CARDIAC FUNCTION DURING VAGUS ESCAPE

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Summary: It is generally believed that the stimulation of vagus nerve has no direct effect on ventricular myocardium. But recent work has demonstrated clear-cut negative inotropic effect of vagal stimulation on ventricles. In an attempt to study further the effect of vagal stimulation on heart, 15 dogs were studied hemodynamically under nembutal anaesthesia. Bilateral vagotomy caused 9% elevation of heart rate whereas arterial pressure and cardiac output increased by 5% and 3% respectively. Stroke volume output decreased by 8%. Stimulation of the cut peripheral end of vagus caused cardiac standstill followed by vagus escape. During the steady state of vagus escape there was marked reduction in arterial pressure, heart rate and cardiac output, but the stroke volume was significantly elevated above the mean control. These findings suggest that when heart rate decreases, the stroke volume increases in order to restore the decreased cardiac output and that this happens inspite of the negative inotropic effect of vagal stimulation. Thus the Frank-Starling mechanism has a very significant role in an intact organism with normal hemodynamics.

Key words: cardiac output; indicator dilution technique; bilateral vagotomy; stroke volume output; Frank-Starling mechanism; vagus escape

INTRODUCTION

In 1845 Weber brothers showed that vagal stimulation causes dramatic slowing and even asystole of the heart. Although the effect of vagal stimulation on sinoatrial node, atrial muscle and atrioventricular node is well known, its effect on ventricular myocardium is still a subject of controversy. Many investigators hold that vagal stimulation has no direct effect on the ventricular contractility (8, 9, 18, 21). Contrary to this other workers have reported a clear cut direct negative inotropic effect of vagal stimulation on ventricular myocardium (4, 5, 16, 23).

The present study was planned to elucidate the effect of vagal stimulation on cardiac function. Arterial pressure, heart rate, cardiac output and stroke volume were determined before and after bilateral vagotomy and during vagus escape in anaes thetized dogs with closed chest and breathing spontaneously.

MATERIAL AND METHODS

The study was conducted on 15 healthy mongrel dogs of either sex, weighing between 10.03 and 20.01 *kg*. To anaesthetize the animal, nembutal sodium (Abbott Laboratories) was injected slowly into a leg vein, the dose being 30 *mg/kg*.

After giving a mid-line incision over the anterior surface of the neck, carotid sheaths on both the sides were exposed. Carotid arteries and vagus nerves were carefully dissected free in the middle of the neck. A polyethylene T tube was positioned in the right common carotid artery. Its side limb was connected to a mercury manometer used to record carotid arterial pressure on INCO Research Kymograph. Heart rate was calculated from lead II electrocardiogram.

Cardiac output was determined by Stewart's single injection indicator dilution technique as described by Hamilton *et al.* (7). 0.5% Evan's blue (T-1824) dissolved in normal saline was used as an indicator. The concentration of the dye was determined by means of Spekker Absorptiometer (HILGER) with Cambridge Spot Galvanometer. The mean concentration of the dye during its first circulation was calculated according to Kinsman *et al.* (10) by plotting the dye concentration on semilogarithmic ordinates against time in seconds.

After determining the control values, bilateral vagotomy was performed in the mid-cervical region and all the parameters were again recorded.

The effect of stimulation of the cut peripheral end of right and left vagus nerves was determined. Stimuli were delivered from a Multitone Stimulator (Multitone Electric Co. Ltd., London) at 25/sec and 0.01 msec pulse duration. For each experiment the minimum strength of the stimulus causing cardiac standstill followed by escape beats was used and this varied between 5-15 volts.

RESULTS

The results are shown in Table I. The control recordings were taken 1-1½ hr after the induction of anaesthesia. Mean arterial pressure was 136.0 ± 12.2 mm Hg. Heart rate was 149.3 ± 39.4/min. Cardiac output ranged from 1.32 liters to 2.73 liters. It showed good correlation with the body weight and was 145.0 ± 11.4 *ml/kg*/min. Mean stroke volume was 1.05 ± 0.44 *ml/kg*/beat.

Effect of bilateral vagotomy : After the control observations were taken, both the vagi were sectioned in the mid-cervical region. Bilateral vagotomy caused elevation of arterial pressure from the control value of 136.0 ± 12.2 to 142.9 ± 12.5 mm Hg, mean increase being 5%. Heart rate rose from 149.3 ± 39.4 to 162.4 ± 35.4/min, registering an acceleration of 9%. Mean cardiac output increased only slightly from the control value of 145.0 ± 11.4 to 149.4 ± 11.1 *ml/kg*/min, the increase being 3%. Stroke volume output decreased from the control value of 1.05 ± 0.44 to 0.97 ± 0.35 *ml/kg*/beat, the decrease being 8%.

Effect of vagal stimulation : The effect of vagal stimulation on the above mentioned parameters is shown in Fig. 1 and Fig. 3. In the present series no significant difference was found between the hemodynamic effects of right and left vagal stimulation. Stimulation

of either vagus caused cardiac asystole within one or two seconds and the arterial pressure record registered a sudden and profound fall. However the ventricles again started beating while

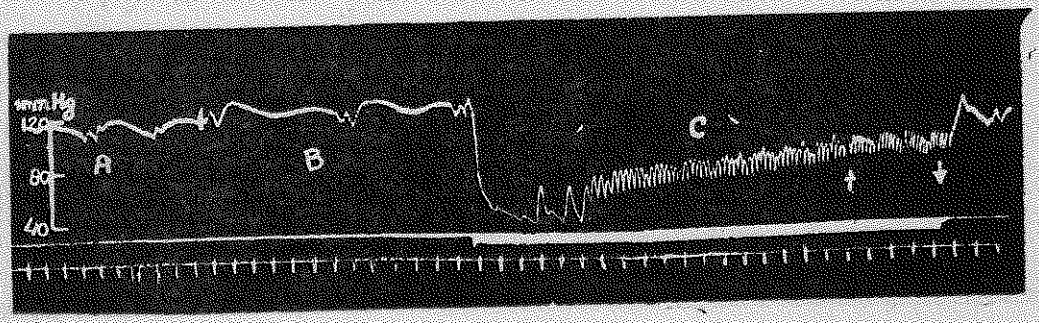

Fig 1: Carotid arterial pressure. From above downwards : arterial pressure; signal marker; time marker, 5 secc. A: Control. B: After bilateral vagotomy. C: Vagus escape: plateau of pressure tracing is indicated by the arrows. Thick signal marker line indicates the period during which cut distal vagus was stimulated.

TABLE I: Arterial pressure, heart rate, cardiac output and stroke volume output initially (C), after bilateral vagotomy (V) and during the steady-state vagus escape (V.E.)

Animal No.	*Arterial pressure mm Hg*			*Heart rate (per min)*			*Cardiac output (ml/kg/min)*			*Stroke vol. (ml/kg/beat)*		
	C	*V*	*V.E.*	*C*	*V*	*V.E.*	*C*	*V*	*V.E.*	*C*	*V.*	*V.E.*
1	150	157	114	194	203	44	117	120	53	0.60	0.59	1.20
2	130	142	80	116	135	76	200	210	57	1.71	1.55	0.75
3	135	145	76	146	154	50	59	68	32	0.42	0.44	0.64
4	142	138	70	226	230	33	139	133	47	0.61	0.57	1.42
5	146	148	122	122	137	76	164	162	139	1.34	1.18	1.82
6	151	160	85	152	166	82	146	151	51	0.96	0.90	0.62
7	115	130	65	240	245	32	107	111	79	0.45	0.45	2.46
8	108	120	64	108	126	52	194	203	84	1.85	1.61	1.61
9	139	146	77	143	155	42	159	164	91	1.11	1.05	2.16
10	140	138	59	127	142	33	143	158	58	1.12	1.11	1.75
11	143	146	71	166	178	76	162	161	99	0.96	0.90	1.30
12	138	149	83	123	137	32	177	178	73	1.43	1.30	2.28
13	131	165	121	134	149	118	124	135	123	0.92	0.90	0.96
14	139	123	79	122	135	54	177	169	56	1.43	1.25	1.27
15	133	137	58	118	145	84	108	118	76	0.91	0.81	0.90
MEAN	136.0	142.9	81.6	149.3	162.4	58.9	145.0	149.4	74.5	1.05	0.97	1.41
S.D. ±	12.2	12.5	16.9	39.4	35.4	26.5	11.4	11.1	28.2	0.44	0.35	0.58
p : C vs. V.E.			>.001		>.001			>.001			>.05	

stimulation of vagus continued (Fig. 2) and this escape interval varied between 3-19 sec. During this escape the heart rate and arterial pressure were much less initially, but both increased pro-

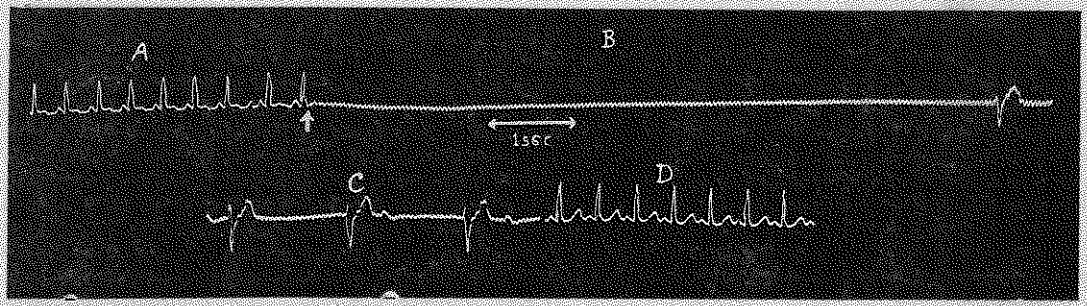

Fig. 2: Effect of vagal stimulation on lead II electrocardiogram. A and D : Control records. At the arrow, right distal vagas was stimulated at 10v., 0.01 msec., 25/sec and the stimulation continued throughout B and C. First escape rhythm occured after 7.6 sec. C : Regular escape rhythms after 3 minutes of continuous stimulation.

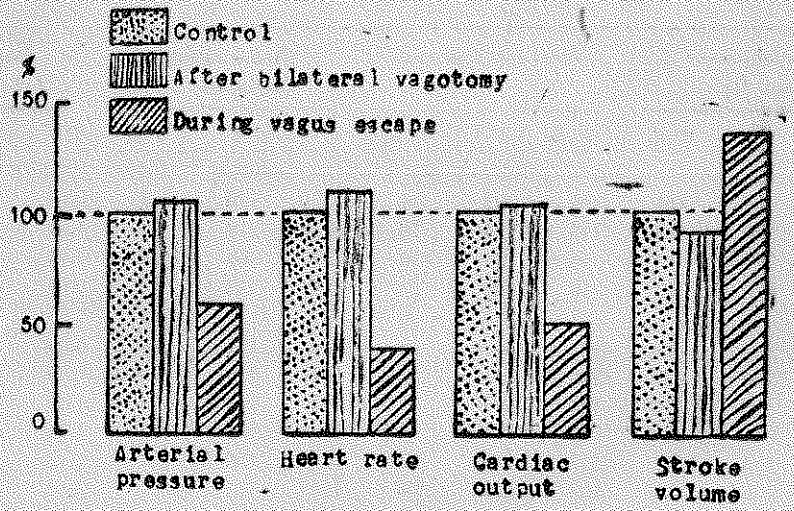

Fig. 3: Percent change after bilateral vagotomy and during steady-state vagus escape. Horizontal broken line indicates mean control values expressed as 100%.

gressively and reached a steady level in 1-3 min. This plateau was maintained throughout the period of stimulation. During this vagus escape, arterial pressure was 81.6 $\pm$ 16.9 on an average, as compared to the control of 136.0$\pm$12.2 mm Hg, mean decrease being 41%. This is statistically significant, p value being >0.001. Heart rate was 58.9$\pm$26.5 as compared to the control value of 149.3$\pm$39.4/min, mean deceleration being 61%. Cardiac output during vagus escape was 74.5$\pm$28.2 as compared to the control value of 145.0 $\pm$ 11.4 *ml./kg./*min,

mean decrease being 49%. Both deceleration response ($p>0.001$) and decrease in cardiac output ($p>0.001$) were statistically significant. Stroke volume during vagus escape was 1.41 ± 0.58 as compared to the control value of 1.05 ± 0.44 *ml/kg*/beat, mean elevation being 35%. This is also significant statistically ($p<0.05$).

DISCUSSION

It is generally believed that vagal stimulation has no direct effect on ventricular myocardium and the physiological text books insist that the motor fibers from vagi do not reach the ventricles (1,19). Changes in arterial pressure during vagal stimulation is attributed to the diminished contribution of the atrium to ventricular filling and to bradycardia. Sarnoff *et al.* (21) related left atrial pressure and left ventricular end-diastolic pressure (LVEDP) with left ventricular stroke work and observed that vagal stimulation caused no change in ventricular contractility and the left ventricle produced as much work from any given end - diastolic pressure during vagal stimulation as without it. Hoffman and Suckling (8) regard that the Purkinje fibers of mammalia are relatively insensitive to acetylcholine. Hutter and Trautwein (9) have obtained similar results. Randall (18) believes that although the effect of vagal stimulation on atrium is marked, there is no discernible effect on ventricles.

On the other hand, several workers have recently reported that vagal stimulation does have a significant depressant effect on the ventricles directly. In this connection it will be interesting to mention that Mitchell (14) has reported small intrinsic ganglia within the ventricles of primates including man. Wang *et al.* (23) reported a decline in coronary sinus flow, cardiac output and arterial pressure during vagal stimulation and all this was attributed to negative inotropic effect of vagus on ventricular muscle. These observations are essentially similar to those of Peterson (16). De Geest *et al.* (5) observed negative inotropic effect by stimulation of distal cut vagus. Daggett *et al.* (4) have obtained similar results. Negative inotropic effect of vagal stimulation has also been reported by other workers (11). Bianco *et al.* (2) found that vagal stimulation increased LVEDP and caused a fall in maximum dp/dt at constant aortic pressure, cardiac input and heart rate.

The present study was conducted on heart *in vivo*. Bilateral vagotomy increased arterial pressure as well as heart rate (Table I). During the plateau of vagus escape, both arterial pressure and heart rate were significantly lower than the control values. Cardiac output also was significantly lower than the mean control, whereas stroke volume output was significantly elevated (Fig. 3). This is due to the fact that during vagus escape, deceleration was more marked than the decrease in cardiac output. It can be presumed that when heart rate decreases, there is an increased diastolic filling and increase in fiber length as a result of which the stroke output increases. Similar results have been obtained by Madan Mohan (13). Such an increase in stroke volume is a compensatory mechanism that increases the cardiac output when bradycardia occurs. Indeed, in one of our experiments (Table I, S. No. 13) the cardiac output

during vagus escape was practically equal to the control even though the heart rate was significantly decreased. Frank and Starling provided evidence that the energy of ventricular contraction was proportional to the ventricular fiber length at the end of the preceding diastole. The operation of this Frank-Starling mechanism was later confirmed in human beings by Peterson (16) and in intact animals by Sarnoff and Mitchell (22). These observations (13, 16, 22) and the present study does not agree with Pickering (17) who came to the conclusion that the generality elaborated by Starling is of importance mostly because it is informative about the heart failure syndrome but "has only limited application to the normal human heart". On the other hand, Linden (12) has proposed by his simple but elegant experiments that increase in cardiac output during exercise occurs by Starling's mechanism as well as by positive inotropism. Several workers believe that the Frank-Starling mechanism does operate in normal intact animals. Hamilton (6) said, "I believe that the Starling's law does play a very important role in everyday life.....". The fact that vagal stimulation does not alter myocardial distensibility has been shown by Mitchell *et al.* (15). Braunwald *et al.* (3) studied intact anesthetized human subjects and concluded that the Starling's law is applicable to man. Sarnoff and Berglund (20) found that in any given physiological state, there was a consistent and reproducible correlation between atrial pressure and ventricular stroke work on the same side.

Therefore, the present study supports the validity of Starling's law *in vivo*. During vagus escape, there is increase in the stroke volume output along with the decrease in heart rate. This occurs inspite of the negative inotropic influence of efferent vagal stimulation on ventricular myocardium. Thus the Frank-Starling mechanism is an important factor which can influence the myocardial contractility in normal hemodynamic condition.

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