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CAROTID SINUS REFLEXES. INFLUENCE OF CENTRAL BLOOD-PRESSURE AND BLOOD SUPPLY ON RESPIRATORY AND VASO-MOTOR CENTRES[1].

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THE reflex and tonic influences of the pulmonary vagus on the activity of the respiratory centre is a well-known and generally accepted fact [Hering and Breuer, 1868; Head, 1889; Haldane, 1922; J. F. and C. Heymans, 1926; C. Heymans, 1928; Hoffmann and Keller, 1929; Hess, 1931; Anrep and Adli Samaan, 1932]. It has been shown by J. F. and C. Heymans [1926] and C. Heymans [1928, 1929 *a*, *b*] that the vago-depressor nerves in dogs are also the centripetal paths of respiratory reflexes in relation with the cardio-aortic blood-pressure; an increase of the arterial pressure in the region of the left ventricle and the aortic arch producing a reflex inhibition of the respiratory centre, while a lowering of blood-pressure in those districts provokes a reflex hyperpnœa. The normal arterial pressure in the left heart and aortic arch maintains a reflex tonus on respiration. The experiments of Moissejeff [1927], C. Heymans [1928, 1929 *a*, *b*], Florey, Marvin and Drury [1928], Bouckaert and C. Heymans [1930], C. Heymans, Bouckaert and Dautrebande [1932], Wright [1930], Koch and Mark [1931], Gollwitzer-Meier and Schulte [1931], and Schmidt [1932] have demonstrated that the pressure in the carotid sinus, the functional homologue of the aortic area, also reflexly regulates the activity of the respiratory centre, by way of the carotid sinus nerves. An increase of blood-pressure in the carotid sinus produces a reflex inhibition of the respiration, or even apnea; a decrease of blood-pressure in the same vascular area produces a reflex hyperpnœa.

[1] Preliminary reports: *C. R. Soc. Biol.*, Paris, 1932, **110**, 996; **111**, 145. *Sunti delle Comm. Scientif. Congr. intern. Fisiologia*, 1932, p. 117.

The rôle and the importance of the cerebral blood flow in the regulation of respiration and circulation have been emphasized by numerous workers [François-Franck, 1877; Marey, 1881; Hédon, 1910; Chabrol, 1922; Gesell, 1923; Roberts, 1924; Anrep and Starling, 1925; C. Heymans and Ladon, 1925; Gesell, 1929; C. F. Schmidt, 1928, 1929, 1932; C. Heymans, 1928; C. Heymans and Bouckaert, 1930; Wright, 1930; C. Heymans, Bouckaert and Dautrebande, 1931, 1932].

It is known that, in normal animals, occlusion of the common carotid arteries stimulates, while the reopening of the same arteries inhibits, the activity of the respiratory centre [Cooper, 1836; Kussmaul and Tenner, 1855; Hill, 1896; Lumsden, 1923; J. F. and C. Heymans, 1926; Gesell, 1929; Schmidt, 1929].

These facts were taken, especially by Gesell and Schmidt, as evidence that the respiratory centre is influenced and regulated directly by changes in the central blood-pressure and blood supply. The same theory of regulation by central blood-pressure and blood supply has been defended [François-Franck, 1877; Hédon, 1910; Chabrol, 1922; Anrep and Segall, 1926; Nash, 1926] for the regulation of the activity of the cardio-regulatory and vaso-motor centres.

Pagano [1900], however, showed that although the occlusion of the common carotids provokes a stimulation of the vaso-motor and cardio-accelerator centres, the same results do not follow after occlusion of the vertebral arteries and the efferent branches of the common carotids; he concluded that the regulation of the vaso-motor and cardio-regulatory centres is effected reflexly, rather than by a direct action on the centres.

Roberts [1924] concluded from his experiments that the respiratory centre is totally insensitive to diminution in its blood supply, until this diminution becomes extreme.

Numerous investigations have shown, by various experimental methods, that the changes in the activity of the respiratory centre [C. Heymans and Bouckaert, 1930; Koch and Mark 1931; C. Heymans, Bouckaert and Dautrebande, 1932], as well as the changes in the tonus and activity of the heart regulatory and vaso-motor centres [Hering, 1927; C. Heymans, 1928; Florey, Marvin and Drury, 1928; C. Heymans, 1929*a*; C. Heymans and Bouckaert, 1930; Wright, 1930; Koch, 1931; C. Heymans, Bouckaert and Dautrebande, 1931, 1932; C. Heymans, Bouckaert and Regniers, 1933] produced by the modifications of blood-pressure and blood flow in the cephalic arterial circulation are not due to changes in the central

blood-pressure, but to the blood-pressure reflexes arising in the carotid sinus. These experiments have shown, indeed, that in dogs the occlusion of neither the centrifugal branches of both carotid sinuses, nor the occlusion of the two vertebral arteries elicited any changes in the activity of the respiratory or cardio-regulating or vaso-motor centres. On the other hand, it has been shown that slight changes of blood-pressure in the carotid sinus produce definite reflex changes in the activity of the respiratory and circulatory centres.

In spite of these clear experimental proofs, obtained by several experimental methods on animals in good general circulatory and respiratory conditions, the theories of direct regulation of respiratory and circulatory centres by changes of blood-pressure and blood supply are still maintained and defended by several workers. Thus, Anrep and Segall [1926], Nash [1926] and Volhard [1930] concluded that the cephalic control of the heart rate by blood-pressure changes does not depend exclusively on the carotid sinus reflexes, but also upon another more central effect. Raab [1932] also says that a slight decrease of the cerebral blood supply directly stimulates the vaso-motor centre. Recently, Schmidt [1932] has reinvestigated the problem of the effect of changes of cephalic blood-pressure and blood flow on the activity of the respiratory centre, and although he generally confirms our observations and conclusions concerning the effects of carotid sinus reflexes on the respiratory centre, he also concludes from his experiments that the respiratory centre is directly affected by alterations in its blood supply, and that the respiratory effects of alterations in cephalic blood-pressure may be due either to carotid sinus reflexes or to alterations in central blood flow, or to both. Schmidt believes that influence of change in the central blood flow is quite as sensitive as, and decidedly more powerful than the reflex influence, but he makes the reservation that the sensitivity of the central mechanism is more variable than the reflex one.

Considering the importance of the problem for the physiology of respiration and circulation, and in order to submit our previous conclusions to a new and still more severe control, we have performed a new series of experiments with new methods, now to be described.

Experiments.

Method (Fig. 1). Dogs are anæsthetized with choralosane (orthochloralose, 0·8 g. pro kg. intravenous); this anæsthetic maintains a good respiration and a normal circulation. One carotid sinus is prepared following the technique of Moissejeff [1927]: the large efferent (centri-

fugal) branches of the carotid sinus are ligaturated, its innervation remains intact; thus the blood of this common carotid artery may perfuse the carotid sinus through the more minute efferent branches, and so the carotid sinus pressure may be changed by compression and decompression of the carotid artery which may be done without directly changing the central blood-pressure and blood flow. The carotid sinus of the other side is denervated, and after ligature of all the efferent branches of the carotid

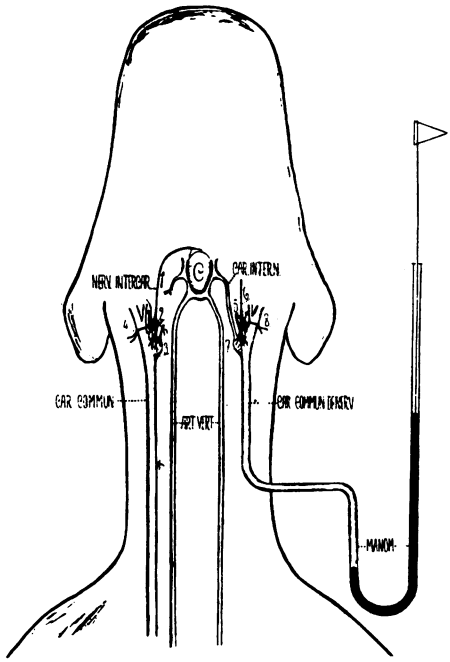

Fig. 1.

sinus except the internal carotid, the central end of the common carotid artery is connected with a mercury manometer, in order to measure the pressure in the circle of Willis, *i.e.* the intra-central arterial blood-pressure, following the technique of Hürthle [1889]. The two vertebral arteries are isolated, the general arterial blood-pressure is registered in the femoral artery, and the respiratory plethysmogram is registered. With this method it is possible to modify the internal carotid sinus pressure, or to clamp the vertebral arteries, and at the same time to record the changes in central blood-pressure, in general arterial blood-pressure and in the respiratory movements.

Results.

(1) *Effects of occlusion and release of the vertebral arteries upon the central blood-pressure, and upon the activity of the respiratory and vaso-motor centres.*

The curves of Fig. 2 A show that in a dog prepared by the method described above, the occlusion of both vertebral arteries provokes an immediate and abrupt fall of the central blood-pressure from 80 to 40 mm. Hg; but the general blood-pressure, and the activity of the vaso-motor and the respiratory centres are unaffected, although the central blood-pressure remains low throughout the vertebral occlusion, during which time the central circulation is only provided by the spinal arteries.

These experiments demonstrate that the occlusion of the vertebral arteries does not cause general hypertension (in agreement with Pagano [1900], C. Heymans [1928], Florey, Marvin and Drury [1928]) or hyperpnœa, although the central blood-pressure is very much reduced; further, that the release of the same arteries does not influence the vaso-motor or respiratory centres, although the central blood-pressure is now much increased.

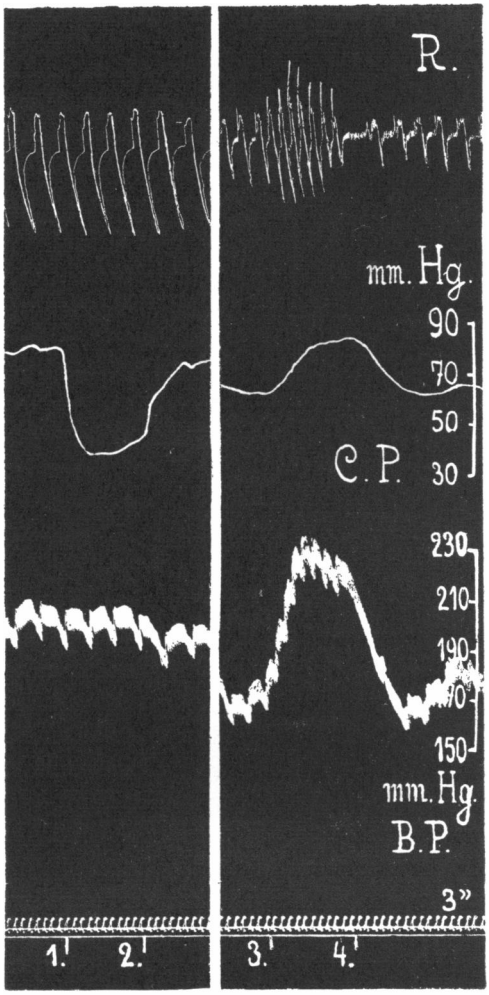

Fig. 2. Dog prepared following the method of Fig. 1. Upper record, pneumogram (*R*). Middle record, central blood-pressure (*C.P.*). Lower record, general arterial blood-pressure (*B.P.*). At 1, occlusion of the two vertebral arteries. At 2, re-opening of the two vertebral arteries. At 3, lowered pressure in the circulatory isolated carotid sinus. At 4, normal pressure restored inside the isolated carotid sinus.

Schmidt [1932] has recently confirmed this observation; he has also measured the average decrease of central blood flow, and found a reduction of 25 p.c. in the cerebral flow on clamping the vertebral arteries in dogs. Schmidt believes that the absence of hyperpnœa under these conditions may merely mean that the anæmia so produced was not great enough. We believe, if a reduction of cerebral blood flow must be greater than 25 p.c. before the respiratory centre responds to it, that such a mechanism has no proper physiological signification or importance as a means of central regulation of the activity of the respiratory centre. The same restriction applies to the direct sensitivity of the vaso-motor centre to changes of central blood-pressure and blood flow.

In a second group of experiments we have re-investigated the influences of carotid sinus pressure upon the central blood-pressure and blood flow and upon the activity of the medullary centres.

(2) *Effects of carotid sinus pressure upon the central blood-pressure, cerebral blood flow, and activity of the respiratory and vaso-motor centres.*

(*a*) *Carotid sinus pressure and central blood-pressure.*

The same method (Fig. 1) was used, and a typical result is shown in Fig. 2 B. By clamping the common carotid, the pressure in the isolated but innervated carotid sinus is lowered; the blood inside the carotid sinus indeed escapes through the small arterial branches which were not ligatured, but the occlusion of this common carotid has no direct influence on the central blood supply. The curves show that the decrease of pressure in the isolated carotid sinus produces an immediate reflex general arterial hypertension and a marked hyperpnœa, although the central blood-pressure is at the same time very much increased from 65 to 88 mm. Hg. The increase of carotid sinus pressure at 4, Fig. 2 B, produces an immediate reflex fall of general blood-pressure with a marked decrease of central blood-pressure and an inhibition of the respiratory centre.

The results of another typical experiment are shown in the curves of Fig. 3. Here, lowering of the central pressure by clamping the two vertebral arteries (1–2, Fig. 3) has no effect on general circulation or respiration, whereas lowering of the carotid sinus pressure (3–4, Fig. 3) provokes a reflex general hypertension and a stimulation of the respiratory centre, in spite of an attendant increase in the central blood-pressure from 55 to 75 mm. Hg. This reflex stimulation of vaso-motor and respiratory centres persists during the 7 min. of low carotid sinus pressure and high central pressure; the return to normal carotid sinus pressure at 4, Fig. 3, provokes

an immediate reflex inhibition of the vaso-tonic and respiratory centres, together with a fall of the central pressure. These experiments clearly demonstrate that a considerable reduction of the central blood-pressure by clamping the vertebral arteries has no direct stimulating effect on the respiratory and vaso-motor centres, while on the contrary a decrease of the carotid sinus pressure produces reflex stimulation of the vaso-motor and respiratory centres, although the central blood-pressure is thereby increased.

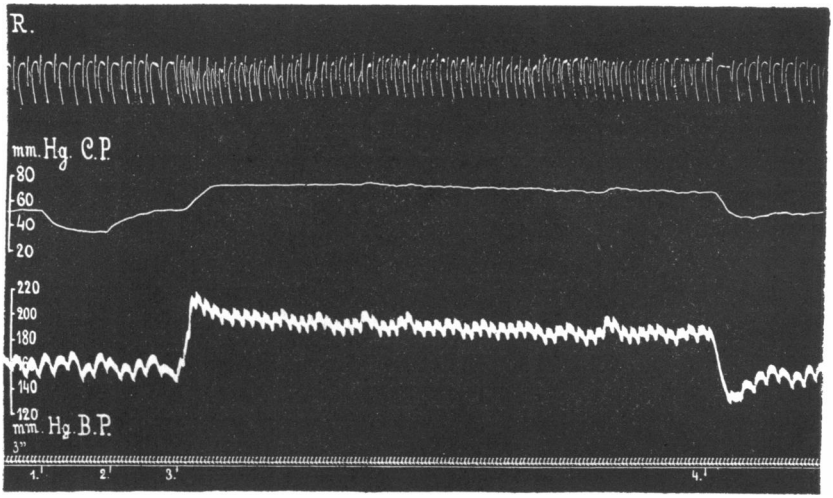

Fig. 3. Dog prepared following the method of Fig. 1. Upper record, pneumogram (*R*). Middle record, central arterial blood-pressure (*C.P.*). Lower record, general arterial blood-pressure (*B.P.*). At 1, occlusion of the two vertebral arteries. At 2, reopening of the two vertebral arteries. At 3, low pressure in the isolated but innervated carotid sinus. At 4, normal pressure in the carotid sinus.

(*b*) *Carotid sinus pressure, central blood flow and cerebral vaso-motor tonus.*

The influence of the carotid sinus reflexes upon the vascular tonus in the centres themselves, and upon the cerebral blood flow, has been further investigated.

The problem of the regulation of the cerebral blood flow, and the question whether the cerebral blood vessels possess an active vaso-motor innervation, or whether they, and hence the cerebral blood flow, are, on the contrary, passive and dependent only upon the general blood-pressure, have long been the subjects for discussion and investigation. Nothnagel [1867], Schuller [1874], Vulpian [1875], Cavazzani [1893], Wie-

chowski [1902, 1905], Muller and Siebeck [1907], Kurusu [1928], Forbes [1928], Forbes and Wolff [1928], conclude in favour of the existence of cerebral vaso-motor nerves; on the contrary, Schulz [1866], Riegel and Jolly [1871], De Boeck and Verhoogen [1890], Roy and Sherrington [1890], Bayliss, Hill and Gulland [1895], Hill and Macleod [1900], Florey [1925] and others do not accept the existence of an autonomic vaso-motor cerebral regulation. According to Cobb [1929] it has been shown that, physiologically, pial vessels may constrict or dilate in response to appropriate stimulation, but Hill's statement, strictly speaking, still holds: "There is no evidence of a causation of cerebral anæmia by spasm of the cerebral arteries."

Our previous experiments [1928] have shown that the blood vessels arising from the external carotid artery, the cephalic peripheral arteries, react to the carotid sinus vaso-motor reflexes in the same way as the muscular and splanchnic arteries. The same fact has been shown by Anrep and Segall [1926], and ourselves [1928], for the aortic-depressor reflexes.

Rein (1929, 1931) has shown that clamping of one common carotid artery produces a definite increase of blood flow through the other common carotid. He attributes this change of cephalic blood flow to a reflex vaso-dilatation in the cephalic, cerebral, circulation, caused by the low carotid sinus pressure. But several factors of mechanical and circulatory origin could be involved in this change of one carotid blood flow after cutting off the blood flow in the other common carotid.

Keller [1930] concludes from his experiments that the blood flow through the internal carotid is in general "druckpassiv" in dogs, but he also accepts an autonomic peripheral regulation of the cerebral vessels and the cerebral blood flow.

It was found by Gollwitzer-Meier and Schulte [1932] that on raising the arterial pressure in the isolated carotid sinus, the reflex fall of general arterial pressure is associated with an initial constriction and a secondary dilatation of the arteries of the retina. The constriction is accepted to be a passive effect and the dilatation an active reflex vaso-motor reaction. It is thought that the vessels of the brain participate actively to the general reflex regulation of the blood-pressure in a similar manner. Several objections may be made to these experiments and conclusions, and we therefore think that the question of the influence of the carotid sinus reflexes on the cerebral vessels and especially on the cerebral blood flow needs to be re-examined.

I. Carotid sinus pressure and central blood flow.

Method (Fig. 4). Dogs were anæsthetized with chloralosane, one carotid sinus was isolated from the circulation, its innervation remaining intact; the pressure may be modified artificially in this isolated but

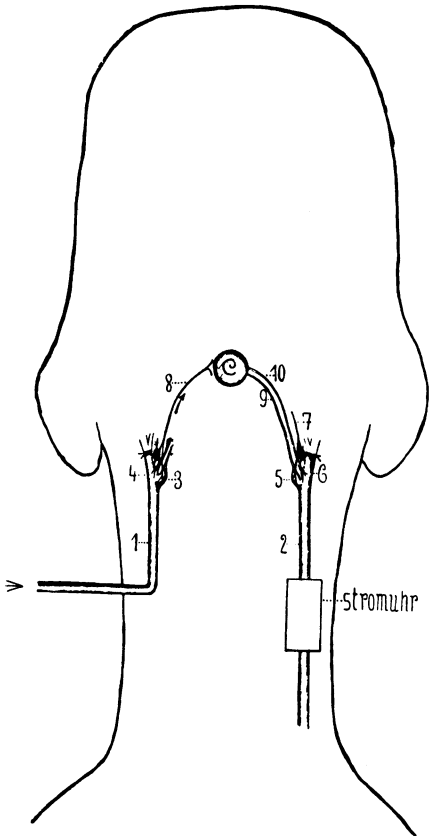

Fig. 4. 1–2, common carotid arteries. 3, ligaturated internal carotid artery with normal carotid sinus innervation. 4, ligaturated external carotid artery. 5, denervated carotid sinus. 6, ligaturated external carotid artery. 7, carotid sinus nerve cut. 8, carotid sinus nerve with normal central connections. 9–10, internal carotid and occipital arteries connecting the denervated carotid sinus and the common carotid blood stream with the central nervous system.

innervated carotid sinus (technique of Moissejeff [1927]. The carotid sinus on the other side was denervated and the external carotid artery ligatured, the blood flow in this common carotid artery (internal carotid

and occipital artery supplying the cerebral circulation), and in a femoral artery, was measured by means of a mechanical Stromuhr of Weese [1932], or by a thermoelectric Stromuhr[1] of Rein [1931]. The general blood-pressure and the heart rate of the dog were measured in the femoral artery, the respiration of the animal is also registered.

The results of a typical experiment are shown in the following table:

Carotid sinus pressure	General arterial blood-pressure	Central blood flow per min. (one carotid)	Respiratory rate per min.
165 mm. Hg	60 mm. Hg	200 c.c.	10
20 mm. Hg	180 mm. Hg	450 c.c.	20

Fig. 5 shows a schema of the results of several experiments; a lowering of pressure in the isolated innervated carotid sinus produces a reflex increase of the tonus of the vaso-constrictor centre, with increase of femoral arterial blood-pressure and heart acceleration, but at the same time, one observes a decrease in the femoral blood flow and a considerable increase in the central blood flow and a stimulation of the respiratory centre. Conversely, an increase of the pressure in the isolated innervated carotid sinus brings about a reflex inhibition of the activity of the vaso-constrictor and respiratory centres, although the central blood supply is decreased.

These experiments thus demonstrate that a low carotid sinus pressure produces a reflex increase of the activity of the vaso-motor, cardio-acceleratory and respiratory centres, although at the same time not only the central blood-pressure but also the central blood supply is increased. These experimental facts clearly show once more that the activities of the vaso-motor, cardio-regulatory and respiratory centres are not regulated and influenced directly by the central blood-pressure and blood supply (theories of Gesell, Schmidt and Raab) but indirectly by the reflexes of the carotid sinus, especially by the carotid sinus pressure.

The central blood flow is dependent on the general arterial pressure, the cerebral and medullary blood vessels not participating actively in the general vaso-motor reflex regulation of the circulation, *i.e.* the blood vessels of the central nervous system are "passive." The carotid sinuses are the main reflex regulatory vascular zones for the central blood-pressure and the cerebral blood flow.

In case of a fall in the arterial blood-pressure, the heart frequency, the

[1] The experiments with the Thermostromuhr were performed in the Physiological Institute of Prof. A. K. Noyons, at Utrecht. We wish to express to Prof. Noyons our best thanks.

arterial and venous vaso-motor tonus, the adrenal secretion and the respiration are stimulated and increased by way of the aortic and carotid sinus reflexes; the arterial and venous vaso-motor tonus is increased in the peripheral and splanchnic areas and the blood flow in these areas

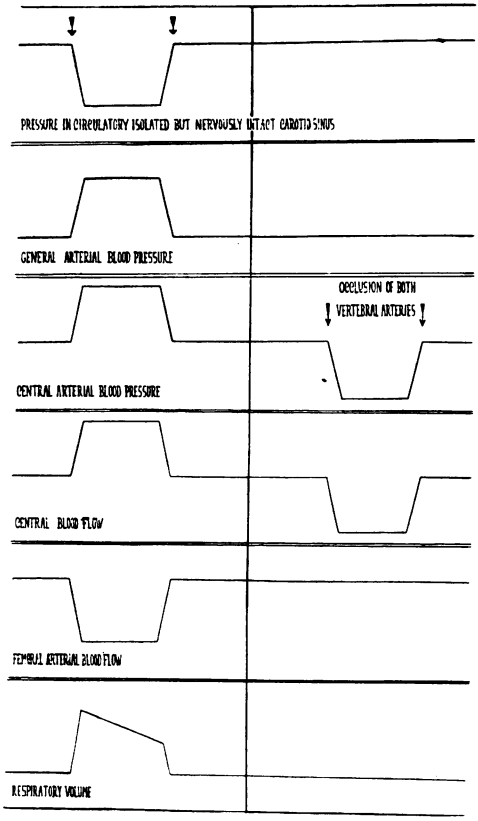

Fig. 5. Influence of the central blood-pressure and the carotid sinus pressure on the general blood-pressure, the central arterial blood-pressure, the central arterial blood flow, the femoral arterial blood flow, the respiratory volume. Dogs prepared following the method of Fig. 4. Up, increase. Down, decrease.

is diminished [C. Heymans, 1929*a*; Rein, 1931], but the blood flow is increased, with the increase of the general blood-pressure, in the intra-central arteries; the arterial blood is thus deflected from the peripheral and splanchnic areas to the central nervous system. In case of an increase of the pressure in the aortic and carotid sinus areas the opposite reactions occur.

II. Carotid sinus reflexes and cerebral vaso-motor tonus.

In order to test our conclusions that the cerebral vessels do not actively participate in the general vaso-motor reflex regulation of the circulation, we have instituted pharmacological investigations to compare the state of the cerebral with that of the muscular vessels during the establishment of carotid sinus vaso-motor reflexes[1].

Method. In dogs anæsthetized with orthochloralose, the cardio-aortic and carotid sinus nerves are cut in order to provoke a general arterial hypertension due especially to a strong vascular constrictor tonus; the vascular arterial tonus is measured in a leg by connecting the peripheral end of a femoral artery with a mercury manometer (method of Nolf), the vascular tonus of the cerebral arteries is measured by connecting a mercury manometer with the cephalic end of an internal carotid artery (method of Hürthle). The general blood-pressure is measured in the central end of a femoral artery.

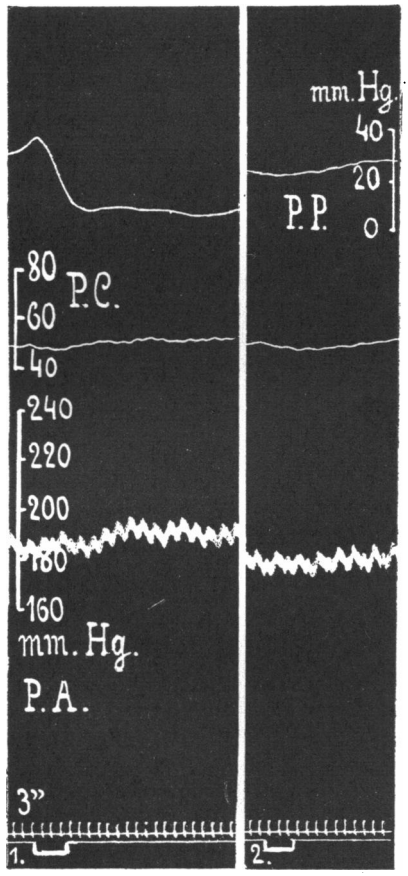

Fig. 6. Dog anæsthetized with chloralosane, aortic and carotid sinus nerves cut. Upper record, vaso-motor tonus of the leg. Middle record, vaso-motor tonus of the cerebral circulation. Lower record, general femoral blood-pressure. At 1, injection into the arterial circulation of the leg of 0·0001 mg. acetylcholine. At 2, injection into the arterial cerebral circulation of 0·002 mg. acetylcholine.

Experiments. The observations of a typical experiment are shown in the curves of Fig. 6. The dog has been prepared as described above. At 1 (Fig. 6) a dose of 0·0001 mg. acetylcholine is injected in the arterial blood stream of the leg, this injection produces an immediate and pronounced relaxation of the arterial peripheral vaso-motor tonus, with a return to the initial vascular tonus after a short

[1] Preliminary report, *C. R. Soc. Biol.*, Paris, 1933; **113**, 74.

time. At 2 (Fig. 6) a dose of 0·002 mg. acetylcholine is injected into the blood stream of an internal carotid artery towards the cerebral circulation and, as shown by the curve, no dilatation of the cerebral vessels occurs and also, as shown by the general blood-pressure, no change in the tonus of the vaso-constrictor centre. Similar experiments have been done with different doses of acetylcholine or histamine, and all clearly show that at low carotid sinus pressures, or after section of the carotid sinus and aortic nerves, the muscular and splanchnic vascular areas are contracted, while the cerebral vessels are, on the contrary, not contracted, but passively dilated by the increase of the general blood-pressure.

These pharmacological controls thus confirm our experimental observations upon the central blood flow changes during the carotid sinus vaso-motor reflexes. The cerebral blood vessels are not constricted by the increased vascular tonus in response to a low arterial blood-pressure in the vaso-sensitive vascular areas of the aorta and carotid sinus, and the centres of regulations of heart rate, and the vaso-motor and respiratory centres are not directly sensitive either to changes in central blood-pressure nor to any but extreme changes in central blood supply.

These observations and conclusions do not, however, exclude the possibility of direct sensitivity of the cardio-regulatory, the vaso-motor and respiratory centres to humoral chemical factors. It is established that acute central anoxæmia or asphyxia causes a direct stimulation of the vaso-constrictor centre, with increase of general blood-pressure, and that a respiratory hyperventilation causes, on the contrary, a fall of the general blood-pressure [Dale and Lovatt Evans, 1922]. The same phenomena occur in dogs with denervated aorta and carotid sinus. The section of the four "Blutdruckzügler" produces, by suppression of the reflex vaso-depressor and cardio-inhibitory tonus, a very considerable and chronic arterial hypertension with tachycardia; the vaso-constrictor and cardio-acceleratory tonus remains very high, although the central blood-pressure and the central blood supply are and remain increased, while the CO_2 content of the arterial blood is low [C. Heymans, Bouckaert and Dautrebande, 1931]. But if the arterial CO_2 content is still further decreased, *e.g.* by an excessive artificial pulmonary ventilation, the central vaso-constrictor tonus under these added pathological conditions is now decreased and the general blood-pressure falls (Fig. 6).

We may conclude that the vaso-motor centre maintains a state of vaso-constrictor tonus in consequence of the arterial CO_2 content, but that this tone is mainly depressed and regulated reflexly by the arterial blood-pressure and not directly by the central blood-pressure nor by the

central blood supply; and further, that only very low cerebral pressure and extreme decreases of cerebral blood flow (acute anoxæmia or asphyxia) may directly stimulate the vaso-tonic centres, while a considerable decrease of the CO_2 content of the arterial blood does diminish the tonic activity of the vaso-motor centre.

The experiments described in a recent paper [C. Heymans, Bouckaert and Dautrebande, 1931] have shown that, in agreement with

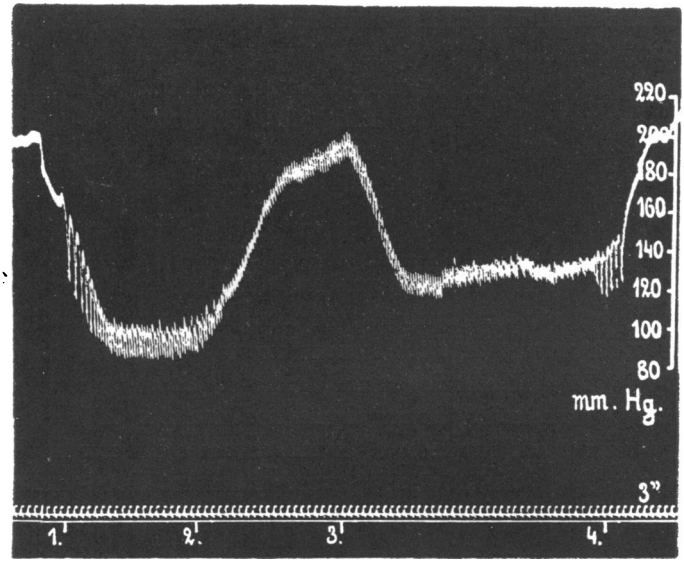

Fig. 7. Dog, anæsthetized with chloralosane; cardio-aortic and carotid sinus nerves cut. Curve of the general femoral blood-pressure. At 1, pulmonary artificial hyperventilation with air. At 2, pulmonary artificial ventilation with air and CO_2. At 3, pulmonary artificial hyperventilation with air. At 4, artificial respiration stopped.

Roberts [1924], anoxæmia has no, or very little, direct stimulatory effect on the respiratory centre; it has also been shown that the respiratory response of the animals to CO_2 inhalation is diminished after denervation of the aorta and carotid sinus. These facts were confirmed recently by the experiments of Schmidt [1932], Selladurai and Wright [1932]. But the respiratory centre certainly is more directly sensitive to the arterial CO_2 content than is the vaso-motor centre. Our experiments show, indeed, that the decrease of central blood-pressure and blood supply, produced by the occlusion of the vertebral arteries or by the occlusion of the efferent branches of the common carotid arteries or

by the occlusion of the carotid arteries after carotid sinus denervation, does not provoke a direct stimulation of the respiratory centre; and on the other hand that the decrease of arterial pressure in the aortic arch or in the carotid sinus does provoke a reflex stimulation of the respiratory centre; these same experiments further show that the reflex changes of respiratory activity, produced by the changes in carotid sinus or aorta pressure, are counteracted after a short time by the humoral factors resulting from the pulmonary hyperventilation. Hence, while the arterial blood-pressure, the tonus of the vaso-motor centre, of the animals remains high during low carotid sinus and aorta pressure or after denervation of the aorta and carotid sinus, the hyperpnœa does not persist.

It may thus be said that the arterial blood-pressure regulates the activity of the respiratory centre especially through the aortic and carotid sinus reflexes; but that the chemical humoral factors have also a reflex as well as an important central regulatory effect on lung ventilation.

Summary.

1. In dogs, the low cerebral blood-pressure, and the reduction of cerebral blood supply produced by occlusion of the efferent branches of the common carotids, by the occlusion of the vertebral arteries, or by the occlusion of the denervated common carotid arteries, do not directly stimulate the vaso-motor, cardio-regulatory, nor the respiratory centres.

2. At low carotid sinus pressure, the vaso-tonic and respiratory centres are stimulated reflexly by way of the carotid sinus nerves, although the cerebral pressure and the cerebral blood flow are both increased by these vaso-motor reflexes.

Conversely, at high carotid sinus pressure, the vaso-tonic and respiratory centres are depressed by the carotid sinus reflexes, although the cerebral blood-pressure and blood supply are at the same time decreased by these circulatory reflexes.

3. The vaso-motor, cardio-regulatory, and respiratory centres are not directly sensitive to the physio-pathological changes in cerebral blood-pressure and in cerebral blood supply, unless these are very extreme.

4. The cerebral blood supply is passively dependent on the general and the cephalic arterial pressure, which is regulated by the aorta and carotid sinus reflexes. In case of decrease of cephalic arterial pressure the blood is deviated by means of the carotid sinus reflexes from the peripheral and splanchnic areas to the cephalic circulation. Conversely, in case of arterial hypertension, the carotid sinus reflexes cause blood to be deviated from the encephalic circulation to the peripheral and splanchnic areas.

5. The arteries in the central nervous system do not participate actively in the "general" reflex regulation of the blood-pressure.

6. The tonus of the arterial vaso-constrictor centre, which is normally in a state of reflex inhibition because of the normal blood-pressure acting on the nerve endings of the aortic and carotid sinus areas, is mainly maintained by the arterial CO_2 tension; this central vaso-constrictor tonus is reduced if the CO_2 content of the arterial blood is much decreased.

7. The respiratory centre is more directly sensitive than the vaso-motor centre, not to anoxæmia but to the CO_2 content of the arterial blood. By low carotid sinus and aorta pressure, or after section of the aorta and carotid sinus nerves, the general blood-pressure increases and remains chronically very high, although the cerebral blood-pressure and the cerebral blood flow are both subnormal, and the CO_2 content of the arterial blood low; but the activity of the respiratory centre which at first is also increased, returns progressively to normal, and later may sometimes be decreased.

8. For the regulation of the blood-pressure, the aorta and carotid sinus nerves are of predominant physiological importance. For the lung ventilation, the aorta and carotid sinus reflexes have also an important, though not so predominant a regulatory function.

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