THE EFFECTS OF HALOTHANE ON THE INTERACTIONS BETWEEN
MYOCARDIAL CONTRACTILITY, AORTIC IMPEDANCE,
AND LEFT VENTRICULAR PERFORMANCE

IV: HAEMODYNAMIC RESPONSES TO VAGUS NERVE STIMULATION

B. J. GERSH AND C. PRYS-ROBERTS

SUMMARY

The effects of electrical stimulation of the vagus nerves have been studied in anaesthetized dogs, before and after bilateral interruption of the cardiac sympathetic nerves. During constant heart rates, maintained by right atrial pacing, vagus nerve stimulation caused small but significant reductions of myocardial contractility, but these were minor compared with the effects of other negative interventions such as halothane anaesthesia and coronary artery ligation. When atrial pacing was withdrawn during vagus nerve stimulation, the ensuing bradycardia was associated with further marked reduction of myocardial contractility and in cardiac output. Vagus nerve stimulation depressed left atrial systole and left ventricular filling, and this might be expected to have greater effect in the halothane depressed heart than in the undepressed heart of a conscious animal. Halothane decreased the spontaneous heart rate of sympathectomized and vagotomized dogs, probably by a direct effect on the sino-atrial pacemaker. It is unlikely that increased vagal activity during halothane anaesthesia could significantly depress myocardial contractility, but these many mechanisms may contribute to the overall impairment of left ventricular performance at slow heart rates.

Bradycardia frequently occurs during halothane anaesthesia, and has been attributed to increased vagal activity (Pittinger, Cullen and Watland, 1957; Wyant et al., 1958; McGregor et al., 1958; Mahaffey et al., 1961; Shinozaki, Mazuzan and Abajian, 1968). The bradycardia has been implicated in the reduced cardiac output noted during halothane anaesthesia (Jörfeldt and Lofström, 1964), and it has been suggested that increased vagal activity during halothane anaesthesia may cause a reduction of myocardial contractile force due to a direct action on ventricular muscle (Jörfeldt et al., 1970). The effects of vagus nerve activity on the left ventricle has been studied in some detail, and although earlier studies concluded that vagal activity exerted powerful effects on heart rate and atrial contraction, it was generally believed that there was little effect on ventricular performance (Gesell, 1916; Linden and Mitchell, 1960). More recent studies have drawn varying conclusions, some suggesting that vagus nerve stimulation has a marked negative inotropic effect (DeGeest et al., 1965; Levy et al., 1966b; Daggett et al., 1967), while others have been unable to find a significant effect (Schreiner et al., 1957; Rushmer, 1958; Furnival, Linden and Snow, 1968).

Using methods described in previous papers in this series, we have studied the effects of vagus nerve stimulation in sympathectomized animals, and in those with intact sympathetic nervous systems, in order to assess the possible role of vagus nerve activity in the causation or maintenance of myocardial depression during halothane anaesthesia.

METHODS

The preparation of 13 mongrel dogs for these studies, followed the methods described in a previous publication (Prys-Roberts et al., 1972). All the experiments described in this paper were performed during chloralose/urethane narcosis. The vagus nerves were isolated in the neck and cut, and the peripheral ends were preserved for stimulation. In some animals, experiments were performed both before and after bilateral cardiac sympathectomy as


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pathectomy was performed at the outset. In all but previously described; while in others, cardiac sympathectomy was chosen for stimulation.

Control observations were obtained with the heart rate maintained constant by pacing the right atrium at a rate of 5–10 beats/min above the animal’s spontaneous heart rate. All observations were made with ventilation halted for 10–15 sec. Following the initiation of vagus nerve stimulation, a second series of observations was made 20–30 sec after the onset of stimulation while the heart rate was still maintained by atrial pacing. While maintaining nerve stimulation, the pacing stimulus to the right atrium was turned off, and a further series of observations was made 20–30 sec after the cessation of atrial pacing, a second series of observations was made 20–30 sec after the onset of stimulation while the heart rate was still maintained by atrial pacing. While maintaining nerve stimulation, the pacing stimulus to the right atrium was turned off, and a further series of observations were made during the ensuing period of bradycardia. Stimulation parameters were selected by trial and error in each animal, in order to ensure maximal reduction of heart rate on turning off the atrial pacemaker, yet without producing atrioventricular block or cardiac arrest during the period of vagal stimulation with simultaneous pacing. The mean stimulus parameters used in the experiments on sympathectomized animals were square wave pulses of 5 V, 3 msec duration at a frequency of 7 Hz (range 2–10 V, 2–4 msec, 5–20 Hz). In the experiments in which the cardiac sympathetic nerves were intact, the mean stimulus parameters were: 4 V, 4 msec duration, at a frequency of 10 Hz (range 2–10 V, 3–4 msec, 5–20 Hz).

RESULTS

The haemodynamic changes resulting from 22 experiments in 9 bilaterally sympathectomized animals are summarized in table I, and a record from a typical experiment is shown in figure 1. Following the cessation of atrial pacing, a mean reduction of heart rate of 48 beats/min was achieved, and this was accompanied by significant reductions of aortic systolic pressure (−11%), aortic diastolic pressure (−15%), max LV dP/dt (−23%), max LV (dP/dt)/IP (−13%) and of cardiac output (−24%). During this period of bradycardia, there was a significant increase in left ventricular end-diastolic pressure LVEDP (+17%). Increases in peak aortic flow (+16%) and stroke volume (+20%) did not achieve significance.

In the same animals, vagal stimulation during atrial pacing produced smaller but still significant reductions of aortic pressure, max LV dP/dt, max LV (dP/dt)/IP, and peak aortic flow. In contrast with the results during the period of bradycardia, LVEDP fell by 17% and stroke volume by 7%. In 6 experiments in which left atrial pressure was also measured, at a constant heart rate, vagus nerve stimulation decreased the height of the “a” wave of the atrial systole from 7.2 to 3.2 mm Hg, whereas the mean atrial pressure rose from 5.3 to 6.8 mm Hg (both significant at the 5% level).

The haemodynamic changes resulting from vagus nerve stimulation in 13 experiments in 4 animals with intact cardiac sympathetic nerves are summarized in table II. In the absence of atrial pacing a mean reduction of heart rate of 62 beats/min was achieved, and this was accompanied by significant reductions of aortic systolic pressure (−16%), aortic diastolic pressure (−26%), max LV dP/dt (−27%), max LV (dP/dt)/IP (−16%) and cardiac output (−32%). LVEDP increased significantly (+20%) and stroke volume increased by 21%. During the period of vagus nerve stimulation at a constant heart rate, the changes were similar in magnitude and direction to those observed in the sympathectomized animals.

### Table I. Summary of haemodynamic changes produced by vagus nerve stimulation in 9 cardiac sympathectomized dogs (22 experiments).

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beat/min)</th>
<th>Aortic pressure (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Max (dP/dt) (mm Hg/sec)</th>
<th>Max (dP/dt)/IP (sec^-1)</th>
<th>Stroke volume (ml)</th>
<th>Cardiac output (l/min)</th>
<th>Peak flow (ml/sec^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>155 (17) 118 (13) 96 (13)</td>
<td>93 (13) 4.2 (1.9)</td>
<td>2100 (520)</td>
<td>38 (6) 15 (3)</td>
<td>2.19 (0.55)</td>
<td>183 (69)</td>
<td></td>
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</tr>
<tr>
<td>B</td>
<td>155 (17) 112 (13) 87 (13)</td>
<td>3.5 (1.8)</td>
<td>1930 (460)</td>
<td>36 (5) 14 (3)</td>
<td>2.01 (0.51)</td>
<td>174 (68)</td>
<td></td>
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</tr>
<tr>
<td>C</td>
<td>107 (19) 105 (16) 79 (13)</td>
<td>4.9 (1.8)</td>
<td>1620 (400)</td>
<td>33 (6) 18 (5)</td>
<td>1.67 (0.65)</td>
<td>212 (98)</td>
<td></td>
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</tbody>
</table>

Mean difference B—A: 0.0001 < 0.001 < 0.001 < 0.001 < 0.001 < 0.001 < 0.025 n.a. n.a.

Measurements of stroke volume, cardiac output and peak flow obtained on only 5 occasions both during right atrial pacing and after discontinuation.
EFFECTS OF HALOTHANE ON INTERACTIONS—IV

FIG. 1. Haemodynamic responses to stimulation of the left vagus nerve in a dog in whom the cardiac sympathetic nerves had been divided bilaterally. During stimulation of the left vagus nerve while the heart rate was maintained constant by right atrial pacing, note the reduction of aortic blood pressure, stroke volume and peak aortic flow, and the slight decrease in max LV dP/dt. LVEDP was reduced, and the sharp increment of pressure corresponding to atrial systole was absent, as was the "a" wave of the left atrial pressure trace. The right-hand panel shows the marked bradycardia which ensued when atrial pacing was discontinued during vagus nerve stimulation. This was associated with marked reductions of myocardial contractility and further reductions of aortic pressure and cardiac output.

TABLE II. Summary of haemodynamic changes produced by vagus nerve stimulation in 4 dogs with intact cardiac sympathetic nerves.

<table>
<thead>
<tr>
<th>Heart rate (beat/min)</th>
<th>Aortic pressure (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Max (dp/dt) (mm Hg/sec⁻¹)</th>
<th>Max (dp/dt)/IP (sec⁻¹)</th>
<th>Stroke volume (ml)</th>
<th>Cardiac output (l/min)</th>
<th>Peak flow (ml/sec⁻¹)</th>
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<tbody>
<tr>
<td>A</td>
<td>154 (20) 125 (19) 100 (19) 5.0 (2.5) 2520 (980) 38 (8) 14 (5) 2.19 (0.83) 165 (96)</td>
<td></td>
<td></td>
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<tr>
<td>B</td>
<td>154 (20) 118 (23) 94 (22) 4.0 (1.9) 2380 (900) 36 (8) 13 (5) 2.00 (0.83) 138 (94)</td>
<td></td>
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<tr>
<td>C</td>
<td>92 (25) 105 (28) 74 (27) 6.0 (1.7) 1850 (830) 32 (10) 17 (8) 1.48 (0.60) 170 (118)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean difference B—A</td>
<td>0 -7 6 -1.0 -140 -2 (2) -1 0.19 7</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mean difference C—A</td>
<td>0 -62 -20 -26 -20 1.0 670 -6 (5) 3 + 0.71 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(B—A)/A %</td>
<td>0 -40 -16 -26 -20 -27 16 -16 21 16</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Significance (P): (B—A)</td>
<td>-0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001</td>
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<tr>
<td>Significance (P): (C—A)</td>
<td>-0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001 &lt; 0.001</td>
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A: control values during right atrial pacing prior to vagus nerve stimulation; values are the mean, with the SD in brackets.
B: values during vagus nerve stimulation with heart rate maintained constant by right atrial pacing; values are the mean, with the SD in brackets.
C: values during vagus nerve stimulation without pacing; values are the mean, with the SD in brackets.
Significance (P): obtained by a Student's paired two-tailed t-test.
Measurements of stroke volume, cardiac output and peak flow obtained on 9 occasions and all other haemodynamic variables measured on 13 occasions.

DISCUSSION

It has been universally accepted that vagal stimulation results in a slowing of heart rate, and since the studies of Weber and Weber (1845) and Gesell (1916) there has been general agreement that the strength of atrial contraction is depressed by increased vagal activity. The importance of atrial contraction to ventricular filling has been emphasized by many (Gesell, 1916; Wiggers and Katz, 1922; Linden and Mitchell, 1960; Skinner et al., 1963). Mitchell, Gupta and Payne (1965) concluded that the absence of atrial systole reduced stroke volume by 20% at low heart rates, and by almost double that amount at fast heart rates. In hypovolaemic animals, absence of atrial systole reduced stroke volume by 15% (Snyder et al., 1966). Mitchell and Shapiro (1969) have concluded that when the normal heart is deprived of atrial activity, compensatory mechanisms maintain the cardiac output at rest, but in the depressed heart, these mechanisms are absent.
and the output of the heart falls. Sarnoff and his colleagues (1960) demonstrated that vagus nerve activity depressed atrial contractility as evidenced by the height of the "a" wave of atrial systole, raised mean atrial pressure and reduced LVEDP. The changes of these variables noted in our study at a constant heart rate, are consistent with the findings of previous investigators, and suggest that a reduction of atrial contractile force during systole impairs left ventricular filling, and the consequent reduction of cardiac output can be explained on the basis of the Frank-Starling mechanism. Wildenthal, Mierzwiak and Mitchell (1969) demonstrated that vagus nerve stimulation had no effect on ventricular diastolic distensibility, and it seems reasonable to assume that under the conditions of our studies the changes in LVEDP accurately reflect changes in left ventricular volume. During the period of bradycardia, cardiac output fell despite the increased LVEDP and stroke volume, and these changes reflect the increased time available for diastolic filling.

An alternative explanation of the observed haemodynamic changes during vagus nerve stimulation lies in the more controversial concept that vagal stimulation results in direct negative inotropic effects on the left ventricle. Before discussing the results of this and other studies, it is worth while emphasizing that the stimulation parameters used by other workers have varied considerably, and that these differences can account for many of the rather controversial and contradictory findings (DeGeest et al., 1965; Daggett et al., 1967; Harman and Reeves, 1968). The intensity of stimulation used by these authors was considerably higher than those used in the present study. We found that with greater intensity of stimulation than that used in any one animal third-degree atrioventricular block ensued, thus preventing the control of heart rate by atrial pacing alone. The reduction in contractility which was observed during the present study was small but consistent, but of much smaller magnitude than the corresponding changes induced by halothane and other negative inotropic agents (pentobarbitone and coronary artery ligation) demonstrated by Gersh (1970).

During the period of bradycardia produced by vagal stimulation without atrial pacing, a much greater reduction in contractility occurred, but much of this could be accounted for by the negative inotropic effects of a change in heart rate per se, the interval-strength relationship (Bowditch, 1871; Rosenblueth et al., 1959; Linden, 1968).

DeGeest and his colleagues (1965) demonstrated that vagus nerve stimulation reduced the peak pressure (−7% to −34%) developed in the paced isovolumic ventricular preparation, and that there was no difference between the effects of stimulating the right or left vagus nerves. These findings have been supported by those of Levy and his colleagues (1966a, 1969), while Daggett and his colleagues (1967) found a greater depression of ventricular performance. Harman and Reeves (1968) and Wildenthal, Mierzwiak and Mitchell (1969) have demonstrated smaller changes. Levy and his colleagues (1966b, 1969) have clearly shown that the negative inotropic effect of vagus nerve stimulation is potentiated in the presence of increased sympathetic nervous activity, and it has been suggested that adrenaline may increase the quantity of acetylcholine liberated at cholinergic nerve endings per stimulus (Krnjevic and Miledi, 1958). Alternatively, it has been suggested that acetylcholine antagonizes the inotropic effects of sympathetic nerve stimulation and the effects of catecholamine infusions (Hollenberg, Carriere and Barger, 1965; Dempsey and Cooper, 1969). In the present study there was no significant difference between the effects of vagal stimulation in animals with and without cardiac sympathetic innervation, but in the animal in which the greatest reduction of contractility occurred, the heart rate was 190 beats/min, and this undoubtedly reflects a high level of sympathetic activity. Since the high control heart rates in the studies of DeGeest and associates (1965) and Daggett and associates (1968) were associated with large negative inotropic changes, it is possible that their animals were subject to sympathetic activation. In many of the published studies which purport to show no effects of vagal stimulation on ventricular performance (Rushmer, 1958; Sarnoff et al., 1960; Schreiner et al., 1957) the intensity of stimulation used was too low. Furnival, Linden and Snow (1968), using a right heart bypass preparation at a constant/aortic pressure, showed that vagal stimulation of the vagus nerve at an intensity sufficient to reduce the heart rate from 152 to 93 beats/min, caused a decrease of max LV dP/dt of 171 mm Hg sec−1 when heart rate was controlled by atrial pacing, a result very similar to that of the present study.

CONCLUSIONS

The decrease in myocardial contractility (negative inotropism) induced by stimulating vagus nerves in dogs with and without intact cardiac sympathetic innervation, is small in comparison with the changes
produced by other negative inotropic influences, and the role played by vagal activity during halothane anaesthesia is likely to be predominantly related to vagal slowing of heart rate, and the consequent effects on both myocardial contractility and on cardiac output. Vagus nerve stimulation depresses atrial transport, and in the halothane-depressed heart such action may be expected to have greater effects on ventricular filling than in the depressed heart of the conscious animal. Halothane diminishes heart rate in the sympathectomized and vagotomized dog (Prys-Roberts et al., 1972) by reducing the firing rate of the sino-atrial pacemaker, and in considering the haemodynamic effects of halothane related to the reduction in heart rate, this effect must also be taken into account.

ACKNOWLEDGEMENTS

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IV: REACTIONS HEMODYNAMIQUES A LA STIMULATION DU NERF VAGUE

SOMMAIRE

Les effets de la stimulation électrique du nerf vague ont été étudiés chez des chiens anesthésiés, avant et après interruption bilatérale des nerfs sympathiques du cœur. À fréquence cardiaque constante, maintenue par pacing auriculaire droit, la stimulation du nerf vague cause des réductions petites mais significatives de la contractilité du myocarde, mais elles étaient mineures comparées aux effets d'autres interventions négatives, comme l'anesthésie à l'halothane et la ligature de l'artère coronarienne. Lorsqu'on arrête le pacing auriculaire durant la stimulation du vague, on observe, associée à la bradycardie connue, une nouvelle réduction marquée de la contractilité myocardiale et du débit cardiaque. La stimulation du nerf vague déprime la systole auriculaire gauche et le remplissage du ventricule gauche, et on croit que ceci pourrait avoir un effet plus prononcé sur le cœur déprimé par l'halothane que sur le cœur non-déprimé de l'animal conscient. Halothane réduit la fréquence cardiaque spontanée chez des chiens sympathectomisés et vagotomisés, probablement par influence directe sur le pacemaker sino-auriculaire. Il est invraisemblable que l'activité vagale accrue durant l'anesthésie par halothane pourrait significativement déprimer la contractilité myocardiale, mais ces mécanismes divers peuvent contribuer à la détérioration générale des performances du ventricule gauche à fréquence cardiaque lente.