Effects of Vagus Stimulation and of Acetylcholine on Myocardial Contractility, O₂ Consumption and Coronary Flow in Dogs

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During vagus nerve stimulation the heart rate was maintained at a constant level by an electric pacemaker. Under these conditions no changes were found in ventricular function curves, myocardial oxygen consumption and coronary blood flow. Acetylcholine infusion, with heart rate maintained constant, caused decreased myocardial contractility and coronary and peripheral vasodilation.

STUDIES on myocardial contractility and coronary flow during vagal stimulation have yielded inconsistent results. This may be due to the fact that in most studies heart rate was not maintained constant and both ventricular function and coronary blood flow are influenced by changes in heart rate. When heart rate was maintained constant, no change in myocardial contractility was found. In the present study ventricular function and coronary blood flow were measured during vagal stimulation with the heart rate maintained at a constant level.

Although acetylcholine is liberated during vagus nerve stimulation, its effects differ from the vagal effect in several respects. A marked decrease of contractility has been found in heart-lung preparations. Coronary vasodilation has been reported in fibrillating cross-perfused hearts and in the living animal. In the present study the effects of acetylcholine on the myocardium and on coronary and peripheral circulation have been examined in the living animal.

METHOD

Twenty-eight mongrel dogs weighing from 12 to 29.5 Kg. were premedicated with morphine (1.2 to 2.5 mg./Kg. body weight) and anesthetized with chloralose (22 to 89 mg./Kg. body weight) and urethane (220 to 910 mg./Kg. body weight). The chest was opened. Systemic blood flow (cardiac output minus coronary blood flow) was measured with a Potter electroturbineometer connected to the aorta. In 12 dogs the left main coronary artery was cannulated with a Gregg cannula, and the flow through it was measured with a Skipley-Wilson rotameter. In 2 experiments coronary sinus outflow was collected through a modified Morawitz cannula and measured with a rotameter, thus avoiding dissection of the tissue around the left coronary artery. Right and left atrial, pulmonary arterial, and aortic pressures were measured with electromanometers and/or strain gauges. All these values were recorded continuously on a Sanborn four-channel polyviso.

Blood was sampled from a catheter placed far into the coronary sinus via the right jugular vein. Blood-gas analyses were performed according to Van Slyke and Neill. In one experiment coronary sinus oxygen saturation was measured continuously by means of a Colson cuvette densitometer.

A reservoir which contained dextran and blood from a donor dog was connected with the femoral artery and vein in such a way that the circulating blood volume could be varied at will. Data for ventricular function curves were obtained by step-wise infusions of 75-200 ml. blood at 1 min. intervals. The hematocrit readings ranged from 30 to 71 per cent in the different animals.

Ventricular stroke work and function curves were plotted in the conventional manner. Since ventricular function curves vary with aortic pressure and with heart rate, the present curves were obtained at similar pressure levels and at a constant heart rate.

A constant ventricular rate was maintained in several ways: 1. The right atrium (9 dogs) or ventricle (7 dogs) was stimulated at rates somewhat in excess of the natural rate. 2. After producing complete heart block by tying the A-V bundle of His, the right ventricle was electrically stimulated at desired rates.

The vagus nerves were excited both in the neck.
and in the chest. Effective vagal stimulation was ascertained before and after each run. With the pacemaker turned off, a decrease in rate of at least 50 per cent of the control value was required. In hearts with surgical A-V block, depression of the atrial contractility was the criterion for effective vagal stimulation.

Acetylcholine chloride (Merck) (2.3 to 2200 \( \gamma/\text{Kg. body weight/minute} \)) or acetyl-\( \beta \)-methylcholine iodide (Betacholyl Vitrum)* (0.03-7 \( \gamma/\text{Kg. body weight/min.} \)) were infused by means of a Braun syringe pump into the inferior vena cava or into the left coronary artery tubing. The acetyl-\( \beta \)-methylcholine has a slower breakdown and a minimal ganglionic stimulating effect.

RESULTS

Effects of Vagal Stimulation

Vagus nerve stimulation with the heart rate maintained constant evoked no significant changes in aortic or left atrial pressures, cardiac output, and left coronary flow; when the artificial pacemaker was turned off the heart rate fell immediately, aortic pressure stayed the same, while left atrial pressure decreased slightly. The left coronary flow showed a brief increase and thereafter decreased markedly.

Ventricular Function Curves. Ventricular function curves were obtained over a wide range of filling pressures and work, before, during and after vagal stimulation while the heart rate was maintained constant at rates between 60 and 200/min. Figure 1 shows the effect of vagal stimulation on ventricular function curves in a dog with A-V block. There was no change in the relation between ventricular stroke work and atrial pressure although atrial contractility was markedly reduced.

Coronary Blood Flow. During the ventricular function runs with constant heart rate, the relation between coronary flow and effective aortic pressure did not change in 3 dogs (fig. 2). Thus no evidence was obtained that the

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* Generously supplied by Vitrum and Dr. Bo Holmstedt, Stockholm, Sweden.
vagus influenced coronary vascular tone. Also, there were no significant changes in coronary sinus oxygen saturations in the 2 dogs where this was measured together with coronary flow. To ascertain whether the lack of vagal effect on coronary blood flow was caused by vagus nerve damage due to the dissection of the coronary artery, the coronary sinus outflow was measured in 2 dogs. The results were the same as in the dogs in which the coronary artery had been dissected. Oxygen saturations of the coronary sinus blood showed no significant change for a given perfusion pressure.

Acetylcholine

Acetylcholine infusion into the femoral vein decreased aortic pressure and left coronary flow pari passu. Varying degrees of A-V block with irregularities occurred. Therefore, conclusions about changes in coronary vascular tone could not be drawn. Such changes in heart rate were prevented by means of surgical A-V block and subsequent stimulation of the ventricles.

Fig. 2. Left coronary blood flows and coronary sinus oxygen saturations (ordinates), net perfusion pressures, cm. H$_2$O (abscissa) before ($\bullet$), during (left X, right +) and after ($\Delta$, $O$) vagus nerve stimulation. Same experiment as in figure 1.

Fig. 3. Ventricular function curves before ($\bullet$), during ($\Delta$) and after ($O$) infusion of acetyl-β-methylcholine into the left coronary artery in a dose of 0.18-0.45 γ/Kg. body weight/min. Heart rate maintained at 184 to 219 by electric stimulation of the left ventricle without previous A-V block. Systemic resistance maintained equal by constriction of aortic tubing. Drug infusion was increased at the higher blood flow levels to prevent increased dilution.
In one dog the ventricular rate was maintained constant by electric stimulation without previous A-V block. The data reported below were all obtained at a constant heart rate.

**Ventricular Function Curves.** Ventricular function curves showed marked depression of both ventricles in 3 dogs when acetylcholine was infused intravenously; the peripheral resistance was maintained constant by aortic constriction.

In 7 dogs the acetylcholine was infused into the left coronary artery thus avoiding the peripheral vasodilation. There was a marked lowering of the left ventricular function curve while the right showed little change (fig. 3).

When the drug was infused at a low, constant rate, the control and the drug curves of ventricular function and coronary flow approached each other at high work levels of the heart. This may be due to increased dilution of the drug accompanying the increased blood flow. This dilution effect was eliminated in the experiment shown in figures 3 and 4 by increasing the drug infusion rate at the higher steps of the ventricular function curve.

The relation between myocardial oxygen consumption and left ventricular work was not changed. Thus, the induced depression of myocardial contractility (work per filling pressure) is not accompanied by any change in myocardial efficiency (work per oxygen consumption).

**Coronary Blood Flow.** When left coronary flow was plotted against coronary perfusion pressure, it was found that infusion of acetylcholine was accompanied by coronary vasodilation (fig. 4). At any level of coronary perfusion pressure the coronary flow was higher with acetylcholine than without (demonstrated in 4 dogs). Furthermore, the oxygen saturation of the coronary sinus blood was significantly higher during the drug infusion.

**DISCUSSION**

**Vagal Stimulation**

The hemodynamic effects of vagal stimulation occurred equally with left or right nerve stimulation. In the present study vagus nerve stimulation did not affect the contractility of the ventricles when their rate was maintained at a constant level. Several other authors have claimed a negative inotropic effect. However, Peterson's data were limited to stroke volume calculations from aortic pressure tracings in man. The changes were observed after carotid sinus stimulation and may have been caused by mechanisms other than direct vagal effects on the heart. Other authors, who maintained ventricular rate constant, found no change in contractility. This is in line with the findings of Cullis and Tribe, indicating that vagus fibers do not reach the ventricles.

There was likewise no change in coronary flow during vagal stimulation when studied at comparable levels of heart rate and aortic pressure. This confirms similar results recently obtained by Denison et al. This is contrary to other reports, indicating either coronary vasodilation or vasoconstriction. It is hard to conceive that the vagus would act as a coronary vasoconstrictor since its chemical transmitter is a coronary vasodilator.
Lochner and associates\textsuperscript{17} found that during vagus nerve stimulation for $\frac{1}{2}$ min. there was a marked increase in coronary sinus oxygen saturation together with the fall in heart rate. A similar initial rise in coronary sinus oxygen saturation occurred in one of our experiments but this was followed by a return to control level after $\frac{1}{2}$ min. This probably represents the adjustment period of the coronary vessels following the decreased myocardial oxygen consumption rather than a direct vagal effect on the coronary vessels.

Effects of Acetylcholine

Acetylcholine does not change the length-tension relation of isolated papillary muscles.\textsuperscript{18} The observed lowering of the ventricular function curves by acetylcholine probably represents a true change in contractility rather than a change in heart muscle tone. Since mechanical factors which could influence coronary flow were excluded, the increase in coronary flow represents a true coronary dilation.

While the effects of acetylcholine occurred consistently in all of our dogs, the order of these events varied. When acetylcholine was given intravenously, peripheral vasodilation was the first effect to occur; during intracoronary infusion, atrioventricular block and/or the negative inotropic effect appeared first. The thresholds for the different events lay so close together that for therapeutic application of acetylcholine one must consider its effects as complex.

The cardiac oxygen consumption was not changed for a given work by drug infusion, the relation between "pressure work" and "volume work" being about the same. This demonstrates that inotropic and efficiency effects of drugs are not necessarily associated. Experiments on isolated atria have demonstrated that acetylcholine depresses the oxygen consumption in the beating but not in the quiescent atrium,\textsuperscript{18} indicating that the decrease in oxygen consumption is due to the decreased work rather than "cellular poisoning."

Summary

The influence of vagal stimulation and acetylcholine infusion on the circulation and heart were studied in dogs. Mechanical factors such as heart rate and peripheral resistance were maintained.

Vagal stimulation with heart rate maintained constant did not change the contractility of the ventricles, myocardial oxygen consumption, or coronary blood flow.

Acetylcholine infusion caused atrioventricular block, decreased contractility of the heart muscle, and peripheral and coronary vasodilation. The oxygen consumption of the heart muscle for a given amount of cardiac work was not changed by the drug. When acetylcholine was infused intravenously, the first event to occur was peripheral vasodilation. If the drug was infused into a coronary artery, atrioventricular block and/or the negative inotropic effect occurred first. The thresholds for the various drug effects lie very close together.

Summario in Interlingua

Le influentia de stimulation vagal e del infusion de acetylcholina super le circulation e le corde esseva studiate in canes. Factores mechanic, i.e. frequentia cardiac, resistentia peripheric, etc., esseva tenite constante.

Stimulation vagal, sub iste conditiones, non alterava le contractilitate del ventriculos, le consumption myocardial de oxygeno, o le fluxo coronari de sanguine.

Le infusion de acetylcholina causava bloco atrio-ventricular, un reduceite contractilitate del musculo cardiac, e vasodilatation peripheric e coronari. Le consumption de oxygeno per le musculo cardiac correspondente a un date quantitate de labor cardiac non esseva alterate per le droga. Quando acetylcholina esseva infundite per via intravenose, le prime effecto manifeste esseva vasodilatation peripheric. Quando le droga esseva infundite in un arteria coronari, le prime occurrentias consequente esseva bloco atrio-ventricular e/o le negative effecto inotropic. Le limines pro le varie effectos del droga es proximissime le unes al alteres.

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