Neural Effects on Sinus Rate and Atrioventricular Conduction Produced by Electrical Stimulation from a Transvenous Electrode Catheter in the Canine Right Pulmonary Artery

TERRY B. COOPER, GILBERT R. HAGEMAN, THOMAS N. JAMES, AND ALBERT L. WALDO

SUMMARY We studied the effects on sinus rate and atrioventricular (AV) conduction of electrical stimulation from a 12-polar electrode catheter advanced into the right pulmonary artery of 21 anesthetized dogs. In each experiment, the distal tip of the electrode catheter was positioned at a standard fluoroscopic site, and a sequence of bipolar electrograms was recorded during sinus rhythm from the 11 adjacent catheter electrode pairs using a standardized technique. Within each sequence of electrograms, a characteristic change in the polarity of the atrial complexes was identified at a site in the proximal right pulmonary artery. This recording site was labeled the site of initial polarity transition. Stimulus-strength response testing was performed from each electrode catheter pair during spontaneous sinus rhythm and during atrial fibrillation. The least stimulus strengths required to slow sinus rate or to depress AV conduction were obtained using an electrode pair at a proximal right pulmonary artery site identified as the optimal stimulation site. This stimulation site was at, or immediately proximal to, the recording site of initial polarity transition. Stimulation distal to the site of initial polarity transition precipitated atrial fibrillation using stimulus strengths which were very low compared to stimulus strengths required to precipitate atrial fibrillation at more proximal sites. Negative chronotropic and negative dromotropic effects persisted throughout 5-minute periods of stimulation from the optimal stimulation site and could be modulated by varying stimulus parameters. Using neurophysiological and neuropharmacological techniques, we demonstrated that these effects were produced by stimulation of preganglionic parasympathetic efferent nerve fibers.


IN PREVIOUS anatomical studies, cardiac nerve fibers and nerve endings have been described in both the heart and the paracardiac region (Coleridge et al., 1961; Cooper et al., 1967; Glomset and Cross, 1952; Mizeres, 1955; Nonidez, 1939; Randall and Armour, 1977). The distribution and function of cardiac nerves have been clarified further by the application of a variety of interventions, including electrical stimulation (Armour et al., 1975; Geis et al., 1973; Kaye et al., 1970; Kralios et al., 1975; Norris and Randall, 1977; Randall and Armour, 1974; Randall et al., 1972; West and Toda, 1967). Since the great vessels of the heart can be entered easily with catheters, many intravascular sites in the paracardiac region are accessible for the introduction of electrical stimuli. However, the effects of catheter electrode stimulation from such sites have not been described previously.

During in vivo studies designed to identify the origin of atrial complexes recorded from an electrode catheter positioned in the canine right pulmonary artery (Cooper et al., 1977), we observed that electrical stimuli introduced through the catheter electrodes produced depression of both sinus rate and atrioventricular (AV) conduction. Therefore, we initiated this study to investigate systematically the effects of electrical stimulation from a multipolar electrode catheter placed in the right pulmonary artery. The present study (1) demonstrates that cardiac nerves that supply the sinus and AV nodes can be stimulated from the right pulmonary artery using an electrode catheter, (2) describes different ways to modulate these neural effects, (3) defines a standardized technique to record a sequence of bipolar electrograms from the catheter electrodes, (4) correlates the sequence of bipolar electrograms recorded from the catheter electrodes with the effects of bipolar stimulation from the catheter electrodes, and (5) characterizes the nerve fibers that mediate the observed effects.
Methods

Twenty-one adult mongrel dogs weighing 17-26 kg were anesthetized with sodium pentobarbital (30 mg/kg iv) and ventilated with a Harvard respirator using room air. After a midline thoracotomy, the pericardium was opened and the heart supported in a pericardial cradle. A Hoffman-type 5-polar electrode plaque (Waldo et al., 1971) was sutured to the epicardium in the region of the sinus node, and two Teflon-coated stainless steel wire electrodes with a 5-mm interelectrode distance were inserted superficially into the portion of Bachmann's bundle immediately beneath the right pulmonary artery. A bipolar Castillo catheter was advanced from the left carotid artery into the noncoronary cusp of the aortic valve to record a His bundle electrogram for the assessment of AV nodal (A-H interval) and His-Purkinje (H-V interval) conduction (Urthaler and James, 1975). A 12-polar electrode catheter with ring electrodes 2 mm wide and with 2-mm interelectrode distances, shown diagrammatically in Figure 1, was introduced into a femoral vein and advanced under fluoroscopic observation through the right side of the heart into the right pulmonary artery. In each experiment, the distal tip of the catheter was positioned at or just beyond the lateral border of the superior vena cava on anteroposterior fluoroscopic projection. The relationship of the right pulmonary artery and, therefore, the electrode catheter to various cardiac and paracardiac structures is depicted in Figure 2. Adjacent electrodes on the catheter were paired, and each of the 11 electrode pairs was assigned a number, beginning with the most distal pair. The most distal pair was labeled right pulmonary artery 1 (RPA 1), the next pair was labeled RPA 2, and so on, moving proximally with the most proximal electrode pair labeled RPA 11. To compare the amplitude and polarity of electrograms recorded to these electrode pairs, the recording sensitivity was calibrated and the distal-proximal recording sequence standardized so that a 1-mV square wave test signal recorded with a bandpass between 0.1 and 500 Hz from each of the catheter electrode pairs had a uniform amplitude and polarity. A sequence of electrograms composed of bipolar recordings from the 11 catheter electrode pairs during sinus rhythm was obtained.

Each of the bipolar electrograms recorded from the catheter electrodes was assigned a polarity based on its dominant deflection, i.e., the deflection with the greatest excursion from baseline. A polarity transition then was defined as occurring between two sites if the atrial complexes recorded from these electrode pairs, the recording sensitivity was calibrated and the distal-proximal recording sequence standardized so that a 1-mV square wave test signal recorded with a bandpass between 0.1 and 500 Hz from each of the catheter electrode pairs had a uniform amplitude and polarity. A sequence of electrograms composed of bipolar recordings from the 11 catheter electrode pairs during sinus rhythm was obtained.

Each of the bipolar electrograms recorded from the catheter electrodes was assigned a polarity based on its dominant deflection, i.e., the deflection with the greatest excursion from baseline. A polarity transition then was defined as occurring between two sites if the atrial complexes recorded from these sites were of opposite polarity. The polarity of an atrial complex composed of deflections of equal excursion above and below baseline was defined as indeterminate. A site of polarity transition was defined as the location where an atrial complex of indeterminate polarity was recorded from an electrode pair positioned between electrode pairs that recorded atrial complexes of opposite polarity or the location between the midpoints of two adjacent electrode pairs that recorded atrial complexes of opposite polarity. The most proximal site of polarity transition was defined as the site of initial polarity transition.

Electrograms and electrocardiograms were monitored on a DR-12 Electronics for Medicine switched-beam oscilloscope and recorded on photographic paper moving at either 50 or 100 mm/sec.
These data also were recorded on magnetic tape using a Honeywell 5600 tape recorded for later playback and analysis. Electrocardiograms were recorded with a bandpass between 0.1 and 500 Hz. Electrograms were recorded with a bandpass between 12 and 500 Hz or 40 and 500 Hz. Electrical stimuli were introduced via the right pulmonary artery catheter electrodes using a Medtronic 1349A programmable pulse generator. Stimulation from the right pulmonary artery catheter electrodes was performed using a constant stimulus duration (2.0 msec) and, with the exception of frequency response testing, using a constant stimulus frequency (20 Hz). Atrial pacing was performed through the plaque electrodes in the sinus node region with stimulus strengths 2 times threshold for atrial capture using a Medtronic 2572 pulse generator.

In single experiments, a change in rate greater than 2 standard deviations from the control rate was considered significant. Statistical analysis of grouped data were performed using either Duncan’s new multiple range test or Student’s paired t-test, and differences were considered significant if P values were <0.05 (Steel and Torrie, 1960). Rates are expressed as mean ± SEM beats/min in the text.

Analysis of Effects of RPA Stimulation on Sinus Rate

Initially, we studied the effects of stimulation on sinus rate. Stimulus-strength response testing was performed from each catheter electrode pair during spontaneous sinus rhythm in 12 dogs. Stimulus strength was increased with 2- to 10-mA increments to a maximum stimulus strength of 50 mA. Stimulation was maintained for 20 seconds at each stimulus strength, and at least 30 seconds elapsed between stimulation periods. The mean sinus rates during each stimulation were used to compare the effects of stimulation from each of the 11 bipolar stimulation sites. The optimal stimulation site for depression of sinus rate was defined as the location of the electrode pair from which stimulation produced significant slowing of the least stimulus strength.

Stimulus-frequency response testing was performed with constant stimulus strength during sinus rhythm from an electrode pair at the optimal stimulation site in five dogs. A stimulus strength was selected that slowed the sinus rate at least 20% below the control rate. Mean sinus rates were determined during the 30 seconds prior to stimulation, during each 30-second interval (0–30 seconds, 30–60 seconds, etc) after stimulation was initiated, and also during the first and second 15-second intervals (300–315 seconds and 315–330 seconds, respectively) after stimulation was discontinued.

Analysis of Effects of RPA Stimulation on AV Conduction

In nine dogs, stimulus-strength response testing was performed from each catheter electrode pair during atrial fibrillation sustained by atrial pacing from the plaque electrodes with 500–800 pulses/min (constant rate within each experiment). Stimulus strength was increased with 2- to 10-mA increments to a maximum stimulus strength of 50 mA. Stimulation was maintained for 30 seconds with each stimulus strength, and at least 30 seconds elapsed between stimulation periods. The mean ventricular rates produced by each stimulus strength were used to compare the effects on AV conduction of stimulation from each of the 11 bipolar catheter electrodes (Carlen and Katz, 1929). The optimal stimulation site for depression of AV conduction was defined as the location of the electrode pair from which stimulation produced significant slowing of the ventricular response rate to atrial fibrillation with the least stimulus strength.

In five dogs, RPA stimulation with constant stimulus strengths was performed for 5 minutes during atrial fibrillation sustained by atrial pacing. Stimulation were introduced through the electrode pair at the optimal stimulation site for depression of AV conduction. A stimuli strength was selected that slowed the ventricular rate at least 20% below the control ventricular rate. Mean ventricular rates were determined during the 30 seconds prior to stimulation, during each 30-second interval after stimulation was initiated, and also during the first and second 15-second intervals after stimulation was discontinued.

Physiological and Pharmacological Interventions

The following interventions were performed in selected dogs: (1) bilateral cervical vagotomy; (2) bilateral stellate ganglion extirpation; (3) intravenous administration of propranolol hydrochloride, 0.5–1.0 mg/kg; (4) intravenous administration of hexamethonium bromide, 1–2 mg/kg; and (5) intravenous administration of atropine sulfate, 0.2–1.0 mg/kg. After propranolol administration, neural blockade was tested by supramaximal right stellate ganglion stimulation, and, after administration of either atropine or hexamethonium, neural blockade was tested by supramaximal right cervical vagal stimulation. Before and after each intervention, electrical stimulation was performed for 30 seconds.
from the electrode pair at the optimal stimulation site for depression of either sinus rate or AV conduction. A stimulus strength was selected that slowed sinus rate or reduced the ventricular response rate during atrial fibrillation at least 20% below the control rate prior to any intervention.

Localization of Catheter Electrode Pairs

During each experiment, the position of the electrode catheter was verified repeatedly using anterior-posterior fluoroscopic observation, such that the distal tip of the catheter was maintained at or just beyond the lateral border of the superior vena cava during collection of data. The electrode pairs at (1) the optimal stimulation site for depression of sinus rate, (2) the optimal stimulation site for depression of AV conduction, and (3) the site of initial polarity transition were identified, and the fluoroscopic locations of these electrode pairs were assessed during each experiment. At the termination of each experiment, the electrode catheter was left in place, and the anatomical locations of the electrode pairs were determined by gross dissection.

Results

Characteristics of Bipolar Electrograms Recorded from the Right Pulmonary Artery

In Figure 3, a sequence of bipolar electrograms recorded from the 11 catheter electrode pairs during sinus rhythm is presented from a representative experiment. Within the electrogram sequence recorded from each experiment, the polarity and amplitude of the atrial complexes varied from site to site in a predictable fashion. Within the electrogram sequence recorded from each experiment, the polarity and amplitude of the atrial complexes varied from site to site in a predictable fashion.

Polarity of the Atrial Complexes

The site of initial polarity transition was recorded from an electrode pair located in the proximal right pulmonary artery in each experiment, and this recording site served as a reliable index of catheter electrode position. Both the polarity and the morphology of atrial complexes recorded proximal to the site of initial polarity transition remained stable during sinus rhythm. However, atrial complexes recorded distal to the site of initial polarity transition often varied in polarity and morphology within a single experiment (e.g., during or transiently following vagal stimulation or following stimulation from the catheter electrodes). During atrial pacing from the sinus node region, the initial polarity transition was recorded from the same electrode pair as during sinus rhythm. In contrast to sinus rhythm, variation in the polarity and morphology of the atrial complexes recorded from electrode pairs distal to the site of initial polarity transition was minimal during atrial pacing, suggesting that the major changes in polarity and morphology observed during sinus rhythm were produced by pacemaker shift (Bouman et al., 1968; Steinbeck and Ludernitz, 1977).

Amplitude

The amplitude of atrial complexes recorded within the right pulmonary artery varied from site to site in a predictable fashion (Fig. 3). Atrial complexes recorded from an electrode pair at or adjacent to the site of initial polarity transition had a relatively low, if not the lowest, amplitude compared to recordings from other sites, whereas atrial complexes with the greatest amplitude always were recorded distal to this site (Fig. 3). In addition, the amplitude of the ventricular complexes varied at different right pulmonary artery sites. Ventricular complexes with greater amplitude than that recorded at the site of initial polarity transition could be recorded both proximally and distally to the site of initial polarity transition. If the catheter were moved proximally (toward the pulmonary valve), the amplitude of ventricular complexes in electrograms recorded from the proximal catheter electrode pairs increased.

Effects of RPA Stimulation during Sinus Rhythm

In Figure 4, the results of stimulus-strength response testing from each of the electrode pairs in a representative experiment are presented. In each
Stimulation at sites proximal to the optimal stimulation site either failed to precipitate atrial fibrillation with a maximum stimulus strength of 50 mA or precipitated atrial fibrillation using stimulus strengths above that required to produce atrial fibrillation at the optimal stimulation site. Stimulation from these proximal sites produced either no sinus slowing or less sinus slowing than that produced when the same stimulus strength was applied at the optimal stimulation site (Fig. 4).

Although Randall and Armour (1974) and Armour et al. (1975) demonstrated that stimulation of thoracic cardiac nerves could precipitate atrial fibrillation, atrial fibrillation precipitated by stimulation from the catheter electrodes in this study was due to direct myocardial rather than neural stimulation. This was demonstrated by two observations. First, stimulus strengths that produced 1:1 atrial capture with a pacing rate just faster than that of the spontaneous sinus rate (e.g., 3 Hz) precipitated atrial fibrillation when applied at high frequency (20 Hz) precipitated atrial fibrillation when applied at high frequency (20 Hz) through the same electrode pair. Second, after neural blockade produced by administration of propranolol and atropine, stimulation with the above stimulus parameters from the same sites continued to produce either 1:1 atrial capture or atrial fibrillation, respectively. Although a difference between the threshold stimulus strength for myocardial excitation and for release of autonomic mediators has been demonstrated under experimental conditions using very brief stimuli (Vincenzi and West, 1963), the stimulus duration (2 msec) was not varied in this study.

In Table 1, the results of stimulus-strength response testing from the optimal stimulation sites in 12 dogs are presented. The sinus rate was slowed significantly from the control rate with stimulus strengths of 5 mA or more. In addition, significant modulation of the negative chronotropic effect on sinus rate was demonstrated by comparing the rates produced by different stimulus strengths. Stimulation with stimulus strengths greater than 20 mA from this site usually produced either asystole, slow sinus rates with premature atrial contractions and high grade AV block, or atrial fibrillation with slow ventricular rates. In the representative experiment presented in Figure 5, stimulation with 5 mA from the optimal stimulation site produced sinus slowing, whereas stimulation from the same site with 10 mA...
produced not only sinus slowing, but also complete AV block and depression of the AV junctional escape rhythm (Urthaler et al., 1973).

In Figure 6, the results of stimulus-frequency response testing in five dogs are presented. During stimulation with constant stimulus strength, the negative chronotropic effect on sinus rate was altered markedly by frequency variation below 20 Hz, but little additional effect was produced by using higher frequencies.

The effects of 5-minute periods of continuous RPA stimulation during spontaneous sinus rhythm are presented in Figure 7. Stimulus strength ranged from 10 to 25 mA [mean (±SE) 16 ± 2 mA] but was held constant within each experiment. The sinus rate slowed significantly below the control rate (P < 0.001) throughout the period of stimulation. Although the rate during the first 30 seconds of stimulation was slower than that during the last 30 seconds (P < 0.05), the sinus rate did not change significantly during the final 4 minutes and 30 seconds of stimulation. During the first 15 seconds after stimulation was discontinued, the sinus rate remained below the control rate (P < 0.001). However, during the next 15 seconds, the rate no longer differed significantly from the control rate (Fig. 7).

Effects of RPA Stimulation on AV Conduction

In Figure 8, the effects of stimulus-strength response testing from each catheter electrode pair on the ventricular response rate during atrial pacing-induced atrial fibrillation are presented from a representative experiment. In each experiment, the electrode pair at the optimal stimulation site for depression of AV conduction was located at the optimal stimulation site for depression of sinus rate and at or just proximal to the recording site of initial polarity transition.

In Table 2, the ventricular response rates to atrial fibrillation produced by RPA stimulation with variable stimulus strengths from the optimal stimula-
Effects on the ventricular rate of stimulation with variable stimulus strengths from each of the 11 catheter electrode pairs during atrial pacing-induced atrial fibrillation in a representative experiment. The sequence of bipolar electrograms and effects of stimulation on sinus rate from this experiment are presented in Figures 2 and 3, respectively. Note that electrode pair RPA 8, which was at the optimal stimulation site for sinus slowing (Fig. 3), was also at the optimal stimulation site (+) for depression of AV conduction since depression of the ventricular rate was produced with less stimulus strength from this electrode pair than from pairs more proximal or distal. In addition, electrode pair RPA 8 was just proximal to the electrode pair (RPA 7) at the recording site of initial polarity transition (*).

Modulation of Ventricular Response to Atrial Fibrillation with Variable Stimulus Strength from Optimal Stimulation Site

<table>
<thead>
<tr>
<th>Stimulus strength (mA)</th>
<th>Ventricular rate* (beats/min)</th>
<th>No. of dogs</th>
<th>( P )†</th>
<th>( P )‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>231 ± 7</td>
<td>9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5</td>
<td>203 ± 11</td>
<td>0</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>10</td>
<td>132 ± 18</td>
<td>9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>20</td>
<td>68 ± 12</td>
<td>9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Overall test of differences in rate between the various stimulus strengths, \( F(3,24) = 79.8, P < 0.0001 \).

† Significance of ventricular rate change when compared with control (0 mA) by Duncan’s multiple range test.

‡ Significance of modulation of ventricular rate, i.e., significance of change in ventricular rate that occurs with each increment in stimulus strength (0-5 mA, 5-10 mA, 10-20 mA) by Duncan’s multiple range test.
Influence of Selected Interventions on the Neural Effects of RPA Stimulation

The data in Table 3 show that, after vagotomy, vagotomy plus stellectomy, or vagotomy plus propranolol administration, sinus rate and AV conduction during atrial fibrillation were significantly depressed by stimulation from the optimal stimulation site. Since the effects of RPA stimulation on sinus rate and AV conduction persisted after bilateral cervical vagotomy alone or with bilateral stellate ganglion extirpation, a central reflex whose afferent or efferent component was mediated via the vagi or stellates was not responsible. RPA stimulation continued to slow sinus rate and depress AV conduction after vagotomy and propranolol indicating the effects were not primarily dependent upon either sympathetic tone or circulating catecholamines.

Atropine was administered in four dogs after vagotomy plus either stellectomy or propranolol administration. Prior to atropine administration, the control sinus rate was slowed significantly (from 126 ± 16 to 83 ± 14 beats/min; \( P < 0.01 \)) by RPA stimulation [mean (±SE) 16 ± 2 mA]. After atropine administration, the control sinus rate was not changed significantly (from 125 ± 14 to 126 ± 13 beats/min) by RPA stimulation using the same electrode pair and stimulus parameters. Since atropine blocked the depressant effects of RPA stimulation that persisted after vagotomy and either stellectomy or propranolol administration, these effects were mediated by parasympathetic efferent nerve fibers.

In another five dogs, hexamethonium was administered. The sinus rate was slowed significantly (from 130 ± 9 to 84 ± 7 beats/min; \( P < 0.005 \)) by RPA stimulation [mean (±SE) 19 ± 2 mA] before hexamethonium administration, but after hexamethonium administration, stimulation using the same electrode pair and stimulus parameters did not slow the sinus rate significantly (from 119 ± 5 to 117 ± 5 beats/min). The depressant effects of stimulation on AV conduction during atrial fibrillation also were diminished or abolished following administration of either atropine or hexamethonium, but control effects during atrial fibrillation were not determined in each of these dogs due to the duration of the protocol. Since both the negative chronotropic and dromotropic effects were abolished by the administration of hexamethionium, the parasympathetic efferent nerve fibers stimulated were determined to be predominantly preganglionic, rather than post-ganglionic (Amory and West, 1962; McEwen, 1956).

Localization of the Optimal Stimulation Site

The effects of stimulation from the catheter electrodes on sinus rate and AV conduction were studied sequentially rather than simultaneously. With the limitations inherent in such a study, the same

<table>
<thead>
<tr>
<th>Experimental condition</th>
<th>Before stimulation</th>
<th>During stimulation</th>
<th>mA*</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>154 ± 9†</td>
<td>92 ± 11†</td>
<td>15 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vagotomy (n = 5)</td>
<td>114 ± 4†</td>
<td>86 ± 5†</td>
<td>16 ± 3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Vagotomy + propranolol (n = 4)</td>
<td>125 ± 7†</td>
<td>93 ± 8†</td>
<td>16 ± 2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>209 ± 4§</td>
<td>56 ± 11§</td>
<td>19 ± 3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Vagotomy (n = 4)</td>
<td>142 ± 3§</td>
<td>67 ± 10§</td>
<td>21 ± 4</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Vagotomy + propranolol (n = 4)</td>
<td>144 ± 3§</td>
<td>82 ± 10§</td>
<td>16 ± 2</td>
<td>&lt;0.025</td>
</tr>
</tbody>
</table>

* Mean (±SE) stimulus strength delivered at 20 Hz.
† \( P \) values for rate before vs. rate during stimulation by Student’s t-test.
‡ Mean (±SE) sinus rate.
§ Mean (±SE) ventricular rate.
electrode pair was identified consistently both as the electrode pair at the optimal stimulation site for depression of sinus rate and the electrode pair at the optimal stimulation site for depression of AV conduction. The location of this catheter electrode pair was determined by three techniques: (1) using anterior-posterior fluoroscopic projection, this electrode pair was medial to the superior vena cava, anterior to the tracheal bifurcation, and distal to the main pulmonary artery; (2) by correlation of the effects of stimulation with the sequence of electrogams, the electrodes at this stimulation site were identified at or immediately proximal to the recording site of initial polarity transition; and (3) on gross anatomical dissection, these electrodes were positioned in the right pulmonary artery just distal to the bifurcation of the main pulmonary artery, above the left atrial portion of the transverse cardiac sinus, and proximal to the point at which the right pulmonary artery crosses Bachmann’s bundle (Fig. 2).

Discussion

This study demonstrates that electrical stimulation from an electrode catheter introduced transvenously into the right pulmonary artery of the anesthetized dog can depress both sinus rate and AV conduction by the excitation of preganglionic parasympathetic efferent nerve fibers. The technique presented in this study provides an easy and reliable method to obtain these effects. The most marked effects on both sinus rate and AV conduction were produced from the same stimulation site which was located in the proximal right pulmonary artery. In this region, Mizeres (1955) described a plexus ventral to the tracheal bifurcation and dorsal to the right pulmonary artery which receives filaments from several nerves, including the craniovalgal and left recurrent laryngeal nerves. He also described the entrance of caudovagal nerve branches into the dorsal right atrial wall. Stimulation of these latter three major vagal branches, inspite of their mixed sympathetic-parasympathetic composition, has been demonstrated to produce strong parasympathetic-efferent effects on the sinus and AV nodes (Geis et al., 1973; Norris and Randall, 1977; Randall et al., 1972), although stimulation of other vagal branches can exert similar inhibitory effects (Armour et al., 1975; Norris and Randall, 1977). Using stimulation and sectioning techniques, the sites of cardiac entry of parasympathetic pathways have been localized to the superior vena cava, the superior left atrium, and the intrapericardial portion of the right pulmonary artery, (Geis et al., 1973; Kaye et al., 1970, 1975). Cardiac parasympathectomy, leaving the major sympathetic pathways intact, has been accomplished by confining surgical techniques to these regions (Kaye et al., 1975).

The pulmonary artery region might be expected to provide one or more sites from which stimulation would accelerate the sinus rate, since sympathetic innervation to the sinus node has been demonstrated in the peripulmonary region and along the superior vena cava (Armour et al., 1975; Geis et al., 1973; Kaye et al., 1975; Mizeres, 1955; Norris and Randall, 1977; Randall et al., 1972). Stimulation with low stimulus strength from catheter electrodes in the distal right pulmonary artery produced atrial fibrillation in this study. If stimulation of sympathetic nerve fibers coursing through this region to the sinus node occurred, the effects on sinus rate were concealed by atrial fibrillation. Sympathetic cardioaccelerator fibers may have been stimulated from other pulmonary artery sites, including the optimal stimulation site, but the effects masked by simultaneous stimulation of parasympathetic fibers (Levy, 1971), a possibility not excluded by this study.

In addition to observed effects on sinus rate and AV conduction, other neural effects of stimulation on the heart or on peripheral autonomic regulation may have occurred since nerves and plexuses in the paracardiac region of the canine are characterized by their mixed compositions, i.e., afferent and efferent, sympathetic and parasympathetic (Armour, 1974; Mizeres, 1955; Randall et al., 1972). Nevertheless, the effects of stimulation from intravascular paracardiac sites, in addition to the site identified in this study, may be relatively predictable, since a high degree of consistency has been demonstrated in the anatomical pathways of cardiac nerves (Geis et al., 1973; Kaye et al., 1970), and since the distribution of small cardiac nerves is highly localized to discrete cardiac regions (Armour et al., 1975; Kaye et al., 1970; Kralios et al., 1975; Randall et al., 1972). Even more selective effects of neural stimulation might be anticipated in man, since, in contrast to the dog, sympathetic and parasympathetic cardiac nerves have relatively few anatomical interconnections (Randall and Armour, 1977).

On the basis of the data summarized above and the data from the present study, we believe electrical stimulation from intravascular paracardiac sites deserves further investigation. Potential applications of such stimulation in man are clear. For example, by increasing parasympathetic tone to the sinus node or AV node, most supraventricular and reciprocating tachycardias should be either interrupted or controlled (Cantwell et al., 1971; Carlen and Katz, 1959; Levine, 1966). The potential for use of this technique clinically is enhanced by the capability, as demonstrated in this study and others (Levy and Zieske, 1976; Schwartz, 1967), to modulate rapidly or sustain certain neural effects produced by electrical stimulation.

It is important to emphasize that neural stimulation can produce effects which may be undesirable, such as tachy- or bradarrhythmias (Corr and Gillis, 1978; Hageman et al., 1973; Hageman et al., 1975), depression of contractility (Daggett et al., 1967; DeGeest et al., 1965), or alteration of periph-
eral circulatory reflexes (Donald and Shepherd, 1978). Also, the effects of electrical stimulation from specific sites within the great vessels of man are unknown and may differ from the effects produced at similar sites in the canine. Therefore, further studies of the efficacy and safety of intravascular neural stimulation techniques are required before application in man can be advocated.

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