical activation until atrial fibrillation was initiated by higher nerve-stimulation voltages. Incisions in the atrium, on the cranial and coronary sinus surfaces of the A-V node, did not modify the tachyarrhythmias and section of the A-V node-His junction caused the arrhythmias to occur independently in both the atria and ventricles. Autonomic nerve stimulation altered atrial pacemaker location (7) and can generate rapid atrial and ventricular tachyarrhythmias confined to highly localized myocardial regions. The mechanism underlying these neuronally induced tachyarrhythmias appears to be the shifting of pacemaker activity to one or more atrial or ventricular sites capable of extremely rapid firing.

The development of neuronally induced atrial or ventricular tachyarrhythmias may be dependent upon the functioning of the autonomic nervous system, particularly the sympathetic cardiac nerves, which can be abolished by blockade, ventricular standstill ensues, suggesting the intimate relationship between ventricular excitability and local concentrations of catecholamines.

The thesis that the tachyarrhythmia originates from one or more rapidly firing ectopic pacemakers explains the fact that foci can be either in the atrium or ventricle or from both at the same time, depending on the site of neuronal excitation. In the atrium the pacemaker is generally localized near the coronary sinus, although if a strong voltage (i.e., 3 v) is applied to the nerve an extremely irregular atrial tachyarrhythmia ensues in which the pacemaker may be multifocal. In the ventricles a pacemaker may arise from the lower A-V node-His region, and presumably from other sites. These experiments demonstrate a reliable method of producing a variety of tachyarrhythmias, the origins of which are rapidly firing ectopic pacemakers under neural control.

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REFERENCES