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ASSESSMENT BY TWO INDEPENDENT METHODS OF THE ROLE OF CARDIAC OUTPUT IN THE PRESSOR RESPONSE TO CAROTID OCCLUSION*

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In recent years attention has been focused on the effects of the carotid sinus mechanism on the venous system. Experiments in which the venous system was isolated from the effects of cardiac, arterial, and respiratory factors have demonstrated that a decrease in pressure at the carotid sinus, caused either by carotid occlusion or by reducing the perfusion pressure of the isolated sinus, results in widespread constriction of systemic veins (Bartelstone, 1960; Ross, Frahm & Braunwald, 1961). It is claimed that the blood expressed from the venous system as a consequence of this constriction causes an increase in cardiac output which, in turn, contributes to the rise in systemic arterial pressure (Bartelstone, 1960; Ross *et al.* 1961). Heymans & Neil (1958) stated in their monograph that increased output resulting from venoconstriction is probably more important than changes in peripheral resistance in causing the reflex systemic hypertension of sino-aortic origin.

Daly & Luck (1958) found, in dogs with open chests, an increase in lung lobe weight when the perfusion pressure was lowered in the isolated carotid sinuses; in two dogs occlusion of the common carotid arteries resulted in an increase in pulmonary lobar blood flow. Support for the hypothesis of increased cardiac output comes from the work of Leusen, Demeester & De Witte (1954) with the indicator-dilution method; they found cardiac output to be increased by an average of 48 % when pressure in the isolated sinus was decreased. However, in additional experiments (Leusen, Demeester & Bouckaert, 1956) in which the common carotid arteries were occluded, the output increased by an average of only 5 %. Other authors, using the direct Fick method, found no systematic change in output with decrease in carotid sinus pressure (Kenney, Neil & Schweitzer, 1951; Brind, Bianchine & Levy, 1956). Daly & Luck (1958)

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suggested that this might be explained by the potential sampling errors that are inherent in the Fick method for the measurement of cardiac output (Visscher & Johnson, 1953). However, such sampling errors are equally applicable to the indicator-dilution method (Meier & Zierler, 1954), and increased cardiac output has been observed with the Fick method (Charlier & Philippot, 1947).

The purpose of the present experiments was to test, in the intact conscious dog whose reflexes were unaltered by anaesthesia, the concept that a reduction in carotid sinus pressure causes widespread systemic venoconstriction leading to increased venous return, increased intrathoracic blood volume and increased cardiac output.

Two independent methods were used: indicator-dilution and electromagnetic flowmeter. The former permitted measurements of cardiac output and of intrathoracic blood volume, the latter allowed measurement of beat-to-beat changes in output.

METHODS

Experiments were carried out in nine dogs (11–15 kg). The dogs were selected for their friendliness and were trained to lie quietly. On the day before the experiment both common carotid arteries were exposed under light thiopental anaesthesia. A plastic sheath was placed behind each artery and was sutured to the skin. This formed a gutter in which the arteries, isolated from the neighbouring structures, pulsated freely. At the same time a catheter was introduced via the femoral vein and its tip was positioned at the junction of the inferior vena cava and the right atrium; another catheter, introduced via the femoral artery, was positioned with its tip at the aortic valve.

No anaesthesia or medication was given to the dog on the day of the experiment. The carotid arteries were occluded by closing a snare, placed around the artery, against a glass tube. The arterial and venous pressures were monitored via the catheters by means of strain-gauge transducers. The catheter-manometer-galvanometer assemblies had a uniform response up to 8 c/s (Sutterer & Wood, 1960). The zero reference point was midway between the upper and lower aspects of the dog's chest.

Cardiac output was measured by the indicator-dilution method of Hamilton, Moore, Kinsman & Spurling (1932) with indocyanine green (Cardio-green) dye (kindly supplied by Hynson, Westcott and Dunning, Inc.), as the indicator. The dye was injected, via the catheter in the right atrium, by a pneumatic syringe capable of delivering the desired amount in 0·1 sec. A linear potentiometer linked to the syringe piston recorded the instant and magnitude of each injection. The changes in dye concentration in the blood at the aortic root were recorded continuously by a densitometer attached to the aortic catheter.

The volume of blood in the heart and lungs was calculated as the product of the cardiac output and the mean transit time of indicator between injection and sampling sites. The mean transit time of the sampling system, derived as described by Fox, Sutterer & Wood (1957), was subtracted from the mean transit time of the recorded curve to give the true transit time for the lung and heart chambers.

The blood withdrawn during the recording of the dilution curve (about 15–20 ml.) was re-infused to the animal after each curve had been recorded. Calibration curves were constructed for each experiment by drawing known concentrations of indocyanine green in the dog's own blood through the densitometer and recording the deflexions produced.

In three dogs the cardiac output was measured by a square-wave electromagnetic flow-

meter probe, Model 201 B, Carolina Medical Electronics, Inc. (Denison, Spencer & Green, 1955) placed around the main pulmonary artery 1 week before the experiment. The electronic circuit of the flowmeter permitted the measurement of the total forward flow for every 6 sec period. To determine the actual flow, the flowmeter was calibrated against the indicator dilution technique. Intravenous infusions of isopropylnoradrenaline were used to increase the cardiac output in order to obtain a wide range of values in plotting the calibration curve. The calibration line of the flowmeter was linear and passed through the zero point.

The dogs sat, or lay quietly on their sides; they were not disturbed in any way by the compression of the carotids. In fact, they often went to sleep.

RESULTS

A total of 67 bilateral occlusions of common carotid arteries were carried out in the nine dogs, 41 in the six dogs studied with the indicator-dilution technique and 26 in the three dogs studied with the electromagnetic flowmeter. Each carotid occlusion lasted for 2 min and the measurements of cardiac output and of lung and heart blood volume were made during the last minute of occlusion. Control observations were made before each occlusion. In each dog the pattern of response of the cardiac output and of the lung and heart blood volume varied slightly from one carotid occlusion to another; hence for statistical analysis, the data were grouped as a succession of paired observations, each pair consisting of the control values and the values during the succeeding occlusion. In the dogs that went to sleep during a series of observations, no change in the pattern of response was noted.

TABLE 1. Measurements obtained before and during the second minute of carotid occlusion. The indicator-dilution technique was used for 41 observations in six dogs and the electromagnetic flowmeter for 26 observations in three dogs. The results are shown as means ± standard deviations, with ranges in parentheses

	Indicator-dilution technique		Electromagnetic flowmeter on main pulmonary artery	
Variable	Control	During occlusion	Control	During occlusion
Cardiac output (ml./min/kg)	140 ± 22 (106–208)	142 ± 20 (111–197)	163 ± 21 (124–218)	170 ± 24 (134–227)
Lung and heart blood volume (ml./kg)	16·9 ± 3·8 (9·2–23·4)	17·1 ± 3·5 (9·4–21·9)	—	—
Mean aortic pressure (mm Hg)	110 ± 19 (70–150)	150 ± 27 (100–195)	84 ± 10 (73–106)	133 ± 21 (96–166)
Mean right atrial pressure (mm Hg)	0 (−2·5 to +2)	0 (−2 to +2)	−0·3 (−1·3 to +1·1)	−0·3 (−1·3 to +1·1)
Heart rate (beats/min)	97 ± 39 (54–180)	103 ± 40 (60–186)	135 ± 34 (100–186)	157 ± 30 (115–194)
Respiration rate (resp./min)	—	—	30 ± 7 (20–48)	30 ± 6 (20–40)

Indicator-dilution technique

During occlusion the average increase in mean aortic pressure was 40 mm Hg from an average control value of 110 mm Hg. The average values for cardiac output and for lung and heart blood volume during occlusion (142 ml./min/kg and 17·1 ml./kg, respectively) did not differ

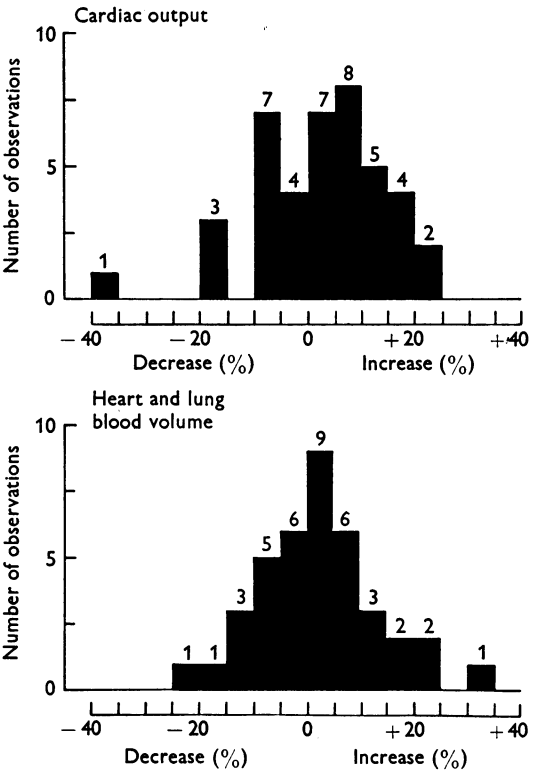

Fig. 1. Distribution of the changes in cardiac output and in heart and lung blood volume during carotid occlusion in six conscious dogs studied by the indicator-dilution technique. The changes are expressed as percentage change from the control value determined just before each carotid occlusion.

from the control values (140 ml./min/kg and 16·9 ml./kg, respectively). The average right atrial pressure remained unchanged during occlusion and the average increase in heart rate was 6 beats/min at the time the cardiac output determinations were made (Table 1).

The cardiac output remained within 10 % of its control value in 26 out of the 41 observations (Fig. 1); it increased by 10–20 % in nine observations and by 20–25 % in two observations. In four observations the

cardiac output decreased by more than 10% (maximal decrease observed was 40% in one observation). The lung and heart blood volume remained within 10% of its control in 26 observations; it increased by 10–20% in five observations, by 20–25% in two observations. It decreased by more than 10% in five observations (maximal decrease observed was 25%). Thus, in approximately 65% of the observations the values for cardiac

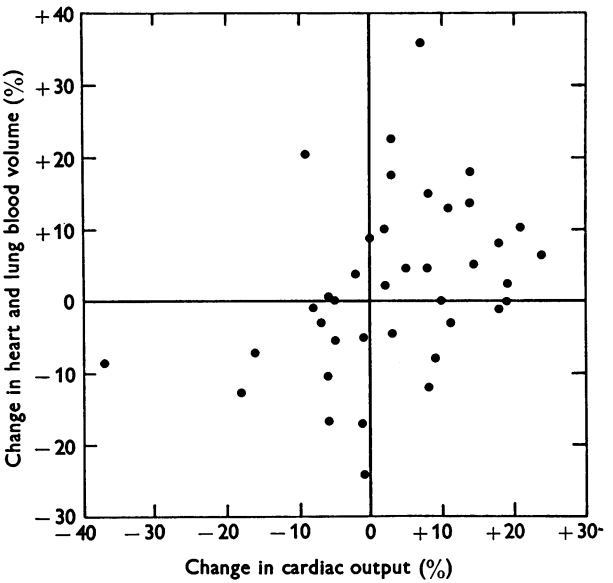

Fig. 2. Percentage change from the control value of lung and heart blood volume plotted against the percentage change in cardiac output during carotid occlusion in six conscious dogs studied by the indicator-dilution technique.

output and for lung and heart blood volume during occlusion remained within 10% of their control values.

That there was a correlation between the changes in cardiac output and in lung and heart blood volume is suggested by the plot of the percentage changes in cardiac output during carotid occlusion against the percentage changes in lung and heart blood volume shown in Fig. 2. There is, however, a wide scatter of values, and changes in cardiac output were noted without a similar change in lung and heart blood volume.

The magnitude of the hypertensive response was independent of the magnitude of the changes in cardiac output and in lung and heart blood volume (Fig. 3). The χ^2 test was used to test whether or not those observations in which the cardiac output increased were also the ones in which the maximal hypertensive response (greater than a 33% increase in mean aortic pressure) occurred; no such correlation was found ($P = 0{\cdot}1$). Like-

wise no correlation was found between right atrial pressure and changes in cardiac output and in lung and heart blood volume.

In two of the dogs carotid occlusions were repeated after infusion of 750 ml. of blood in order to change the initial volume of the capacity vessels. After infusion the right atrial pressure increased by 7 mm Hg and the lung and heart blood volume increased by 5 ml./kg. Three sets of

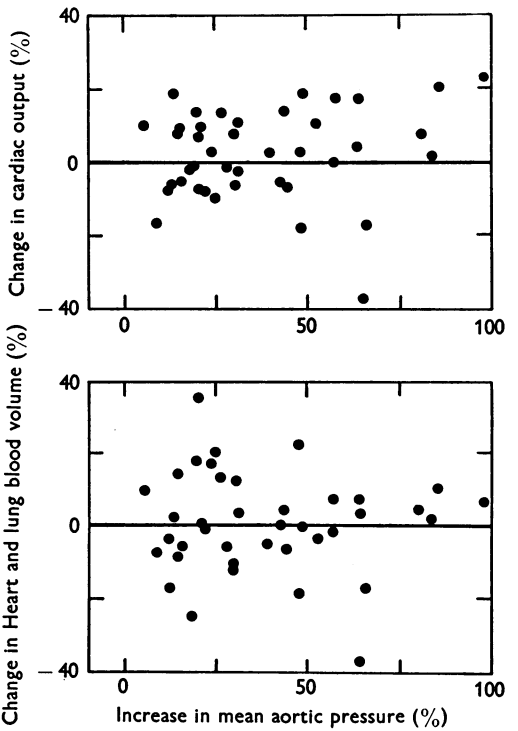

Fig. 3. Percentage change in cardiac output and in lung and heart volume from the control values plotted against percentage increase in mean aortic pressure during carotid occlusion in six conscious dogs studied by the indicator-dilution technique.

observations were then made on each dog during carotid occlusion. Average aortic pressure increased from 109 to 153 mm Hg; average cardiac output increased from 141 to 145 ml./min/kg; lung and heart blood volume changed from 25 to 24·9 ml./kg; and heart rate from 110 to 140 beats/min.

Electromagnetic flowmeter

Each carotid occlusion was invariably followed by a marked increase in mean aortic pressure (average increase, 49 mm from a control of 84 mm Hg; Table 1). The mean of the cardiac outputs measured during the

second minute of carotid occlusion (170 ml./min/kg) was only slightly greater than the control (163 ml./min/kg). The heart rate showed an increase of 22 beats above the control value of 135 beats/min. The means of the right atrial pressure and of the respiratory rate did not change. These results were similar to those obtained in the experiments with the indicator-dilution technique.

The cardiac output was remarkably constant at the onset of occlusion when the systemic arterial pressure was rising rapidly and the heart rate

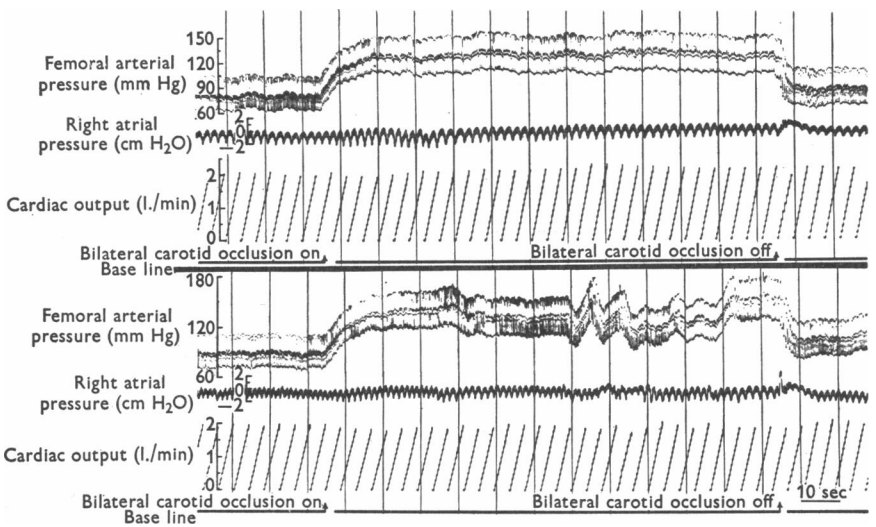

Fig. 4. Two records obtained in a 12 kg dog during carotid occlusion in experiments with the electromagnetic flowmeter. Carotid occlusion was maintained for 2 min. The flowmeter tracing is composed of a succession of steps, each corresponding to a stroke volume. These steps are added by the electronic circuitry of the flowmeter to give the total forward flow (l./min) through the main pulmonary artery every 6 sec. Time marker, 10 sec.

was increasing (Fig. 4). In the observations shown in the lower half of Fig. 4 there were marked fluctuations in arterial blood pressure during the latter period of carotid occlusion. The corresponding changes in flow were minimal and much too small to account for the oscillations in arterial pressure, which often exceeded 30 mm Hg.

The averages and the ranges of all the observations made on one of the dogs, which are typical of the results on the other two dogs, are shown in Fig. 5. In the first 18 sec of carotid occlusion the cardiac output only changed slightly while the blood pressure and heart rate were increasing. The tachycardia was more pronounced in the early part of the period of carotid occlusion. The right atrial pressure remained almost unchanged

during the hypertensive phase. These three dogs were anaesthetized with pentobarbital (20 mg/kg) after observations had been made in the conscious state. Thirteen carotid occlusions were then achieved. The increase in mean aortic pressure averaged 43 mm Hg above the control level of 89 mm Hg. The cardiac output during carotid occlusion (140 ml./min/kg) increased but slightly from its control value (132 ml./min/kg). The heart

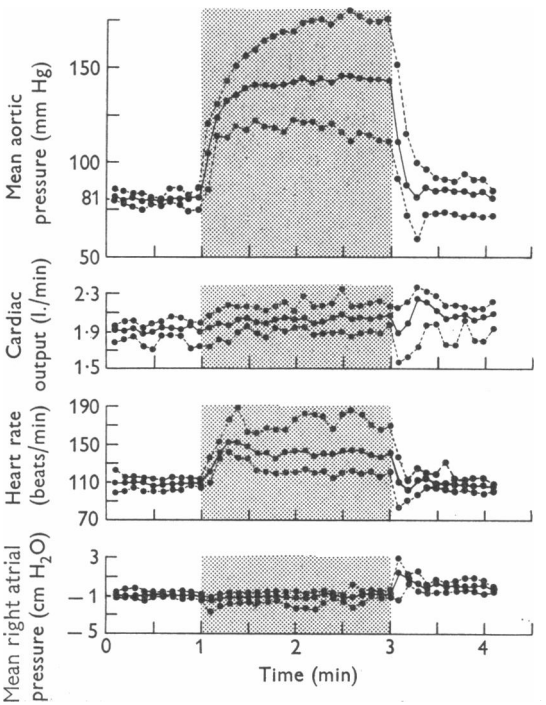

Fig. 5. Mean (dark line) and range (interrupted lines) of observations of nine carotid occlusions in one dog (11 kg). Observations were made every 6 sec. The cardiac output was measured by electromagnetic flowmeter.

rate increased by 22 beats/min above its control value of 152. The mean right atrial pressure and respiratory rate did not change.

Two representative tracings of the observations made at the time of release of bilateral carotid occlusion in conscious dogs are shown in Fig. 6. Coinciding with the heart beat immediately after release of the occlusion, the aortic pressure decreased and the heart rate slowed. For one or two beats just after release, cardiac diastole lasted for more than 1 sec. The right atrial pressure increased during this period of slowing of the heart, and there was a marked increase in stroke volume. The blood flow through the main pulmonary artery was decreased during the 6 sec after the

release of the carotid occlusion. The pattern of response at the onset of occlusion was similar to that seen in Figs. 4 and 5. The cardiac slowing, increase in stroke volume, and decrease in total forward flow in the 6 sec after release were not so evident when the dogs were under pentobarbital anaesthesia.

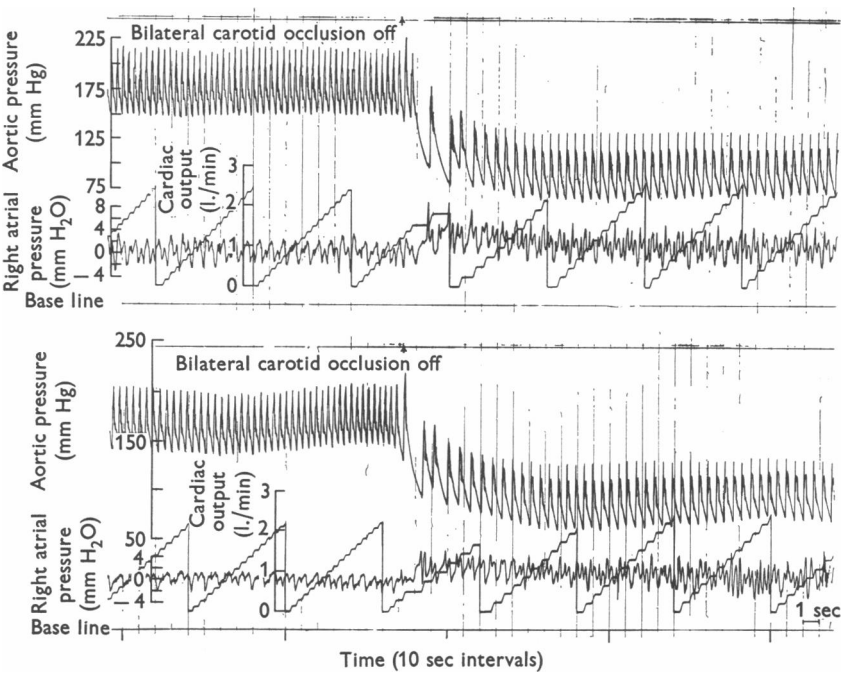

Fig. 6. Two records obtained during the period of release of carotid occlusion in conscious 11 kg dog, showing the changes in aortic and right atrial pressures, cardiac output, and stroke volume. Each step on the flowmeter tracing represents the stroke volume, and the total height of the tracing the accumulated flow during the previous 6 sec. The horizontal branch of each step on the flowmeter tracing corresponds to no forward flow through the main pulmonary artery.

DISCUSSION

The magnitude of the increase in systemic pressure seen during carotid occlusion in the conscious dog is the same as that described previously by Armstrong, Porter & Langston (1961). This increase in pressure is not simply a consequence of the mechanical compression of two large systemic arteries, since a similar occlusion in a dog in whom the carotid sinus has been denervated does not produce this phenomenon (Heymans & Bouckaert, 1930). The extensive anastomoses between the vertebral and carotid systems in the dog ensure an adequate perfusion of the carotid

body during common carotid occlusion (Schmidt, 1932*a*, *b*; Chungcharoen, Daly, Neil & Schweitzer, 1952; Jewell, 1952; Daly & Hazzledine, 1963). The pressure in the carotid sinus was measured in nine dogs anaesthetized with pentobarbital and it averaged 108 mm Hg during bilateral carotid occlusion, a decrease of 30 mm Hg from its control value. This, together with the fact that in the conscious dog there was no tachypnoea, suggests that there was adequate perfusion of the chemoreceptors.

During the second minute of carotid occlusion, when presumably a steady state was present, similar results for changes in cardiac output from control values were obtained by the indicator-dilution and the flowmeter methods. Since these are independent methods, and since the changes in output were inconsequential compared to the increases in systemic arterial pressure, the major, and frequently the sole, cause of the increase in pressure must be a constriction of resistance vessels, presumably the precapillary vessels. This was also true in dogs anaesthetized with pentobarbital. Since the heart rate averaged 135 beats/min in the conscious dog and 152 beats/min in the anaesthetized dog, there was adequate opportunity for the output to increase either by an increase of rate or of stroke volume or of both.

The absence of any important change in cardiac output, combined with the absence of change in right atrial pressure and of a shift of blood to the heart and lungs from the systemic vascular bed, suggests that widespread venoconstriction had not occurred. These findings are in agreement with those of Coleridge & Hemingway (1958), who measured the rates of blood flow in the venae cavae of dogs; they found no evidence with carotid occlusion of an increase in venous return such as might be caused by constriction of veins. Bartelstone (1960) divided the dog's circulation into a cephalad and a caudad zone and found evidence for reflex venoconstriction in the latter zone when the common carotid arteries were occluded. He also reviewed the work of others who have suggested that increased venous return may be an important cause of the rise in arterial pressure with carotid occlusion. Bartelstone stated that if this extra volume of venous return due to reflex venoconstriction is prevented from reaching the heart the arterial hypertensive response to carotid occlusion is greatly reduced. At the moment we cannot reconcile these findings with those in the intact dog reported here.

Recent reports have shown that in other species the cardiac output remains unchanged during carotid occlusion. These observations were made by Groom, Löfving, Rowlands & Thomas (1962) with the indicator-dilution technique in the anaesthetized cat and by Edwards, Korner & Thorburn (1959) with the same technique in the conscious rabbit. Thus,

it appears that no species specificity exists in the cardiac output response in the dog, the cat, and the rabbit. Leusen *et al.* (1956) compared the effect, in dogs, of decreasing the pressure in the isolated sinus with that of carotid occlusion. With the former, cardiac output increased (average 48 %), but with the latter little change in output occurred. Daly & Luck (1958) and Sarnoff, Gilmore, Brockman, Mitchell & Linden (1960) also found that lowering the pressure in the isolated sinus was accompanied by an increase in cardiac output. Thus the magnitude of the stimulus to the heart and systemic vessels may be different in these two circumstances.

Since a steady-state situation is required for estimation of cardiac output by the Fick and by the indicator-dilution methods, these methods cannot be used to detect changes in output during the period of increasing pressure at the onset of occlusion or in the period immediately following release of occlusion. The results with the electromagnetic flowmeter show that, as the systemic pressure was increasing at the onset of carotid occlusion, there was little or no change in cardiac output. As the heart rate increased during this time, the stroke volume decreased. Thus, the increase in pressure at the onset of occlusion also is mediated solely by constriction of systemic resistance vessels. Identical findings have been reported by Polosa & Rossi (1961) using the aortic pulse contour method and an electromagnetic flowmeter to measure cardiac output.

On release of occlusion, with the sudden rise in carotid sinus pressure (about 40 mm Hg in the first 0·5 sec), there is a reflex slowing of the heart, presumably via vagal impulses. The accompanying rise in venous pressure can be attributed to the marked slowing of the heart, and the subsequent increase in stroke volume to the increased filling pressure. The total forward flow is decreased and this must contribute to the decrease in systemic pressure and to the rapid fall in this pressure compared to the slower rise at the onset of occlusion.

Thus, when the carotid sinus pressure is reduced, the resultant increase in systemic pressure is due to constriction of the resistance vessels. By contrast, when the carotid sinus pressure increases, the cardiac output may decrease as the heart slows, and this contributes to the decrease in systemic pressure. Some of the controversy concerning the role of cardiac output in baroreceptor responses may stem from a failure to appreciate that the one situation is not the converse of the other.

SUMMARY

1. Two independent methods have been used in dogs to test the concept that widespread constriction of systemic veins by causing an increase in cardiac output contributes to the rise in systemic pressure during bilateral carotid occlusion. The indicator-dilution method permitted measurements,

during steady-state conditions, of cardiac output and of intrathoracic blood volume. An electromagnetic flowmeter placed around the main pulmonary artery allowed beat-to-beat changes in output to be followed.

2. The systemic arterial pressure increased markedly during carotid occlusion (97–142 mm Hg), but neither method showed any significant change in cardiac output. This was true even when the pressure was rising rapidly at the onset of occlusion. There was no evidence for a shift of blood from the systemic to the intrathoracic vascular bed.

3. On release of occlusion there was a transient slowing of the heart, a rise in right atrial pressure and an increased stroke volume. In spite of the increase in stroke volume, the cardiac output decreased in the 6 sec following release of occlusion. This contributed to the drop in systemic pressure.

4. It is concluded that when the carotid sinus pressure is reduced the resulting rise in systemic pressure is due solely to constriction of the resistance vessels. By contrast, when the carotid sinus pressure rises, the output may fall as the heart slows, and this contributes to the decrease in systemic pressure. The one situation is therefore not the converse of the other.

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