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CAROTID SINUS REFLEXES AND CARDIAC OUTPUT IN DOGS

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There is no agreement in the literature about the influence of the carotid sinus nerves and aortic nerves on cardiac output; this is perhaps surprising in view of the central position cardiac output changes must assume in any general discussion of the reflex regulation of cardiovascular function.

Tigerstedt (1908), while stimulating the central end of the aortic nerve in rabbits with both vagi cut and with the stellate ganglia excised, found from aortic stromuhr measurements that the output of the ventricle may be increased during the phase of intense peripheral vasodilatation. He noticed that there was an increase in venous return and considered this factor to be responsible for the increase of cardiac output during this stage.

Jarisch & Ludwig (1926), using a cardiometer, observed a decrease in cardiac volume in six, no change in thirty, and an increase (maximum of 20%) in thirty-nine stimulations of the aortic nerve in nine rabbits. Similar results were obtained by the same authors when they stimulated the carotid sinus nerves.

Riml (1929), applying the Fick principle to oxygen consumption in rabbits, found that occlusion of both common carotid arteries produced either an increase or a decrease in cardiac output.

Heymans, Bouckaert & Dautrebande (1931), applying the Fick principle to CO_2 production, observed a rise of cardiac output on occlusion of the common carotid arteries in dogs. They found, however, a fall of cardiac output when using a cardiometer or when calculating the output according to the formula of Liljestrand & Zander (1928)

$$\left(\text{Cardiac output} = \frac{\text{Pulse pressure} \times \text{heart rate}}{\text{Mean arterial blood pressure}}\right).$$

Gollwitzer-Meier & Schulte (1931) obtained variable results in dogs on

raising the carotid sinus pressure, cardiac output changes being studied by cardiometric technique.

Holt, Rashkind, Bernstein & Greisen (1946), employing Stewart's (1921) method, found an average reduction of cardiac output of 7% when they stimulated the carotid sinus nerve in dogs.

Charlier & Philippot (1947), applying the Fick principle to oxygen consumption, reported that occlusion of the common carotid arteries increased the cardiac output, right auricular and ventricular pressure and cardiac work. The increase in cardiac output was directly related to the increase in right auricular pressure. Similar results were recently reported by de Vleeschhouwer, Pannier & Delaunois (1949).

Moe, Rennick, Capo & Marshall (1949) were unable to confirm the findings of Charlier & Philippot. They state that carotid occlusion caused little or no alteration of cardiac output. Moe *et al.* (1949) used the cardiometric method.

Because of its fundamental importance it was decided to re-examine the problem. A summary of our findings has been previously published (Kenney, Neil & Schweitzer, 1949).

METHODS

Dogs were used, anaesthetized by chloralose (0·08–0·1 g./kg. body wt., intravenously) or by sodium pentobarbital (30–40 mg./kg. body wt., intraperitoneally). Respiration and oxygen usage were recorded in most experiments by the closed circuit method, using a spirometer of 1500 ml. capacity, CO_2 being absorbed by soda lime. An air circulating pump was used in some experiments. In three experiments, ventilation volume, O_2 usage and CO_2 production were measured by the open circuit method (Douglas, 1911).

Arterial blood samples were obtained from a common carotid or femoral artery. Mixed venous blood samples were collected from the depth of the right atrium or from the ventricle by means of a catheter passed through the right external jugular vein. The exact position of the catheter was checked by post-mortem examination. Arterial and mixed venous blood samples (5 ml.) were usually obtained simultaneously and always at the mid-point of a determination of O_2-usage lasting several minutes. They were taken into heavily greased glass syringes which contained 0·1 ml. of a concentrated heparin solution. A globule of mercury was then introduced into the syringe and the nozzle of the latter sealed with a polythene cap. The syringes were shaken gently and stored on ice. Ostwald pipettes of 1 ml. capacity were filled with blood from the syringes, which were agitated beforehand; the oxygen content of the blood was determined by the Van Slyke manometric apparatus (Neill & Van Slyke, 1924). Duplicate estimations were made from each sample.

From the A.-V. oxygen differences and the simultaneous oxygen usage cardiac output was calculated according to the Fick equation.

Blood pressure was recorded from a femoral artery. In many experiments readings of right atrial pressure were obtained from a saline manometer attached to the catheter in the right heart. Attempts to alter cardiac output were made in three ways: (*a*) by occlusion of both common carotid arteries; (*b*) by alteration of the blood pressure in one or both carotid sinuses which were isolated from the systemic circulation, and perfused by means of a Dale-Schuster or Hemingway (1933) pump; (*c*) by stimulation of a carotid sinus nerve using a rectangular wave electronic stimulator as described in a previous communication (Neil, Redwood & Schweitzer, 1949).

In the perfusion experiments blood in the perfusion system was equilibrated with a gas phase consisting of 95% oxygen and 5% carbon dioxide. Heparin was injected intravenously (5 mg./kg. body wt.) in all experiments.

RESULTS

Effect of bilateral carotid occlusion on cardiac output

Experiments were performed on five dogs in which oxygen usage was determined by closed circuit spirometry. The results are presented in Table 1. There was no significant change in cardiac output during bilateral carotid occlusion in two experiments (1 and 2). Exp. 3 showed a fall in cardiac output of approximately 11·5%. In Exp. 4 carotid occlusion apparently caused a rise

TABLE 1. Effect of bilateral carotid occlusion on cardiac output in dogs

Exp.	Wt. (kg.)	O_2 content: Arterial (ml./100 ml. blood)	O_2 content: Venous (ml./100 ml. blood)	A.-v. O_2 diff.	O_2 usage (ml./min.)	Heart rate/min.	B.P. (mm. Hg)	Cardiac output (ml./min.)	Conditions
1 (N)	10	18·5	13·1	5·4	83	176	130	1540	Control
		—	13·1	5·4	83	198	160	1540	(*a*) Carotids
		—	13·0	5·5	83	192	160	1510	(*b*) occluded
		18·4	13·0	5·4	83	180	130	1540	Control
2 (N)	9	21·6	16·0	5·6	76	180	140	1355	Control
		—	15·8	5·8	76	198	180	1310	(*a*) Carotids
		—	15·8	5·8	76	204	170	1310	(*b*) occluded
		21·6	15·8	5·8	76	180	135	1310	Control
				Both vagi cut					
		19·9	13·5	6·4	86	240	145	1340	Control
		—	13·7	6·2	86	234	190	1390	(*a*) Carotids
		—	13·7	6·2	86	240	180	1390	(*b*) occluded
		19·8	13·6	6·2	86	238	140	1390	Control
3 (N)	7·25	19·4	12·0	7·4	70	156	140	950	Control
		—	11·1	8·3	70	186	200	840	(*a*) Carotids
		—	11·1	8·3	70	192	190	840	(*b*) occluded
		19·2	12·1	7·1	70	176	140	990	Control
				Both vagi cut					
		19·2	12·2	7·0	70	176	150	1000	Control
		—	12·2	7·0	68	184	170	970	(*a*) Carotids
		—	11·2	8·0	68	192	170	850	(*b*) occluded
		19·2	12·0	7·2	68	162	120	945	Control
4 (N)	11·3	17·5	13·4	4·1	84	196	155	2050	Control
		18·0	13·9	4·1	100	226	230	2440	(*a*) Carotids
		—	13·7	4·3	100	226	230	2330	(*b*) occluded
		18·1	14·1	4·0	97	200	155	2420	Control
		—	13·9	4·2	97	200	155	2300	Control
		17·9	13·9	4·0	92	216	230	2300	(*a*) Carotids
		—	14·3	3·6	100	216	230	2740	(*b*) occluded
		17·7	14·0	3·7	100	200	145	2700	Control
		17·5	14·0	3·5	92	200	145	2630	Control
5 (N)	22·5	21·6	17·5	4·1	100	170	150	2440	Control
		21·4	16·9	4·5	100	156	210	2220	(*a*) Carotids
		—	16·9	4·5	100	156	210	2220	(*b*) occluded
		21·5	16·7	4·5	100	165	140	2220	Control
		—	16·35	4·9	100	143	210	2040	(*a*) Carotids
		21·25	16·65	4·6	100	144	210	2170	(*b*) occluded
		—	17·15	4·1	96	153	150	2340	Control
6 (N)	13·7	21·6	17·4	4·2	118	168	145	2820	Control
		21·6	17·2	4·4	121	180	145	2740	Control
		21·9	17·6	4·3	124	200	190	2890	Carotids occluded
		21·2	17·2	4·0	115	180	140	2880	Control
		21·0	16·4	4·6	127	180	140	2760	Control
		21·8	17·0	4·2	112	192	190	2670	Carotids occluded
		21·1	16·9	4·2	103	190	135	2460	Control

(N) = Animal under nembutal anaesthesia.

in cardiac output of the order of 20% over the original value, but after the release of occlusion the cardiac output did not return to the initial figure. Repetition of carotid occlusion again increased cardiac output by about 15% (second sample), but once more the release of occlusion did not restore the original value of cardiac output. In Exp. 5 two results were obtained in successive carotid occlusion experiments. (*a*) There was an apparent reduction of cardiac output by 10%. The control estimation, however, showed no change in cardiac output after release of the carotid clamps. (*b*) In a second experiment, where both carotids were occluded, there occurred a further fall in cardiac output of about 10%. In this instance release of the carotid arteries increased cardiac output to a level which was greater than that observed immediately before the second occlusion. Sectioning of both vagi (Exps. 2 and 3) did not materially alter the effects of carotid occlusion on the cardiac output.

In every experiment carotid occlusion raised the mean right atrial pressure. This rise in atrial pressure was of the order of 0·5 cm. H_2O and was unrelated to the effect of carotid occlusion on cardiac output.

The results of these experiments are not in agreement with those of Charlier & Philippot (1947) who claimed that cardiac output invariably increased during carotid occlusion. These authors employed the open-circuit method of determination of oxygen usage; their animals, therefore, inspired room air. In our experiments, pure oxygen was inspired. This difference of oxygen tension in inspired air might be of importance, as carotid occlusion affects carotid chemoreceptor discharge as well as baroreceptor stimulation (Euler & Liljestrand, 1943). The discrepancy between our results and those of Charlier & Philippot might be due to a difference in the degree of chemoreceptor stimulation arising from the experimental circumstances. Three experiments were therefore performed in which the oxygen usage of the animals was determined by the open-circuit method, the animals breathing air. Exp. 6 is representative of this series; bilateral carotid occlusion did not materially affect cardiac output. Variations in cardiac output which were obtained upon carotid occlusion were no greater than those found with repeated sampling during control conditions.

Effect of raised intrasinusal pressure on cardiac output

Experiments were performed in which one carotid sinus, isolated from the systemic circulation, was perfused. In some of the experiments the opposite sinus nerve was cut. In one experiment both isolated carotid sinuses were perfused. In most cases bilateral vagotomy was performed during the course of the experiments. Fig. 1 is representative of the effects of raising the sinus pressure on one side. The results obtained are shown in Table 2. They show, with one exception, that no significant change in cardiac output occurred during the period of increased intrasinusal pressure in animals with intact vagi. It is clear that the small variations in cardiac output which were recorded fell within the

range of spontaneous variations of cardiac output and cannot be attributed to effects of carotid baroreceptor stimulation. In only one instance (Exp. 15) was a noteworthy fall of cardiac output obtained by raising the intrasinusal pressure. In most experiments bilateral vagotomy did not materially affect the results of raising intrasinusal pressure, but in Exps. 9 and 15 a significant decrease of cardiac output was obtained after section of the vagi. This decrease in cardiac output was 10 and 20% respectively. After bilateral vagotomy difficulty was occasionally experienced in assessing the O_2 usage during the initial effects of raised intrasinusal pressure because of prolonged reflex apnoea, followed by hyperventilation (e.g. Exp. 11).

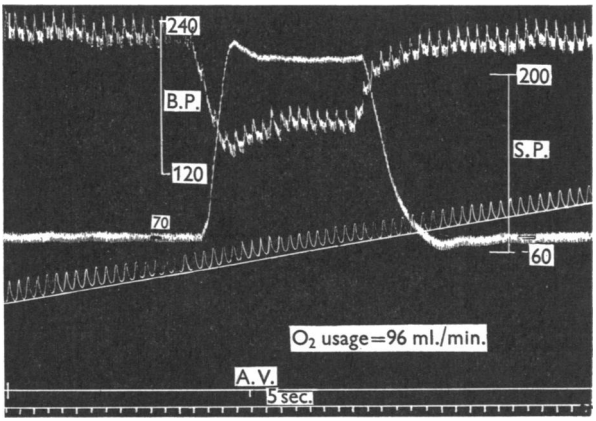

Fig. 1. Dog. Chloralose anaesthesia. Right carotid sinus isolated and perfused. Left carotid sinus nerve cut. Both vagi intact. Records from above downwards: arterial blood pressure, sinus perfusion pressure, respiration and O_2 usage by closed circuit spirometry, signal marker and time in 5 sec. During a period of raised perfusion pressure, samples of arterial and mixed venous blood were simultaneously withdrawn at mark 'A.V.'.

Effect of electrical stimulation of the carotid sinus nerve on cardiac output

Two representative experiments are shown in Table 3 (Exps. 16 and 17). In neither case was a significant change in cardiac output observed which, in animals with vagi intact, could be attributed to effects of stimulation of the carotid sinus nerve. In none of these experiments, with the type of stimulation used, was any marked cardiac slowing observed. After double vagotomy a fall in cardiac output of approximately 20% occurred during the period of nerve stimulation in one of these animals (Exp. 17).

DISCUSSION

In only one of our experiments did any significant change of cardiac output occur as a result of our procedures.

Conflicting results in the literature, summarized in the Introduction, may be classified and compared according to the various techniques.

TABLE 2. Effects of increased perfusion pressure of the isolated carotid sinus on cardiac output in dogs

Exp.	Wt. (kg.)	O_2 content: Arterial (ml./100 ml. blood)	O_2 content: Venous (ml./100 ml. blood)	A.-v. O_2 diff.	O_2 usage (ml./min.)	Heart rate/min.	B.P. (mm. Hg)	Cardiac output (ml./min.)	Conditions
7 (N)	11·75	20·5	16·5	4·0	67	182	160	1675	Control
		—	16·1	4·4	72	168	90	1635	(*a*) Raised
		20·5	16·1	4·4	72	168	100	1635	(*b*) perfusion
		—	16·0	4·4	72	168	100	1600	(*c*) pressure
		20·5	16·4	4·1	68	186	140	1660	Control
				Both vagi cut					
		20·5	16·5	4·0	64	192	80	1600	Control
		20·5	16·4	4·1	64	138	40	1560	(*a*) Raised
		—	16·4	4·1	64	132	30	1560	(*b*) perfusion pressure
		20·5	16·5	4·0	64	186	90	1600	Control
8 (N)	10·75	24·3	13·1	11·2	125	—	—	1120	Control
		—	13·1	11·2	125	—	—	1120	Raised perfusion pressure
		24·2	12·9	11·3	118	—	—	1050	Control
				Both vagi cut					
		24·2	13·1	11·1	112	—	—	1010	Control
		—	13·2	11·0	112	—	—	1020	Raised perfusion pressure
		24·2	13·1	11·1	112	—	—	1010	Control
9 (C)	25·0	22·6	16·1	6·5	225	180	180	3460	Control
		—	16·7	5·9	200	150	110	3400	(*a*) Raised
		22·6	16·3	6·3	215	162	130	3410	(*b*) perfusion pressure
		—	—	6·3	215	192	180	3410	Control
				Both vagi cut					
		22·6	16·0	6·6	240	172	150	3640	Control
		—	17·4	5·2	175	176	50	3360	(*a*) Raised
		—	17·3	5·3	180	166	50	3400	(*b*) perfusion pressure
		—	15·8	6·7	250	180	180	3730	Control
10 (C)	21·0	18·4	13·4	5·0	130	164	185	2600	Control
		18·4	14·4	4·0	100	148	105	2500	Raised perfusion pressure
		—	13·5	4·9	128	158	180	2610	Control
		—	13·4	5·0	130	140	110	2600	Raised perfusion pressure
		18·3	13·3	5·0	130	156	175	2600	Control
				Both vagi cut					
		18·0	12·3	5·7	119	168	165	2090	Control
		—	12·2	5·8	120	162	90	2060	Raised perfusion pressure
		17·9	12·2	5·7	117	168	180	2050	Control
		17·9	12·2	5·7	120	160	175	2100	Control
11 (C)	25·0	19·4	13·9	5·5	152	156	180	2760	Control
		19·4	13·5	5·9	168	126	95	2850	(*a*) Raised
		19·4	12·4	7·0	168	138	135	2400	(*b*) perfusion pressure
		19·4	12·3	7·1	170	156	185	2390	Control
				Both vagi cut					
		20·2	12·6	7·6	154	172	195	2025	Control
		20·1	11·8	8·3	171	166	105	2060	(*a*) Raised
		20·1	11·8	8·3	161	170	115	2060	(*b*) perfusion pressure
		20·0	11·7	8·3	171	178	200	2060	Control
12 (C)	9·1	17·25	10·75	6·5	88	130	135	1370	Control
		17·5	11·5	6·0	110	118	150	1850	Control
		17·25	11·1	6·15	97	88	80	1570	Raised perfusion pressure
		17·0	11·0	6·0	91	126	145	1510	Control
				Both vagi cut					
		17·6	11·2	6·4	105	120	145	1640	Control
		17·4	11·0	6·4	?	110	60	?	Raised perfusion pressure
		17·2	11·0	6·2	110	126	150	1770	Control

TABLE 2 (*cont.*)

Exp.	Wt. (kg.)	O_2 content: Arterial (ml./100 ml. blood)	O_2 content: Venous (ml./100 ml. blood)	A.-v. O_2 diff.	O_2 usage (ml./min.)	Heart rate/min.	B.P. (mm. Hg)	Cardiac output (ml./min.)	Conditions
13 (C)	14·5	12·5	5·5	7·0	97	162	165	1380	Control
		—	5·5	7·0	100	126	95	1430	Raised perfusion pressure
		12·65	5·45	7·2	100	168	160	1370	Control
		12·8	6·25	6·55	99	164	170	1500	Control
		12·75	5·75	7·0	99	134	100	1410	Raised perfusion pressure
		—	5·75	7·0	99	168	165	1410	Control
		12·8	5·8	7·0	105	176	165	1500	Control
		—	5·7	7·1	100	152	105	1410	Raised perfusion pressure
14 (N)	16·7	20·5	16·4	4·1	95	182	200	2320	Control
		—	16·5	4·0	96	148	100	2400	Raised perfusion pressure
		20·4	16·1	4·3	98	178	220	2280	Control
		—	16·0	4·4	95	156	150	2160	Raised perfusion pressure
		20·4	16·0	4·4	96·5	190	205	2190	Control
		—	15·8	4·6	93·5	156	115	2030	Raised perfusion pressure
		20·0	15·35	4·65	93·0	184	195	2000	Control
15 (C)	13·0	21·0	15·4	5·6	61	176	190	1080	Control
		20·4	10·8	9·6	60	134	95	630	(*a*) Raised
		20·15	15·25	4·9	60	168	140	1200	(*b*) perfusion pressure
		20·0	14·5	5·5	60	174	200	1100	Control
				Both vagi cut		Interval 40 min.			
		21·0	11·1	9·9	63	188	160	635	Control
		—	9·4	11·6	60	184	80	520	Raised perfusion pressure
		21·0	11·2	9·8	63	196	180	640	Control

(C) = Animal under chloralose anaesthesia.
(N) = Animal under nembutal anaesthesia.

TABLE 3. Effect of electrical stimulation of the central end of the carotid sinus nerve on cardiac output in dogs

Exp.	Wt. (kg.)	O_2 content: Arterial (ml./100 ml. blood)	O_2 content: Venous (ml./100 ml. blood)	A.-v. O_2 diff.	O_2 usage (ml./min.)	Cardiac output (ml./min.)	Conditions
16 (N)	12·5	21·5	16·5	5·0	82	1640	Control
		21·4	16·7	4·7	78	1660	(*a*) L. carotid sinus
		21·4	14·5	6·9	100	1450	(*b*) nerve stimulation
		21·4	15·4	6·0	87	1450	Control
				Both vagi cut			
		21·4	15·0	6·4	80	1250	Control
		21·4	14·5	6·9	80	1160	(*a*) L. carotid sinus
		21·4	14·5	6·9	80	1160	(*b*) nerve stimulation
		21·4	13·9	7·5	82	1090	Control
17 (N)	12·0	20·8	16·6	4·2	84	2000	Control
		20·8	16·2	4·6	82	1785	(*a*) L. carotid sinus
		20·8	16·2	4·6	82	1785	(*b*) nerve stimulation
		20·8	16·2	4·6	82	1785	Control
				Both vagi cut			
		20·8	16·2	4·6	72	1565	Control
		20·7	15·8	4·9	62	1265	(*a*) L. carotid sinus
		20·8	15·8	5·0	62	1240	(*b*) nerve stimulation
		20·8	15·5	5·3	80	1510	Control

(N) = Animal under nembutal anaesthesia.

(1) *Methods employing the Stewart technique.* Holt *et al.* (1946), using the dye T1824, found that stimulation of the carotid sinus nerve trunk caused an average fall in cardiac output of 7% (range −23 to +34% in six experiments).

(2) *Methods employing stromuhr or cardiometric measurement.* Tigerstedt (1908), Jarisch & Ludwig (1926), Gollwitzer-Meier & Schulte (1931), Moe *et al.* (1948) used one or other of these methods.

It is difficult to compare the results of these latter experiments with those obtained by methods which do not entail opening the animal's chest. The heart output in these cardiometric experiments is always far below that determined by the Fick method. The same criticism may therefore be levelled at the interpretations of results obtained with the cardiometer, as has been directed by Stead & Warren (1947) at interpretations based on results obtained by use of the heart-lung preparation.

(3) *Methods employing the Fick principle.* These have been reviewed by Charlier & Philippot (1947).

We are in agreement with their criticisms of the findings of Heymans *et al.* (1931) who used the rate of production of CO_2 and the v.-a. CO_2 difference in the Fick equation. Charlier & Philippot stressed the need for obtaining control cardiac output results which are of the order of 150–160 ml. output/kg. body wt.; it is perhaps more convenient to express cardiac output in terms of 'cardiac index', l./min./sq.m. (Grollman, 1932).

In Table 4 are shown the results from a number of determinations by different authors of the cardiac index of dogs. Wiggers (1944) used a modification of the Stewart technique for cardiac output estimations. Hemingway & Neil (1945; unpubl.) gave the results of cardiac output determinations by the direct Fick method in 18 dogs. These experimental results are compared in Table 4 with those of Charlier & Philippot (1947), of de Vleeschhouwer *et al.* (1949) and of the present series. The figures of the present series are calculated from the control determinations of cardiac output.

TABLE 4. Cardiac index in dogs

Source	No. of exps.	Dog (wt./kg.)	Mean cardiac index (l./sq.m./min.)
Wiggers (1944)	42	10–31	2·81
Hemingway & Neil (1945)	18	6–25	2·66
Charlier & Philippot (1947)	18	6–23	3·06
de Vleeschhouwer *et al.* (1949)	20	7–35	1·54
Present series	18	7–25	2·88

This analysis suggests that the results of de Vleeschhouwer *et al.* (1949) are liable to the same criticism accorded to those obtained with the cardiometer. Otherwise there is good agreement. Nevertheless, despite the similarity between the mean cardiac index obtained by Charlier & Philippot and by us, further analysis shows differences between the experimental conditions of the animals (Table 5).

The mean pulmonary ventilation volume obtained in our experiments is in agreement with that calculated from results of Eckenhoff, Hafkenschiel, Foltz & Driver (1948), in which a mean pulmonary ventilation volume (l./kg. body wt.) of 0·10 was obtained in control conditions in eleven anaesthetized dogs. It would appear that Charlier & Philippot's animals were overbreathing. This is further substantiated by the mean percentage of CO_2 in the expired air of 2·55%, calculated from the values these authors give. In view of the respiratory overactivity, it is difficult to understand why the oxygen usage of

TABLE 5. Ventilation volume and oxygen usage

Source	Mean pulmonary ventilation (l./kg. body wt.)	Mean O_2 usage (ml./kg. body wt.)	Mean A.-V. O_2 diff. (ml./100 ml.)
Charlier & Philippot	0·23	5·37	3·40
Present series	0·10	7·30	5·40

their animals should be so low. Hemingway & Neil (1945, unpubl.) obtained a mean O_2 usage of 7·54 ml. O_2/kg. body wt. In their experiments animals under nembutal and chloralose anaesthesia were used, and O_2 usage was determined by means of closed circuit spirometry, the animals breathing pure O_2. In 15 of our animals these conditions were also observed, whereas Charlier & Philippot employed the open circuit method, the animals breathing room air. Though it is possible that displacement of the spirometer (1500 ml. capacity) entailed a greater respiratory effort and hence a larger O_2 usage, one would expect the pulmonary ventilation volume to be greater with the spirometer, which is not the case. It must be admitted, however, that the breathing of pure O_2 tends to diminish the pulmonary ventilation volume by lessening the carotid chemoreceptor drive to the respiratory centre (Euler & Liljestrand, 1942).

Results of carotid occlusion. Charlier & Philippot record a mean rise of cardiac output of 54·6% (range 17·5–77·9%) in animals with intact vagi, and a mean rise of 60·9% (range 41·1–85·7%) in bilaterally vagotomized dogs. We obtained no evidence that significant changes in cardiac output occur during carotid occlusion, whether the experiment is performed in dogs with intact or cut vagi. Analysis of the techniques employed in these two series may perhaps explain the disagreement in the respective findings. Thus Charlier & Philippot, having taken one sample of expired air during control conditions, assumed that ventilation volume and O_2 usage remained the same for any other 'control' period. One determination of arterial O_2 content was likewise performed in the initial control period, and was assumed to be typical of arterial saturation during the period of occlusion and in the post-occlusion control period. It is possible that this latter assumption is less dangerous than the first, as the animals were breathing room air, and such differences as may be caused by increased respiratory activity would cause only very minor changes of the

amount of O_2 dissolved in the blood. However, an examination of the results presented in this paper, shows that whereas O_2 usage remains fairly steady in many animals over a considerable experimental period, there are several instances of a marked rise occurring during the experiment, so that the post-occlusion values are considerably in excess of the first control readings. But the main reason for the discrepancies shown in the two series of results lies in the great alteration in the oxygen content of the mixed venous blood which occurred during the period of carotid occlusion in all animals used by Charlier & Philippot, and which we did not observe.

Calculation of total peripheral resistance from the results of Charlier & Philippot reveals that the majority of their animals showed a fall in total peripheral resistance during carotid occlusion. Thus, of the eight animals considered in their first paper, five had a diminution of total peripheral resistance (31·5, 17·6, 23·3, 11·7 and 2·0%) and three showed a slight increase (1·3, 4·1 and 1·5%). This is surprising in view of the vasoconstriction shown to occur in these circumstances by the vessels of the skin and abdominal organs (Heymans, 1929; Malméjac, 1934). To the reduction of flow through these areas must be added that due to mechanical obstruction of the carotid circulation. In order to explain an increase in the total blood flow per minute (cardiac output) one must postulate an increase of muscle blood flow sufficient not only to offset but to outweigh the diminution of flow in skin and splanchnic region. There is, however, no evidence that carotid occlusion increases muscle blood flow. McDowall (1950) has recently shown the relative insensitivity of the muscle vessels in the skinned hind leg of the cat to reflex alteration of vasomotor activity by occlusion of the common carotid arteries. Although reflex liberation of adrenaline may cause some vasodilatation in the muscles and the increased activity of sympathetic vasodilator nerves may contribute to this dilatation (Bülbring & Burn, 1935), the action of nor-adrenaline (Folkow & Uvnäs, 1949) and of sympathetic vasoconstrictor nerves may offset these effects. Some increase in muscle blood flow must be postulated to explain the maintenance of cardiac output in the present experiments during the period of carotid occlusion, but it is unlikely that it was as large as may be implied from the experiments of Charlier & Philippot.

With respect to the venous side of the circulation there is likely to be an immediate but transient increase of venous return from the skin and splanchnic areas as blood is forced out of these regions by vasoconstriction. Similarly, constriction of the great veins (Gollwitzer-Meier & Schulte, 1931) drives blood towards the heart. This initial increase in venous return might contribute to the mechanism whereby the heart overcomes the increased arterial pressure. It represents, however, only a transitory phase, and the absolute venous return in the subsequent period can only be guessed. It is clear that return from the skin and splanchnic areas is diminished for the remainder of the occlusion

period; whether this decrease is offset by an increased return from the muscles is largely conjectural. The increased degree of venoconstriction which is sustained during carotid occlusion has two effects—causing both a diminution of capacity of the venous reservoir and an increase of resistance to venous flow back to the heart.

Landis & Hortenstine (1950) have pointed out that the capacity changes in the venous reservoir probably have a greater effect on venous return than changes in resistance to flow. With this view we are in general agreement. However, Landis & Hortenstine quote Fleisch (1931), who 'observed increased venous return to the heart when the pressure in the carotid sinus was reduced, and decreased venous return when pressure in the carotid sinus was increased'. Fleisch (1931), however, showed only that carotid occlusion decreased flow in a perfused section of the colic vein in cats and dogs, and the statement, quoted above, is merely an unjustifiable generalization made on the basis of his experiments.

The increase in right atrial pressure attendant upon carotid occlusion led Charlier & Philippot to argue that this represents an increased venous filling pressure, which is followed in turn by an increased left ventricular output as found in the Starling heart-lung preparation. Two criticisms may be made of their contentions. First, there is no evidence that the rise of right atrial pressure is indeed representative of an increased venous return. Right atrial pressure is equally dependent upon the ability of the heart to move blood from the venous to the arterial side. It is possible that increased resistance to left ventricular ejection due to the rise of systemic arterial pressure may cause back pressure effects upon the right side of the heart. Further, there has been much evidence recently which suggests that the relationship between the rate of venous return and right atrial pressure is not as obvious in the intact circulation as it is in the heart-lung preparation. Thus, Stead & Warren (1947) were unable to find any rise of right atrial pressure on releasing an arterio-venous shunt which had been temporarily occluded by external pressure, despite the fact that such release caused a marked rise of cardiac output. Cohen, Edholm, Howarth, McMichael & Sharpey-Schafer (1948), whilst finding some reduction of right atrial pressure on closing an arterio-venous shunt, pointed out that the reduction of cardiac output attending such a procedure was more closely related to changes in cardiac rate than to alteration of right atrial pressure. In any case, it seems unwise to attempt to equate changes in the minute output of the left ventricle directly to changes in the pressure in the right atrium.

Effects of sinus nerve stimulation. Holt *et al.* (1946) determined the effect of carotid sinus nerve stimulation upon the cardiac output. They found a mean reduction of 7% in cardiac output in six experiments on four animals (range −23 to +34%). The mean reduction of arterial blood pressure was 46·8%. Despite their own experimental findings, however, they proceed to calculate

that 67% of the fall of blood pressure was due to a reduction of cardiac output. This calculation is based on changes of cardiac output determined during the opening of an arterio-venous shunt; they regarded the opening of an arterio-venous shunt as exemplifying a pure reduction of total peripheral resistance. By substituting cardiac output and blood pressure changes corresponding to the alterations of total peripheral resistance obtained in the shunt experiments, for alterations of total peripheral resistance calculated from the results of sinus nerve stimulation, they arrived at the conclusion stated above. It has to be emphasized, however, that an arterio-venous shunt does not merely represent an alteration in total peripheral resistance. There is an accompanying increase in venous return, and particularly an augmentation in the velocity of venous flow. It is unjustifiable to analyse haemodynamic changes occurring in one type of experiment by using results obtained in another.

Effects of increased perfusion pressure in the isolated carotid sinus. The constancy of cardiac output during periods of raised intrasinusal pressure may be explained on the following lines. The fall of systemic pressure due to peripheral vasodilatation will reduce the resistance to systolic ejection and, provided the venous return be sufficient to permit it, a greater stroke volume will be attained. On the other hand, increased capacity of the venous reservoirs resulting from reflex vasodilatation will tend to reduce the venous return to the heart. The actual cardiac output per minute is therefore the resultant of these conflicting factors. In conditions of profound cardiac slowing due to the effects of stimulation of the carotid sinus nerve fibres on the cardio-inhibitory centre, there might well be a diminution of cardiac output. In our experiments, slowing of the heart has not been considerable; this is to be expected in vagotomized animals—in animals with intact vagi the absence of marked slowing may be related to the buffer effects of the aortic nerves (Winder, 1937).

In conclusion, it may be conceded that sudden changes in sinus baroreceptor stimulation may well exert transient effects on cardiac output. These are only capable of measurement by a technique which enables beat-to-beat determination of output such as that of Hamilton & Remington (1947, 1948). The direct Fick procedure is ill-adapted to the study of such changes. Indeed, in this procedure, initial sampling of mixed venous blood removed early in the period of arterial hypertension caused by carotid occlusion may show an oxygen content unrepresentative of that in the pulmonary artery. Shore, Holt & Knoefel (1945) have shown that streaming effects occur in the right atrium due to incomplete mixing of blood from the superior and inferior venae cavae; in the circumstances of carotid occlusion, veno-constrictive changes in the splanchnic area may well cause the return of a considerable quantity of blood of low oxygen content from this region wherein it had previously stagnated. It must be stressed that such a contingency has been guarded against by careful positioning of the catheter in these experiments. Thus, in many instances, the

tip of the catheter has been within the cavity of the right ventricle; in no experiment has the catheter tip been higher than the orifice of the tricuspid valve.

SUMMARY

1. Cardiac output was measured in dogs under nembutal or chloralose anaesthesia by applying the Fick principle to oxygen consumption. The effect of the following conditions on cardiac output was studied: (*a*) occlusion of both common carotid arteries, (*b*) electrical stimulation of the carotid sinus nerve, (*c*) pulsatile perfusion of one or both carotid sinus preparations isolated from the rest of the circulation.

2. In none of these experimental conditions was any substantial alteration in cardiac output observed. Such changes as did occur could be explained on the basis of spontaneous variations in the state of the experimental animal: they could not be attributed to the immediate experimental procedures employed.

3. Some observations and deductions made by other authors conflicting with those presented in this paper are critically examined.

4. Haemodynamic factors responsible for the relative stability of cardiac output under the experimental conditions used are discussed.

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