Effect of Efferent Vagal Stimulation on Coronary Sinus Outflow and Cardiac Work in the Anesthetized Dog

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Efferent vagal stimulation in the anesthetized dog with constant ventricular rate caused either no change in coronary sinus outflow and cardiac work, or a decrease in coronary sinus outflow associated with a greater decrease in cardiac work. When the decreases were observed, they could best be explained by a negative inotropic effect of vagal stimulation on ventricular muscle, rather than by a direct vasomotor effect of vagal stimulation on the coronary bed. Critical review of apparent divergent results previously reported regarding the effect of vagal stimulation on coronary flow reveals that they are not inconsistent with the above hypothesis.

The effect of efferent vagal stimulation on coronary blood flow has been the subject of intensive investigation and dispute since both constrictor and dilator responses of the superficial coronary arteries were reported from visual observations. Despite 100 years of continuous investigation with progressively improved instruments and refined experimental approaches, there is still no agreement as to the role of the vagus nerve in coronary vasomotor control. In the past, many investigations were carried out in which the heart rate was not kept constant. Furthermore, although arterial blood pressure was recorded, cardiac output and hence cardiac work were not measured. Since change in coronary blood flow is affected by change in heart rate or cardiac output, it seemed worthwhile to reinvestigate this subject and relate coronary blood flow to cardiac work before and during vagal stimulation. It was felt that such an approach would produce data that might serve to reconcile some of the diametrically opposed conclusions drawn from other experimental designs.

From analysis of pulse pressure tracings in man, decrease in myocardial contractility associated with vagal slowing of the heart has been described. Until recently, this postulated vagal effect has received little experimental attention, except for observations in the innervated heart-lung preparations uncontrolled as to heart rate, and except for myocardial observations uncontrolled as to cardiac work. The present experiment was designed to study the effect of efferent vagal stimulation on myocardial contractility as reflected by cardiac work when the ventricular rate is kept constant.

Methods

Fifteen dogs weighing between 15 and 29 Kg. were premedicated with morphine sulfate, 2 mg./Kg. intramuscularly, and were anesthetized 30 min. later with chloralose 50 to 100 mg./Kg. intravenously. Through a cervical incision, the common parotid arteries, external jugular veins, and pons nerves on both sides were identified and exposed. A Y-shaped cannula was inserted in the trachea. Both femoral arteries and one femoral vein were exposed, and a slow infusion of physiological saline solution was started through the latter. The left side of the chest was opened and artificial respiration was given with a Palmer Ideal Pump. Room air was supplemented with a steady flow of pure oxygen at the air inlet to insure a greater than 20 per cent oxygen content in the inspired air. The brachiocephalic and the left subclavian arteries, the descending thoracic aorta, and the cardiac branch of the left vagus nerve were dissected. Nerve supplies to the heart were carefully pre-
served. The pericardium was incised and the heart was suspended in a pericardial cradle. After thorough hemostasis, anticoagulation was effected with heparin, 10 mg./Kg. and was maintained for the duration of the experiment with supplementary injections, 5 mg./Kg. every hour.

The left ventricular output, which will subsequently be referred to as cardiac output, was measured by an electromagnetic rotameter\textsuperscript{15} according to the method reported and modified by Wegria, et al.\textsuperscript{16, 17} The blood ejected by the left ventricle was directed through the brachiocephalic and left subclavian arteries into the rotameter. The arterial blood was then returned to the head circulation via both femoral arteries cannulated proximally and distally. The descending thoracic aorta was directed through the brachiocephalic and left subclavian arteries into the rotameter.

In order to preserve the nerve supply to the coronary bed, the coronary sinus outflow was used as an index of left coronary artery flow, thus eliminating the need for dissection around the coronary arteries. This method is justified by the observation that the coronary sinus drains blood only from the left coronary artery,\textsuperscript{18, 19} and in a given dog the coronary sinus outflow represents a constant portion of the left coronary artery flow.\textsuperscript{18} The curved end of a metal cannula was introduced through the left external jugular vein into the coronary sinus, and was held in place by a ligature around the coronary sinus near its entrance into the right atrium. The coronary sinus outflow was directed into a second electromagnetic rotameter and returned to the right atrium through a polyethylene tube inserted via the right external jugular vein.

The mean arterial blood pressure was recorded by a Sanborn pressure transducer connected to the inflow tubing of the left ventricular output rotameter. The mean arterial blood pressure, the cardiac output, and the coronary sinus outflow were recorded continuously and simultaneously on a Sanborn multichannel recorder, Model 150. Heart rate was monitored electrocardiographically at frequent intervals.

The right and left vagus nerves were cut high in the neck. The peripheral end of the right or left vagus nerve, or the cardiac branch of the left vagus nerve was stimulated with repetitive rectangular wave shocks derived from a Grass stimulator. The stimulus applied ranged from 3 to 10 volts, with a frequency of 50/sec. and duration of 1 to 2 msec. The stimulus was classified as "weak" if the ventricular rate was reduced to approximately one-half of its spontaneous rate, and as "strong" if ventricular stand-still was induced with subsequent vagal escape. In order to maintain a constant ventricular rate, the ventricular pacemaker was started at arrow 1 and maintained for these 3 parameters to stabilize at new levels. At this time the vagus nerve was stimulated for 60 to 90 sec. After completion of vagal stimulation, another 60 to 90 sec. were allowed before the ventricular pacemaker was discontinued. A second test of the vagal stimulus followed each run.

Cardiac work was calculated using an arbitrary unit obtained by multiplying the cardiac output\textsuperscript{2} in ml./min. by the mean arterial blood pressure in mm. Hg. Only changes in cardiac work of 10 per cent or more were regarded as significant. When the mean arterial blood pressure was below 70 mm. Hg before the start of the ventricular pacemaker, the run was disregarded.

Results

Eighty-two runs of vagal stimulation were produced in 15 dogs. Similar results were obtained whether the stimulus was applied to the peripheral end of the right or left vagus nerve or to the cardiac branch of the left vagus nerve. Observations on coronary sinus outflow, cardiac output and mean arterial blood pressure in the majority of the runs fell into one of the two following patterns:

First Pattern

No change in coronary sinus outflow, cardiac output and mean arterial blood pressure. This pattern occurred when a weak stimulus was applied to the vagus in 23 runs on 9 animals. A representative recording of one such run is illustrated in figure 1. In this run the ventricular pacemaker was started at arrow 1. It can readily be seen that new levels of coronary sinus outflow, cardiac output and arterial blood pressure are established in agree-

\textsuperscript{2}The cardiac output used in the computation of cardiac work was the left ventricular output plus the coronary sinus outflow; the latter representing 0.4-83 per cent of the left coronary artery flow.
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Figure 1

Simultaneous recordings of coronary sinus outflow (S.F.), cardiac output (C.O.) and arterial blood pressure (B.P.) before, during and after a run of vagal stimulation. Spontaneous heart rate 188/min. Between arrows 1 and 4 heart was driven with ventricular pacemaker at the rate of 225/min. Between arrows 2 and 3 a "weak" stimulus was applied to the peripheral end of the right vagus nerve. Note changes in blood flow and pressure recording patterns as a result of atrial slowing due to vagal stimulation although mean values of all 3 parameters remain unchanged.

Figure 2

Records as in figure 1. Spontaneous heart rate 185/min. Ventricular rate 198/min. between arrows 1 and 4. Strong stimulus to the cardiac branch of the left vagus nerve between arrows 2 and 3. Note the simultaneous fall of coronary sinus outflow, cardiac output and arterial blood pressure during vagal stimulation.

the swings of larger amplitude seen between arrows 1 and 2 reflects an atrial beat occurring fortuitously in proper time sequence with a ventricular beat to result in an increase in ventricular filling. This phenomenon was substantially reduced with atrial slowing during vagal stimulation between arrows 2 and 3, and not observed at all when atrial fibrillation was present (cf. fig. 4).

Second Pattern

Decrease in coronary sinus outflow, cardiac output and mean arterial blood pressure. This pattern was observed in 52 runs, and occurred in all 15 animals studied. In 6 animals this pattern was induced by either "weak" or "strong" vagal stimuli, and in the 9 animals described above in which the first pattern was brought about by a "weak" stimulus, this second pattern was subsequently induced by a "strong" stimulus. The decrease of these 3 parameters was noted to occur simultaneously and immediately as vagal stimulation was applied. The fall in coronary sinus outflow was never observed to precede the fall in cardiac output or arterial blood pressure. A representative run is reproduced in figure 2. In these 52 runs the decrease in coronary sinus outflow during vagal stimulation ranged from 5 to 45 and the corresponding decrease in cardiac output and cardiac output ranged from 5 to 45...
work ranged from 10 to 74 per cent. Figure 3 graphically represents the proportional change in cardiac work (ordinate) and coronary sinus outflow (abscissa). All except 3 points fall to the left of the angle bisector, indicating a proportionally greater decrease in cardiac work than in coronary sinus outflow.

The ventricular rate was not altered by vagal stimulation during the period of ventricular pacemaker. However, the atrial rate was markedly slowed and in some runs atrial fibrillation occurred. Changes in coronary sinus outflow, cardiac output, and arterial blood pressure were independent of the changes in atrial rate or contraction. In one animal in which atrial fibrillation was present throughout the entire experiment, 10 runs of vagal stimulation were carried out, all of them falling into the second pattern. One of these runs is shown in figure 4.

It should be mentioned that in 7 experiments on 2 dogs a small increase in cardiac work with or without change in coronary sinus outflow was observed with vagal stimulation. No explanation is offered for these aberrant runs. In further runs on these 2 animals, one or both of the 2 patterns described above was obtained.

The effect of efferent vagal stimulation on coronary sinus outflow, cardiac output, and arterial blood pressure, as well as the vagal effect on heart rate, was totally abolished by intravenous injection of atropine sulfate in a dose of 0.1 mg./Kg.

Discussion

The coronary sinus outflow was not changed with vagal stimulation in approximately one fourth of the runs. This is in agreement with the findings of Bekenhoff et al. and Gregg. In the current study when coronary sinus outflow was unchanged with vagal stimulation, cardiac output and arterial blood pressure were also unchanged. Similar observations were reported by Schreiner et al. using an atrial pacemaker.

In approximately two thirds of the runs, the coronary sinus outflow fell with vagal stimulation. The reduction in coronary sinus outflow was never observed without a simul-
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The decrease in cardiac work observed in the majority of the experiments can best be explained by a negative inotropic effect of vagal stimulation on the ventricular muscle. First, this effect is vagal in origin since it occurred on stimulation of the vagus nerve high in the neck, above the level reached by the majority of sympathetic cardiac fibers that join the vagus, and furthermore, the effect is entirely abolished by atropine. Second, it is cardiac in origin and not a result of peripheral reflex action since it occurred on stimulation of the cardiac branch of the vagus nerve. Third, it is ventricular in origin because it occurred regardless of the uncoordinated atrial contractions, and indeed, even in the presence of atrial fibrillation. Last, it is not an artifact due to the possible occurrence of functional mitral insufficiency in the presence of a ventricular pacemaker, since this possible occurrence is also inherent in the "control values," and a similar fall in cardiac output and arterial blood pressure has been reported following vagal stimulation when an atrial pacemaker was used.

The negative inotropic effect of vagal stimulation on the ventricular muscle was not always observed when a "weak" vagal stimulus was used. It is interesting to note that using an atrial pacemaker Schreiner et al. and Denison and Green also did not demonstrate this effect. It was noted in the latter investigation and also from the early exploratory experiments in this study that, owing to the vagal effect on the AV node, in the presence of an auricular pacemaker it is difficult to administer a strong vagal stimulus without slowing the ventricular rate.

The primary objection to the hypothesis of a negative inotropic effect of the vagus nerve on the ventricular muscle lies in the oft-cited lack of innervation of the ventricles by this nerve. Support for this statement is based upon heart rate studies showing the absence of vagal effect on ventricular rate after section of the A-V bundle. A thorough review of available anatomical studies revealed that the striking finding was the abundance...
of efferent vagal fibers in the atria. This is in agreement with physiological observations that vagal influence on the atria is easily demonstrated. However, in regard to efferent vagal innervation of the ventricular muscle there is no agreement: one investigator noted a small number of efferent vagal fibers by staining technic;\textsuperscript{27} another investigator concluded that the "main" innervation of the ventricular muscle is by way of the sympathetic but stated also that it is impossible to distinguish parasympathetic from sympathetic fibers in the perimyscular plexus;\textsuperscript{28} the third investigator using degeneration technics could not determine whether vagal fibers to the epicardial ganglia were motor or sensory.\textsuperscript{29} Consequently, the conclusion that there are no motor vagal fibers to the ventricular muscle is not entirely justified. It is hoped that future anatomical studies will clarify the situation and provide a basis for the physiological observations reported herein.

**Summary**

The effect of efferent vagal stimulation on the coronary sinus outflow, cardiac output and arterial blood pressure was studied on 82 runs in 15 anesthetized dogs. Heart rate was kept constant with a ventricular pacemaker before and during vagal stimulation. In one fourth of the runs coronary sinus outflow, cardiac output, and arterial blood pressure remained unchanged with vagal stimulation; in the majority of the runs all 3 parameters was observed. Decrease in cardiac output and arterial blood pressure, and consequently in cardiac work, is attributed to a negative inotropic effect of the vagus nerve on the ventricular muscle. The concomitant decrease in coronary blood flow can be adequately explained without invoking active vasmotor control by the vagus nerve on the coronary blood vessels.

**Summario in Interlingua**

Le effetto de stimulation de nervo vago efferente super le effluss de sino coronari, le rendimento cardiace, e le tension de sanguine arterial esseva studiate in 82 experimentos con 15 anesthesize canes. Le frequentia cardiace esseva mantene constanta con un pacemaker ventricular ante e durante le stimulation vagal. In un quart de experimentos, le effluxo de sino coronari, le rendimiento cardiace, e le tension de sanguine arterial remaneva sin alteration sub le effetto del stimulation vagal. In le majoritate del experimentos, un reduction de omne le 3 magnitudes esseva observate. Le reduction del rendimento cardiace e ergo del tension de sanguine arterial esseva attribuite a un negative effetto inotrpiche che le nervo vago eserce super le musculo ventriculare. Le concomitante reduction del fluxo de sanguine coronari pote esser explicate adeguatemente sin le necessitate de parlar de un active regulation vasmotori exercite per le nervo vago super le vasi de sanguine coronari.

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