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Thomas N. James
Reginald A. Nadeau

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THE EFFECTS OF VAGAL STIMULATION, ESERINE AND ATROPINE ON RETROGRADE PRESSURE IN THE SINUS NODE ARTERY*

THOMAS N. JAMES, M.D., AND REGINALD A. NADEAU, M.D.

Because the sinus node artery passes directly through the sinus node as a disproportionalty large vessel in both man and the dog,1,2 we have conducted a number of studies to examine a possible functional relationship between the caliber of the intranodal artery and pacemaking action of the sinus node. In previous reports it was noted that physical distention of the artery produces sinus bradycardia,3 and that the sinus tachycardia from stellate ganglion stimulation is associated with a concurrent decrease in retrograde pressure in the sinus node artery.4 This paper deals with observations on the effect of cholinergic and anticholinergic stimuli on sinus rhythm and concurrently on retrograde pressure in the sinus node artery.

MATERIAL AND METHOD

All the experimental animals were mongrel dogs prepared for direct perfusion of the sinus node in a standard manner previously described.5 In brief, following intraperitoneal pentobarbital sodium anesthesia (30mg./kg.), the trachea was intubated for mechanical ventilation with room air and the chest was opened with a midsternal incision. The heart was exposed and cradled in the pericardial sac, the right coronary artery dissected free between the atrial appendage and the margo acutus, and a small polyethylene cannula passed through an opening in the ligated right coronary artery up its sinus node branch. Control observations were made on the retrograde pressure in ligated branches of arteries supplying the free wall of the right and left ventricles, and right atrial arteries which supplied the same atrial myocardium as the sinus node artery but not the node. The latter group were dogs with left sinus node arteries (10 per cent of dogs). A transducer was connected to the cannula in the sinus node artery and pressure routinely measured simultaneously with central aortic and right atrial pressures. A tachogram derived with an analog computer from successive R-waves of the electrocardiogram, reflecting instantaneously changes in heart rate, completed the routine measurements made on a master recorder at slow speeds (0.25-1.0 mm./sec.). Through a slave circuit a separate electrocardiogram was recorded on a single-channel electrocardiograph throughout the experiment at 25 mm./sec., and electrocardiographic complexes and intervals were measured on this tracing. During the experiment the ECG was monitored along with the pressure at 50 mm./sec. on a 4-channel oscilloscope.

Both vagus nerves were isolated in the mid-cervical region and either stimulated or cut at that level. For comparative experiments, details of which are reported elsewhere,5 the stellate ganglia were stimulated within the thorax. Stimuli were delivered from an electronic rectangular-wave stimulator in 6-second trains of 1.0 msec. impulses, 30 c.p.s., at supramaximal voltage. For selected experiments, as described later, the duration, voltage and frequency of the stimuli were varied.

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For injection into the sinus node artery the following substances were prepared in Ringer's solution: acetylcholine chloride, 1.0 μg/ml.; atropine sulfate, 1 and 10 μg/ml.; and eserine salicylate 1 and 10 μg/ml. For intravenous administration atropine was used in an amount of 0.2 to 1.0 mg./kg., and isoproterenol hydrochloride in an amount of 0.5 μg/kg. The effect on heart rate of these and other adrenergic and cholinergic substances, studied by direct perfusion of the sinus node, have been reported previously.7-9

Data for this report has been obtained from the following number of dogs: vagal stimulation, 146 dogs; bilateral vagotomy, 15 dogs; intranodal acetylcholine injections, 168 dogs; intranodal atropine, 72 dogs; intravenous atropine, 49 dogs; intranodal eserine, 16 dogs. Over 1000 vagal stimulations have been performed with the routine measurements of pressures and heart rate.

**RESULTS**

Following the asystole from a 6-second supramaximal vagal stimulus, retrograde pressure in the sinus node artery rebounded to a level higher than control and disproportionate to changes in central aortic pressure (Figure 1). Although right atrial

![Figure 1](image1)

**Figure 1**

A brief (six seconds) supramaximal vagal stimulus (RV) produces cardiac asystole with simultaneous decline in central aortic (Ao) and retrograde sinus node artery (SNA) pressures during rising pressure in the right atrium (RA). HR is a tachometric curve indicating instantaneous changes in heart rate. Note the rebound elevation in SNA pressure at a time when central aortic and right atrial pressures have returned to control. Scaled pressures are in mm. Hg, and the heart rate scale is in beats/minute.
VAGAL STIMULATION

pressure rose during the brief asystole, pressure in the sinus node artery at the same
time fell in direct relationship to the fall in central aortic pressure. It had previously
been determined that retrograde pressure in the sinus node artery depended primarily
on central aortic pressure. At the time of the rebound increase in sinus node artery
pressure, the right atrial pressure had already decreased to control level. For com­
parative purposes it is of interest to note that these changes from a 6-second vagal
stimulus are almost directly the opposite of the response to a 6-second stimulation
of the stellate ganglion (Figure 2).

Figure 2
A 6-second supramaximal stimulus of the right stellate ganglion (RS)
produces changes almost directly
the opposite of the vagal stimulus
in Fig. 1. During the stimulus,
pressures in the aorta and ligated
sinus node artery rise while mean
pressure in the atrium decreases
slightly (right atrial pulse ampli­
tude increases). However, at the
end of the stellate stimulus SNA
pressure decreases below control
level while the Ao and RA pres­
sures return to control. Details
of this response to adrenergic
stimulation have been discussed
previously.

A number of factors make it difficult to interpret the significance of the changes
following a supramaximal vagal stimulus, however. These include the influence of
cardiac dilation and distention, the probable adrenal medullary discharge following a
6-second period of asystole, and the unpredictability of the central aortic pressure
response, which sometimes became transiently elevated following the asystole. For this reason experiments were preformed with a submaximal vagal stimulus which was sufficient to slow the heart without stopping it, observing the concurrent response in retrograde pressure in the sinus node artery. Submaximal stimuli were delivered either by lowering the voltage or by reducing the frequency of the stimulus, the required levels determined individually in each animal. Results were most reproducible with a 20 to 30 second stimulus which reduced heart rate approximately 50 per cent. With longer submaximal stimuli vagal escape was an uncontrollable factor.

Submaximal stimuli of 20-30 seconds duration were associated with an initial decrease in both central aortic and retrograde sinus node artery pressures, followed
VAGAL STIMULATION

Figure 4

The effect of a submaximal vagal stimulus on amplitude of the pulse in SNA is illustrated here. Note the SNA pulse amplitude diminishes while RA pulse amplitude does not, although the components of the RA pulse vary relative to each other. The slight delay in onset and disappearance of the changes relative to duration of the stimulus most likely represents the time for local release and destruction of acetylcholine. Although SNA pressure is primarily dependent on Ao pressure, SNA pulse is not dependent on Ao pulse.

by a gradual slight rise in both, even when the suppressed heart rate remained nearly the same. While the central aortic pressure in such experiments only returned to control levels, however, the retrograde pressure in the sinus node artery rose disproportionately, and immediately following cessation of the vagal stimulus it rebounded from 50 to 100 per cent above the control level (Figure 3).

During vagal stimulation there was reduction of the amplitude of the pulses in the sinus node artery, independent of changes in either right atrial or central aortic pulses (Figure 4). These changes could be most clearly demonstrated with brief submaximal vagal stimuli. In a previous study it had been demonstrated that the pulse
in the ligated sinus node artery is due to atrial contraction.\textsuperscript{16} The decreased amplitude of pulse in the ligated sinus node artery following vagal stimulation is just the opposite of the increased amplitude following a stellate stimulus (Figure 5). Prior injection of 10 $\mu$g of atropine into the sinus node artery permitted observation of the effect.

Figure 5

Brief stimulation of the stellate ganglion (RS) produces an opposite effect from vagal stimulation on SNA pulse. Adrenergic stimuli increase the amplitude of all three recorded pulses. Compare to Figure 4 (same dog).
VAGAL STIMULATION

of vagal stimulation which produced ventricular asystole but did not slow the atria; the amplitude of the pulse in these experiments was still reduced by vagal stimulation, though slightly less than in experiments in which the atria were slowed (Figure 6).

Figure 6

Right vagal stimulation (supramaximal) after administration of 10.0 μg of atropine into the sinus node artery produces ventricular asystole due to suppression of A-V conduction, but the sinus node is not suppressed. Atrial contractions continue without slowing, though RA pressure increases because of ventricular arrest. Under these conditions the SNA pulse is still diminished during vagal stimulation, although slightly less than when sinus impulses are conducted through to the ventricles during a submaximal vagal stimulus. Compare to Figure 4.
Despite variation in methods of stimulating the vagus nerves, the local effect on the sinus node and its artery could still have been influenced by a number of extraneous factors, such as catecholamine discharge both locally and systemically. For this reason the effect of local administration of eserine was investigated. During the sinus bradycardia induced by injection of 1.0 \( \mu g \) of eserine into the sinus node artery, the central aortic pressure decreased but the retrograde pressure in the artery increased (Figure 7). The increased retrograde pressure lasted as long as the decreased heart rate, both returning to control levels at approximately the same time.

![Figure 7](Image)

Following injection of 1.0 \( \mu g \) of eserine into the sinus node artery, there is gradual decrease in heart rate and a concurrent diminution in Ao pressure, both of which return to control in about 30 minutes. SNA pressure initially decreases also, but then rises to almost twice control level, a change which is independent of the other pressures. Changes in SNA pressure and heart rate are inversely related and are identical in duration. All these pressures are average (non-pulsatile).
Since administration of atropine produces sinus tachycardia, this afforded another means of determining the local effect of acetylcholine on retrograde pressure in the sinus node artery, by using an anticholinergic substance. Although atropine administered intravenously sometimes produced widening of the central aortic pulse and a small decrease in mean aortic pressure, there was a disproportionate decrease in retrograde pressure in the sinus node artery, concurrent with the increase in heart rate (Figure 8). Furthermore, this same decrease in sinus node artery pressure was

Figure 8

After intravenous administration of atropine the effect on HR and SNA pressure are also inversely related, but opposite to the effect of eserine (Figure 7). Note HR increases while SNA pressure concurrently decreases.
observed during sinus tachycardia from the intranodal administration of 10 µg atropine, though the duration was less prolonged. A similar example of opposite effects on central aortic and retrograde sinus node artery pressures occurs during the sinus tachycardia following intravenous administration of isoproterenol (Figure 9).

Figure 9

The effect of intravenous administration of isoproterenol on HR and SNA pressure is almost the same as that of atropine, although Ao and RA pulses are increased more with the catecholamine. Compare to Figure 8.
VAGAL STIMULATION

Since there were opposite effects by eserine and atropine on both heart rate and retrograde pressure in the sinus node artery, their effects in sequence were observed in six experiments in three dogs. During the sinus bradycardia and associated increase in retrograde pressure in the sinus node artery induced by eserine, atropine was injected into the sinus node artery and immediately reversed both these changes (Figure 10).

![Figure 10](image)

Here the opposing actions of eserine and atropine are demonstrated sequentially. During the sinus bradycardia and increased SNA pressure from administration of eserine into the SNA, similar administration of atropine reverses the effect both on heart rate and retrograde SNA pressure. All these pressures are average.
The effect of supramaximal vagal stimulation on retrograde pressure in a ligated left ventricular artery (LVA) is different from the effect on SNA pressure in that there is no post-stimulus rebound. Antegrade pressure (LCA) in the same artery (the left anterior descending ramus) is measured with a second catheter directed centrally from the point ligation, and as expected behaves in a manner almost identical to Ao pressure. All pressures are average.

Injections of acetylcholine into the sinus node artery regularly produce sinus arrest, but the effect is sustained only during the injection and immediately dissipates afterwards, due to the rapid local action of cholinesterase. Since it was necessary to turn off the stopcock attached to the cannula in the sinus node artery during intraarterial injections, pressures could only be recorded immediately after completion of the injection. It was not possible, therefore, to assess the exact effect of locally injected acetylcholine on the retrograde pressure because of its transient action. Usually after injection there was an increase in amplitude of pulses in the ligated sinus node artery to twice or more control amplitude, but this was sustained for only a few seconds.
Vagal stimulation for the standard 6-second interval produced no rebound in retrograde pressure in ligated ventricular arteries, of either right or left ventricle, in 50 such experiments (Figure 11). There was a rebound increase in retrograde pressure in right atrial arteries not supplying the sinus node, however, of a degree and duration quite similar to that observed in the ligated sinus node arteries. This may have represented increased flow into them from anastomoses with the sinus node artery. Bilateral vagotomy produced variable results because central aortic pressure commonly decreased following the procedure, making interpretation of changes in retrograde sinus node artery pressure unreliable.

DISCUSSION

An inverse relationship has been demonstrated to exist between heart rate and retrograde pressure in the sinus node artery following both cholinergic and anticholinergic stimuli. As examples, eserine produced slowing of the sinus node and increase of the retrograde pressure, while atropine accelerated the sinus node but decreased the retrograde pressure. This inverse relationship is analogous to that observed following stellate stimulation, following administration of adrenergic and antiadrenergic substances, and following physical distention of the sinus node artery by injection of fresh autogenous arterial blood under pressure. The common feature in the responses to this wide variety of stimuli is inverse relationship of heart rate and retrograde pressure in the sinus node artery.

As noted previously, the anatomy of the human and canine sinus nodes suggests a possible functional relationship (other than merely nutrient) between the caliber of the sinus node artery and the rate of pacemaking discharge of the node. The dense collagen framework of the normal sinus node attaches both to the disproportionately large artery which courses directly through the center of the node and to the fibers of the node itself. It was therefore considered that the sinus bradycardia occurring during physical distention of the intranodal artery may be due to relaxation of normal tension present on the sinus node fibers, and that during sinus tachycardia from stellate stimulation the caliber of the intranodal artery decreased and thereby increased the tension on the sinus node fibers. Since the abundant normal anastomoses of the sinus node artery normally enter it after the artery passes through the node, changes in caliber of the intranodal portion of the artery would necessarily be reflected in retrograde pressure as we have measured it.

It is of some interest that the decreased retrograde pressure in the sinus node artery during sinus tachycardia from atropine is similar to results from isoproterenol (Figures 8, 9). However, for eserine and vagal stimulation to increase the retrograde pressure during their slowing effect on the sinus node, one has to assume that there is normally some constriction of the intranodal portion of the artery. Our cannula tip in the ligated artery is downstream (in these experiments, but upstream if the artery were not ligated) from the sinus node, which surrounds the artery at a point between the cannula tip and the area where most of the anastomoses enter the artery. Since a certain amount of tone is normally present in arteries, it is reasonable to believe the sinus node artery is no exception.
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Whether the decreased pulse in the ligated sinus node artery during vagal stimulation is a negative inotropic effect on atrial myocardium is undetermined. Two observations suggest this may be so: 1. This pulse is due to atrial contraction. 2. An opposite effect is produced during adrenergic stimulation. Further studies of a possible negative inotropic effect on atrial myocardium by the vagus are indicated.

Interpretation of the cardiac slowing effect of parasympathomimetic substances as due in part to dilation of the intranodal artery, and the consequent relaxation of tension on the sinus node fibers, is applicable only to the intact sinus node in vivo, since these substances also exert a slowing effect on isolated tissue preparations. But in considering function of the normal sinus node during life it is difficult to ignore the presence of its relatively enormous central artery. The "mechanical" aspects of relating the caliber of the intranodal artery to pacemaking rate of the node do not in any way diminish the importance of current concepts concerning the local synthesis of norepinephrine or acetylcholine. Indeed, it is pertinent to note that the effects on retrograde pressure of the sinus node artery are produced in our experiments by either the induced release or the direct administration of the naturally occurring neurohormones.

SUMMARY

During sinus bradycardia following either vagal stimulation or intranodal administration of eserine, retrograde pressure in the sinus node artery increases. During sinus tachycardia following atropine administered either intranodally or intravenously, retrograde pressure in the sinus node artery decreases. The pressure change is concurrent in both cases with the duration of change in heart rate. Some of the implications of an inverse relationship between retrograde pressure in the sinus node artery and the rate of pacemaking discharge by the node are discussed.

REFERENCES