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The part played by vascular presso- and chemo-receptors in respiratory control

Nobel Lecture, December 12, 1945

The physiology of respiratory control, of the adaptation of pulmonary gas exchanges to the energy requirements of the organism, remains a fundamental problem on which many research workers are engaged.

In this lecture I am privileged to describe contributions which my laboratory has made to the study of a number of physiological, physiopathological and pharmacological mechanisms which act on and control the functioning of the respiratory centre and thereby affect pulmonary ventilation and pulmonary gas exchanges.

It has been known for some time that variations in blood pressure affect respiration. An increase in blood pressure inhibits respiration and sudden marked hypertension may even produce apnea. We also know that hypotension increases respiration. It was generally believed that this interaction between blood pressure and respiration involved a direct action on the respiratory centre exerted by either the blood pressure or the rate of flow in the cerebral circulation. The experiments which I shall now describe suggest that this classical theory should be reconsidered and rejected.

Since 1924, together with my father J. F. Heymans, my first and best teacher, I have been engaged in research projects, using the following experimental technique (Fig. 1): the completely isolated head of a Dog B under chloralose anaesthesia is perfused from a similar Dog A by means of anastomoses between the two common carotids of Dog A and the cephalic extremities of the common carotids of Dog B, and between the external jugular veins of the head B and the corresponding jugular veins of Dog A. The isolated and perfused head of Dog B is connected to the trunk (kept alive by its own circulation and artificial respiration) by the vago-depressor nerves. The vascular anastomoses between the isolated head B and the donor animal A are established by using Payr cannulas (Fig. 2) which prevent coagulation at the point of anastomosis without making use of anti-coagulants. Under these experimental conditions, the cephalic and cerebral circulation of Dog B is entirely independent of the circulation in the trunk,

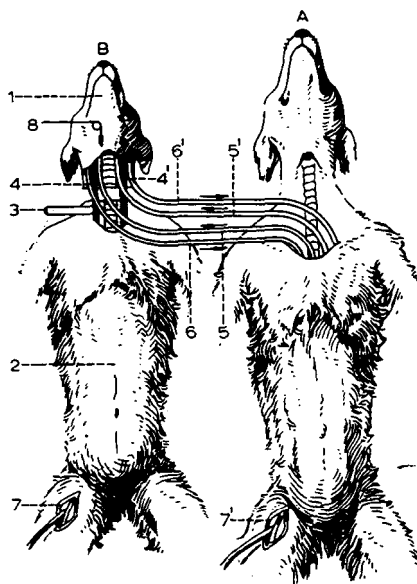


Fig. 1. Diagram of perfusion of an isolated head after J. F. and C. Heymans.

(Perfusion of the isolated head of Dog B by Dog A.)

(1) isolated head of Dog B; (2) isolated trunk of Dog B; (3) tracheal cannula; (4) right vagus nerve of Dog B; (4') left vagus nerve of Dog B; (5) anastomosis between the cephalic extremity of the external jugular vein of Dog B and the cardiac extremity of the external jugular vein of Dog A (right side); (5') anastomosis between the cephalic extremity of the external jugular vein of Dog B and the cardiac extremity of the external jugular vein of Dog A (left side); (6) anastomosis between the cephalic extremity of the common carotid of Dog B and the cardiac extremity of the common carotid of Dog A (right side); (6') anastomosis between the cephalic extremity of the common carotid of Dog B and the cardiac extremity of the common carotid of Dog A (left side); (7) femoral blood pressure in Dog B; (7') femoral blood pressure in Dog A; (8) respiratory movements in the isolated head of Dog B.

but the nervous pathways between head and trunk supplied by the vago-aortic nerves remain intact. The respiratory movements which indicate the activity of the respiratory centre are recorded on the isolated perfused head B which remains in a satisfactory living state.

In some experiments the donor Dog A was replaced by an artificial heart-lung apparatus.

It was noted first of all that hypotension in the isolated trunk circulation of Dog B stimulates the respiratory centre of the perfused head B. Conversely hypertension in the trunk B inhibits the respiratory centre of the perfused

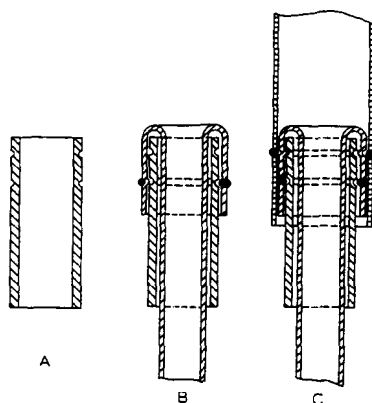


Fig. 2. Payr's cannula for anastomosis between blood vessels.

(A) Longitudinal section of a Payr cannula; (B) one of the vessels attached to the cannula; (C) the second vessel attached to the cannula.

N.B. The anastomosis between vessels is established with intima in contact with intima, so that the blood does not come into contact with the cannula or the sutures.

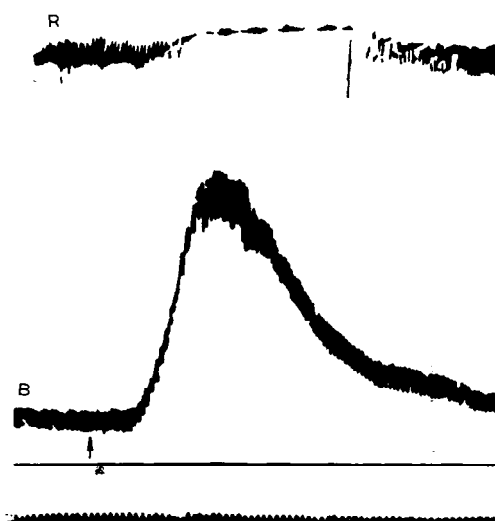


Fig. 3. The isolated head of Dog B is perfused from Dog A. The only link between the isolated head of Dog B and his trunk, kept alive by artificial respiration, is provided by the vago-aortic nerves.

Graph R : Respiratory movements of the isolated and perfused head of Dog B. *Graph B*: Blood pressure of trunk B.

At ↑: intravenous injection of adrenaline into the trunk of Dog B. Hypertension in the trunk B and reflex inhibition (apnea) of the respiratory centre of the perfused head of Dog B.

head B. When a hypertensive dose of adrenaline is injected into the trunk B it was found (Fig. 3) that respiratory movements of the isolated and perfused head B were totally inhibited, producing apnea.

These experimental results therefore demonstrated for the first time that arterial hypotension limited to the trunk produces reflex stimulation of the respiratory centre, while arterial hypertension in the trunk induces reflex inhibition of the respiratory centre, sometimes to the extent of total apnea.

The centripetal pathways of these respiratory reflexes, which are induced by variations of blood pressure in the trunk, are supplied by the vago-aortic nerves which constitute the only link between the trunk B and the isolated and perfused head B.

The next problem was to locate with greater precision the place of origin of these respiratory reflexes. Together with J. F. Heymans we had first of all noted that the respiratory reflexes under consideration persisted after all nervous connections between the trunk B and the perfused head B had been cut, with the exception of those of the cardio-aortic area.

In other experiments the isolated head of Dog B was perfused from Dog A and the isolated heart-lung preparation or the isolated cardio-aortic area of the trunk B was perfused from a third Dog C. The only link between the head B and the isolated heart-lung preparation or the isolated cardio-aortic area of trunk B was provided by the vago-aortic nerves. By using these experimental techniques we were able to observe that when arterial pressure was increased either in the heart-lung preparation or in the isolated cardio-aortic area of trunk B, reflex inhibition of the respiratory centre occurred; conversely, when arterial pressure was reduced in the cardio-pulmonary circulation or in the cardio-aortic circulation of the trunk B, the resulting hypotension limited to these areas initiated a reflex stimulation of the respiratory centre of the perfused head B. These respiratory reflexes did not occur however when the arterial pressure was varied in the isolated pulmonary circulation of the trunk B; in this case the vagus nerve provided the only link between the perfused lungs of the trunk B and the perfused head B.

Thus, this group of experiments carried out between 1924 and 1927 showed that *arterial hypertension in the cardio-aortic vascular area inhibits the activity of the respiratory centre by a reflex mechanism, while arterial hypotension in the same area has a stimulatory reflex effect on the activity of the respiratory centre.*

After Magendie's and Cooper's old experiments it has long been known that clamping of the common carotid arteries produces hyperpnoea, while unclamping of these arteries inhibits respiration.

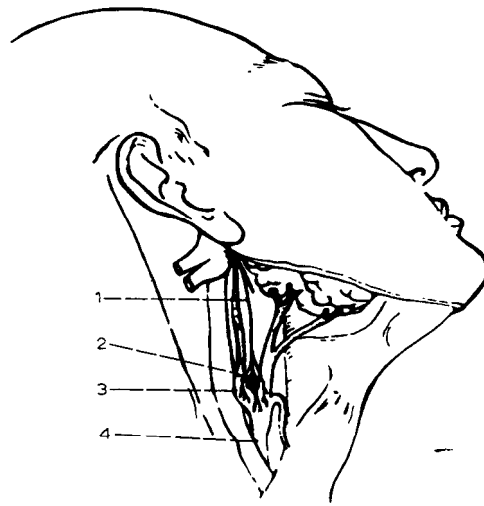


Fig. 4a. Diagram of the carotid sinus in man.
 (1) carotid sinus nerve; (2) glomus caroticum (reflexogenic chemo-receptor) ; (3) beginning of the internal carotid where the reflexogenic presso-receptors are mainly concentrated; (4) common carotid artery.

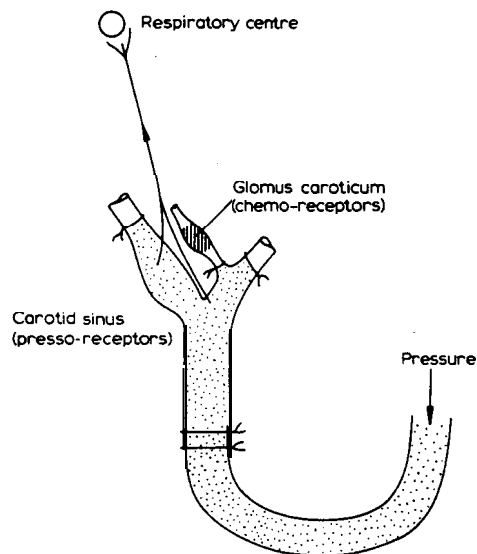


Fig. 4b. Diagram showing the technique by which endo-vascular pressure can be modified in the carotid sinus with nervous links intact but previously isolated as regards circulation and deprived of chemo-receptors.

Using the isolated and perfused head technique, we found that hypotension in the isolated cephalic circulation stimulates the respiratory centre, whereas hypertension in the same area produces respiratory inhibition to the point of apnea. We undertook to examine the mechanism of the interaction between cephalic blood pressure and the activity of the respiratory centre.

According to the classical theory, these respiratory reactions were considered to derive from the direct action of fluctuations in the blood flow, or irrigation, on the respiratory centre. However, in 1900, Siciliano and Pagano had already correctly noted that, although occlusion of the common carotids does in fact give hyperpnoea, occlusion of the efferent branches of the common carotid artery produces no effect on the respiratory centre. These investigators therefore rejected the theory that this hyperpnoea was of central origin and proposed the hypothesis that it was due to a carotid reflex mechanism.

Since 1924 the investigations of H. E. Hering and his associates, particularly E. Koch, and our researches undertaken with our associates, among these J. J. Bouckaert, P. Regniers, L. Dautrebande, and U. S. von Euler, and the work of Moissejeff, G. Liljestrand, Y. Zotterman, C. F. Schmidt, R. Gesell, and other investigators, have made it possible to show that the carotid sinuses, i.e. the arterial regions located in the area where the common carotid artery bifurcates into internal and external carotids and occipital artery, contain receptors, as does the homologous cardio-aortic zone, who, by a reflex mechanism, act upon and regulates the activity of the cardio-vascular centres and of the respiratory centre. Fig. 4a presents the position of the human carotid sinus.

A number of experimental procedures have enabled us to show that an increase in endo-vascular pressure in the carotid sinus produces an inhibition of the respiratory centre to the point of apnea, by a reflex arising from the presso-receptors, and that hypotension in the carotid sinus produces reflex stimulation of the respiration. Fig. 4b shows a diagram of one of the experimental procedures in which fluctuations in the endo-vascular pressure act exclusively on the presso-receptors of the carotid sinus. Fig. 5 shows reflex hyperpnoea produced by hypotension in the carotid sinus, and Fig. 6 shows reflex respiratory inhibition produced by an increase of blood pressure acting on the presso-receptors of the carotid sinus. It should be noted that this respiratory inhibition is particularly evident in animals in which the vago-aortic nerves have been cut.

Apnea induced by intravenous injection of adrenaline is also related to arterial blood pressure which acts upon the respiratory centre by means of

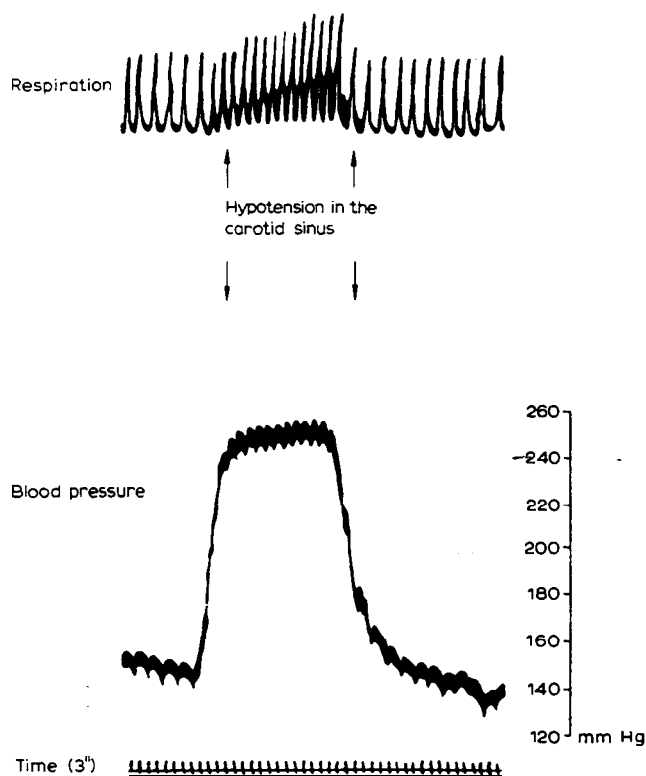


Fig. 5. Hyperpnea in a dog produced by hypotension in the carotid sinus.

the reflex pathways supplied by the presso-receptors of the cardio-aortic and carotid sinus zones.

The several experimental observations summarized above thus demonstrate that *variations in arterial blood pressure act on the respiratory centre by a reflex mechanism involving endo-vascular presso-receptors located in the cardio-aortic zone and in the carotid sinus*. Fig. 7 gives a diagrammatic representation of the points of emergence and pathways of the presso-receptor nerves arising from the cardio-aortic zone and the carotid sinus. It should be remembered at this point that the same presso-receptor nerves also act, by reflex mechanism, on the cardio-vascular centres and in this way possess a regulatory function as regards the systemic blood pressure and the circulation in general.

The next problem was to determine whether or not the respiratory centre is directly affected by variations in arterial blood pressure and arterial rate of flow? Numerous experimental observations carried out by means of dif-

ferent techniques gave a negative answer to this question. The activity of neither the respiratory nor the cardio-vascular centres was modified by (1) clamping the efferent arteries of the carotid sinus, (2) clamping the common carotid after denervation of the carotid sinus, (3) clamping of the vertebral arteries, even after prior clamping of the efferent arteries of the carotid sinus. Fig. 8 shows a graph of such an experiment.

In other experiments an isolated head was perfused and it was observed that considerable reduction in cerebral blood flow beyond physio-pathological limits was necessary before a stimulatory response was obtained by direct action on the respiratory and cardio-vascular centres.

All these observations lead to the conclusion that variations in arterial blood pres-

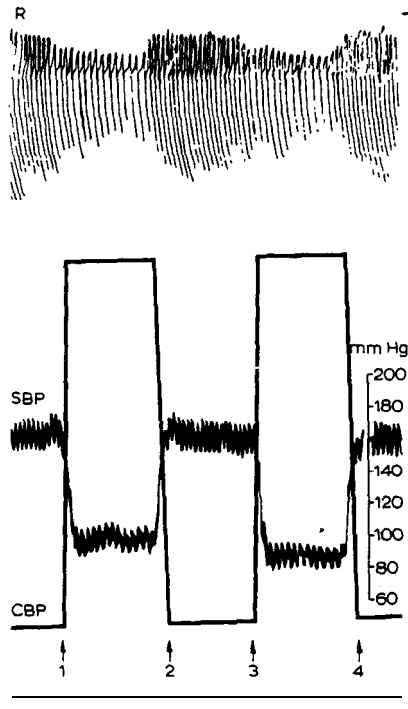


Fig. 6. Dog under chloralose anaesthesia. The vagus nerves are cut. (R) pneumogram; (SBP) systemic blood pressure; (CBP) carotid sinus blood pressure (chemo-receptors excluded). Time in 5-second intervals.

At point 1: increase in the endo-vascular blood pressure within the carotid sinus - marked inhibition of respiration. At point 2: decrease in the endo-vascular blood pressure within the carotid sinus - hyperpnoea. At point 3: same as at 1. At point 4: same as at 2.

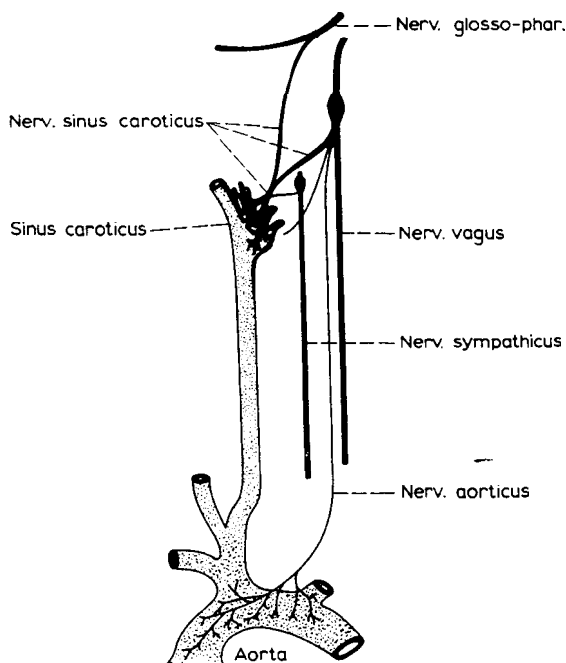


Fig. 7. Diagram of the nervous pathways of the cardio-aortic and carotid sinus zones.

sure exert an effect on the respiratory centre and on the cardio-vascular centres exclusively by a reflex mechanism involving the aortic and carotid sinus receptors. Variations in arterial blood pressure and cerebral bloodflow, within physio-pathological limits, exert no direct effect on the respiratory and cardio-vascular centres.

It had long been accepted as an established physiological fact that the chemical composition of the blood, i.e. the CO, and the oxygen contents, exerted a direct effect on the respiratory centre by controlling and adapting its activity in relation to the metabolic requirements of the organism. It was also accepted that a large number of pharmacological substances exerted a stimulating effect by direct action on the respiratory centre. These physiological and pharmacological concepts have recently undergone considerable modifications.

Making use of the technique involving perfusion of an isolated head linked to the trunk by only the vago-aortic nerves, J.F. Heymans and ourself in 1926 observed that asphyxia or hypoxemia, limited to the systemic circulation, produced reflex stimulation of the respiratory centre, while systemic hypercapnia produced reflex respiratory inhibition. Fig. 9 gives a graphic representation of one of these experiments which demonstrates reflex stimula-

tion of the respiratory centre of the isolated head, induced by asphyxia in the trunk which is connected to the perfused isolated head only by the vago-aortic nerves.

The different techniques described above made it possible to demonstrate

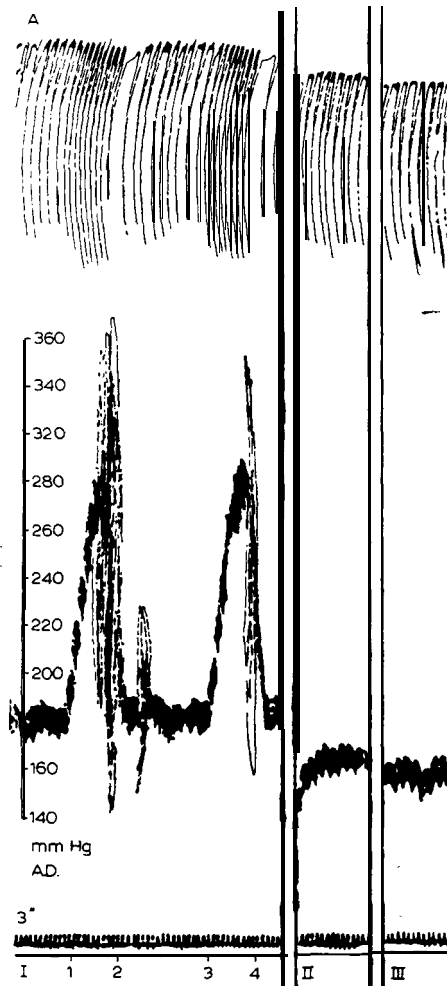


Fig. 8. Dog under chloralose anaesthesia. (A) pneumogram; (AD.) femoral blood pressure. Time in s-second intervals.

Section I (at points 1 and 3): clamping of both common carotid arteries - hyperpnoea and hypertension. *Section I* (at points 2 and 4): unclamping of both common carotid arteries - respiratory inhibition and hypotension. *Section II*: normal respiration and blood pressure. *Between Sections II and III*: the efferent blood vessels from the two carotid sinuses are clamped - no hyperpnoea, no hypertension.

that the reflex impulses from the systemic circulation, produced by conditions of hypercapnia, hypocapnia, or hypoxemia in the blood, arise in the cardio-aortic area which therefore contains reflexogenic chemo-receptors. In the course of the same experiments it was also observed that certain pharma-

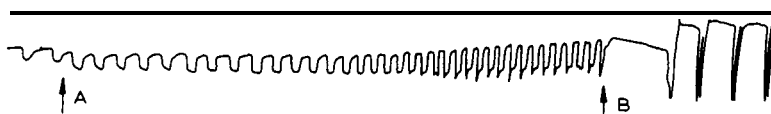


Fig. 9. Respiratory movements of an isolated and perfused head connected to the trunk only by the vagi-aortic nerves.

At *point A*: asphyxia in the trunk induces reflex stimulation of the respiratory centre in the perfused head. At *point B*: the aortic vagi-nerves connecting the-trunk and isolated and perfused head are cut; stimulation of the respiratory centre of the perfused head ceases.

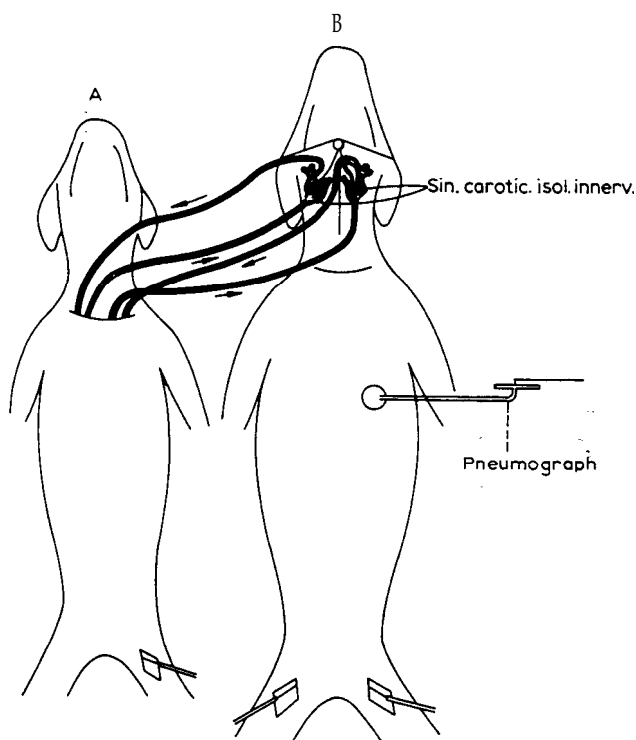


Fig. 10. Diagram of the procedure for perfusion of the carotid sinus with intact nervous connections and isolated circulation in Dog B from Dog A.

cological substances, such as nicotine, produce reflex stimulation of the respiratory centre by means of the same cardio-aortic chemo-receptors.

Our later experiments on the physiological role of the carotid sinus, a vascular zone similar to the cardio-aortic zone, led us to investigate if these arterial areas also showed reflex chemo-sensitivity. Experimental findings showed that this hypothesis was correct.

In this work a number of experimental procedures were used. Among these in particular was a technique involving perfusion of the carotid sinus which was isolated from the systemic circulation, but in which the nerve connections were preserved, either by a donor animal (Fig. 10) or by an artificial heart-lung preparation (Fig. 11).

These experiments demonstrated first of all that the carotid sinus is sensitive to the physiological stimulants contained in the blood, i.e. CO_2 , oxygen, and hydrogen ions.

Hyperapnic blood acts upon the carotid sinus area and induces reflex hy-

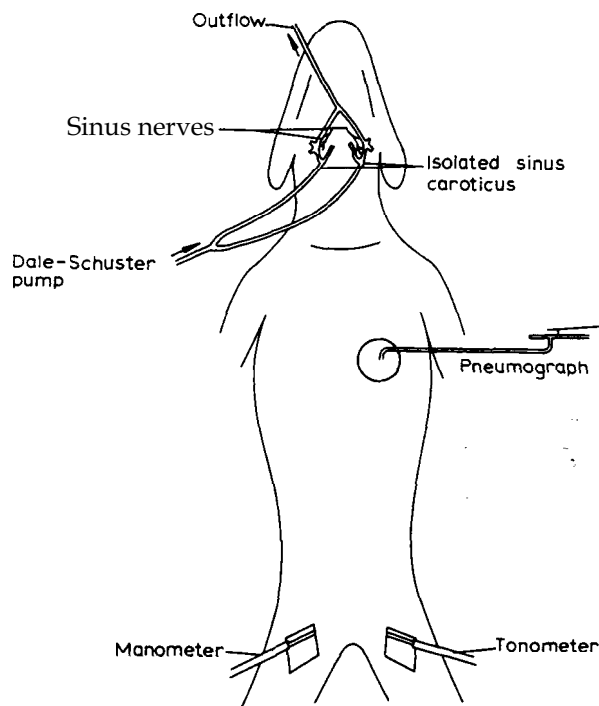


Fig. 11. Diagram of the procedure for the perfusion of the carotid sinus with intact nervous connection and isolated circulation. Perfusion is carried out by means of a Dale-Schuster pump.

perpnoea, while hypocapnic blood produces reflex respiratory inhibition. Hypoxic blood also acts on the carotid sinus area to produce reflex stimulation of the respiratory centre. In the same way hydrogen ions also stimulate the respiratory centre by acting on the carotid sinus chemo-receptors.

These experimental findings were confirmed by many workers, in particular, R. Gayet and D. Quivy, C. F. Schmidt, J. H. Comroe, R. Gesell, T. Bernthal, G. Liljestrand, U. S. von Euler, A. Samaan, G. Stella, Y. Zotterman, Samson Wright, etc.

What is the part played by the chemo-sensitivity of the cardio-aortic and carotid sinus zones in the physiological and physio-pathological regulation of the respiratory centre?

In the case of hypoxemia, our experimental findings and those of A. Samaan, G. Stella, U. S. von Euler, G. Liljestrand, Y. Zotterman, R. Gesell, C. F. Schmidt, and T. Bernthal demonstrated the marked sensitivity to oxygen want of the carotid sinus chemo-receptors.

On the other hand, if the chemo-sensitive nerves from the aortic and carotid sinus areas are cut, the inhalation of a mixture containing a low proportion of oxygen no longer stimulates respiration or blood pressure, but on the contrary produces progressive inhibition of respiration and a drop in blood pressure (Fig. 12), while in the case of an animal in which the chemo-sensitive nerves of the aortic and carotid sinus areas are intact, an identical oxygen want produces marked hyperpnoea and hypertension (Fig. 13),

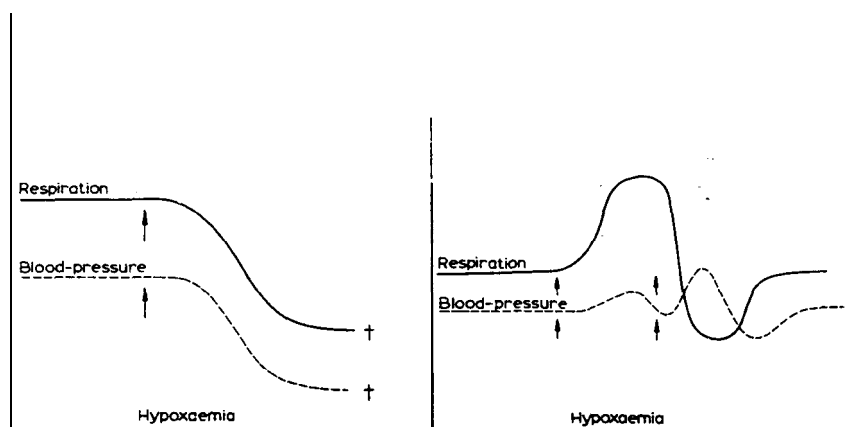


Fig. 12. Inhibition of respiration and circulation (blood pressure) by hypoxaemia in a dog from which the aortic and carotid sinus chemo-receptors have been excluded. Fig. 13. Respiratory and circulatory (blood pressure) reactions to hypoxaemia in a normal dog.

These findings were observed in both anaesthetized and non-anaesthetized animals and clearly demonstrate that a lack of oxygen stimulates respiration and produces hypertension by an essentially reflex mechanism involving the chemo-receptors of the aortic and carotid sinus areas. Hypoxaemia, which acts directly on the medullary centres, exerts a depressive, not a stimulating effect. Only extreme anoxia or anaemia can exert a direct stimulating effect on the respiratory and cardio-vascular centres.

The experiments carried out by C. F. Schmidt and J. H. Comroe proved, in addition, that it is essentially the oxygen tension and not the saturation in oxygen in arterial blood which acts on the aortic and carotid sinus chemo-receptors. This explains why hyperpnoea does not occur in cases of carbon monoxide poisoning and in cases of anaemia or methemoglobinaemia. The oxygen tension in arterial blood is, indeed, normal in such cases. The same workers also demonstrated the important part played by the chemo-sensitivity of the aortic and carotid sinus zones in the reflex stimulation of the respiratory centre when it is depressed by the direct effect exerted by a number of narcotic drugs, such as morphine, ether, and barbiturates. In these cases, hypoxaemia is responsible for this continued reflex stimulation of the respiratory centre, by means of the chemo-sensitive nerves.

The fundamental role of the aortic and carotid sinus chemo-receptors in the respiratory and circulatory reactions arising from lack of oxygen due to low atmospheric pressure at high altitudes was also demonstrated by a number of investigators.

On the question of regulation of the activity of the respiratory centre by CO_2 all workers confirm our experimental findings, viz. that the CO_2 contents of the blood acts upon and stimulates the respiratory centre and cardio-vascular centres by a reflex mechanism involving the aortic and carotid sinus chemo-receptors. The experimental exclusion of these reflexogenic chemo-receptors does not, however, as in the case of oxygen want, prevent the regulating effect of CO_2 on the respiratory centre itself.

What are the respective roles played by the chemo-sensitive reflex mechanism and the direct central mechanism in the regulation by CO_2 of the activity of the respiratory centre? This is still a controversial question.

Basing ourselves particularly on the fact that the chemo-receptors are extremely sensitive to CO_2 and on the fact that CO_2 by acting on the chemo-receptors, can produce and maintain hypercapnia in spite of the central effect of simultaneous decreased CO_2 in the blood, and also on the fact that experimental exclusion of the chemo-receptors increases the alveolar con-

centration of CO_2 , we have suggested that CO_2 exerts an effect on respiration primarily by the chemo-sensitive reflex mechanism, and secondarily by the direct central mechanism (Fig. 14). This hypothesis has received the support of U. S. von Euler, G. Liljestrand, Y. Zotterman, Samson Wright, R. Gesell, T. Bernthal. C. F. Schmidt and J. H. Comroe, however, favour the opposite hypothesis that CO_2 regulates the activity of the respiratory centre primarily by the direct central mechanism and secondarily by the chemo-sensitive reflex mechanism.

The aortic and carotid sinus chemo-receptors are not only sensitive to physiological chemical stimulants but also to a number of pharmacological substances. This was demonstrated in 1926 with J. F. Heymans, in the case of the cardio-aortic zone.

Our experiments carried out later with J. J. Bouckaert, L. Dautrebande, U. S. von Euler, S. Farber, A. Samaan, Shen, Donatelli Marri and other co-workers showed that a number of pharmacological substances such as nicotine, lobeline, cyanide, acetylcholine, and other choline derivatives, and potassium sulphide produced intense stimulation of the chemoreceptors of the carotid sinus and that they therefore stimulate the respiratory and cardiovascular centres by a reflex mechanism. The direct central effects of these substances, on the other hand, are either absent or depressive, or stimulating in very high doses. These findings were obtained by means of a number of experimental procedures as perfusion of an isolated head, the sole link with the trunk being provided by the vago-aortic nerves, perfusion of a carotid

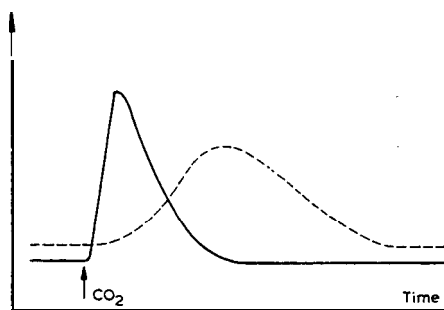


Fig. 14. Diagram of the threshold and intensity of stimulation of respiration produced by the reflex effects of CO_2 on the chemo-sensitive receptors and by the direct central effects of CO_2 .

Threshold and intensity of respiratory reactions to CO_2 : - reflex chemo-sensitive origin; --- direct central origin.

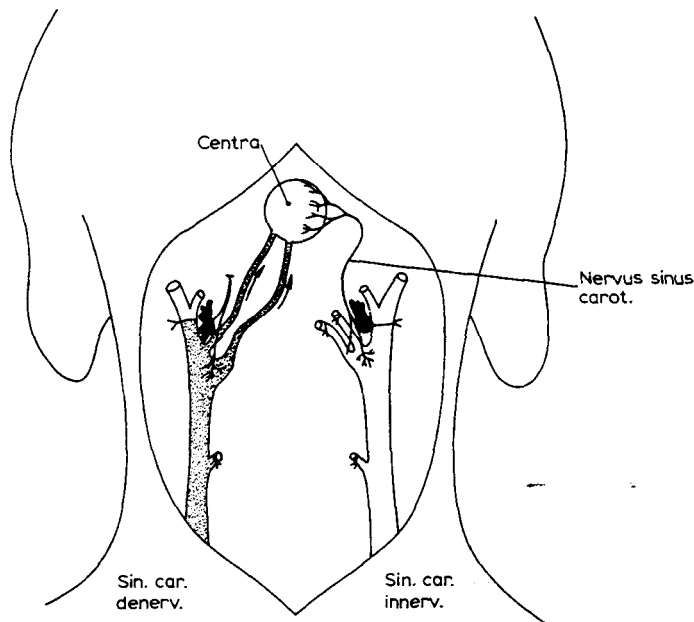


Fig. 15. Diagram of the procedure by which the circulation in the normally innervated glomus caroticum is isolated on one side. The opposite carotid sinus is denervated and the external carotid artery ligatured; the circulation in the common carotid is directed towards the nervous centres.

sinus, isolated from the systemic circulation but with nervous connections intact, alternate injection of the same pharmacological substance into the blood stream of a normal common carotid and a common carotid from which chemo-receptors have been eliminated (Fig.15).

Fig. 16 shows the reflex stimulation of the respiratory centre and of the cardio-inhibitor vagus centre by acetylcholine in contact with the carotid Sinus chemo-receptors. It should be added that acetylcholine directly stimulates the respiratory and cardio-inhibitor centres only when very high doses are administered. If an anticholinesterase (neostigmine) is previously administered, only a slight reinforcement is obtained of the direct central effect of acetylcholine on the respiratory and cardio-inhibitor centres. It should also be noted in this connection that neither does neostigmine reinforce the respiratory and cardio-vascular reflexes arising from the cardio-aortic and carotid sinus zones. This finding does not support the hypothesis that a cholinergic mechanism is involved in the respiratory and cardio-vascular reflexes arising from the presso- and chemo-sensitive aortic and carotid sinus zones.

The reflexogenic chemo-sensitivity of the carotid sinus in regard to a large number of pharmacological substances has been confirmed by many investigators, in particular R. Gesell, T. Bernthal, U. S. von Euler, G. Liljestrand, Y. Zotterman, Samson Wright, C. F. Schmidt, J. H. Comroe, etc., who made important contributions to the study of this new chapter in pharmacology.

What is the anatomical location of the presso- and chemo-receptors in the cardio-aortic and carotid sinus areas?

Histological research carried out by de Castro, Meyling and Gosses, and our own experimental findings, obtained with J. J. Bouckaert and L. Dautrebande in particular, has led to the locating of the carotid sinus chemo-receptors in the glomus caroticum and of the presso-receptors in the walls of the large arteries arising from the carotid artery (Fig. 17).

Various experimental techniques have made it possible to dissociate the chemo-receptor zones from the presso-receptor zones in the carotid sinus.

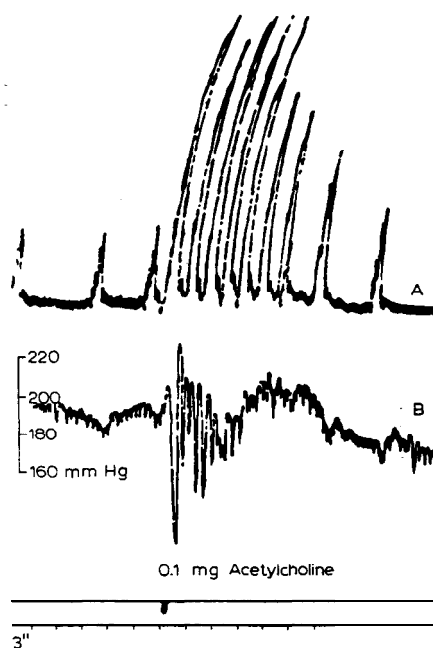


Fig. 16. *Graph A*: pneumogram of a dog under chloralose anaesthesia. *Graph B*: blood pressure and cardiac rate. Time in s-second intervals. Acetylcholine (0.1. mg) is applied to the chemo-receptors of the glomus caroticum. Marked reflex hyperpnoea and bradycardia.

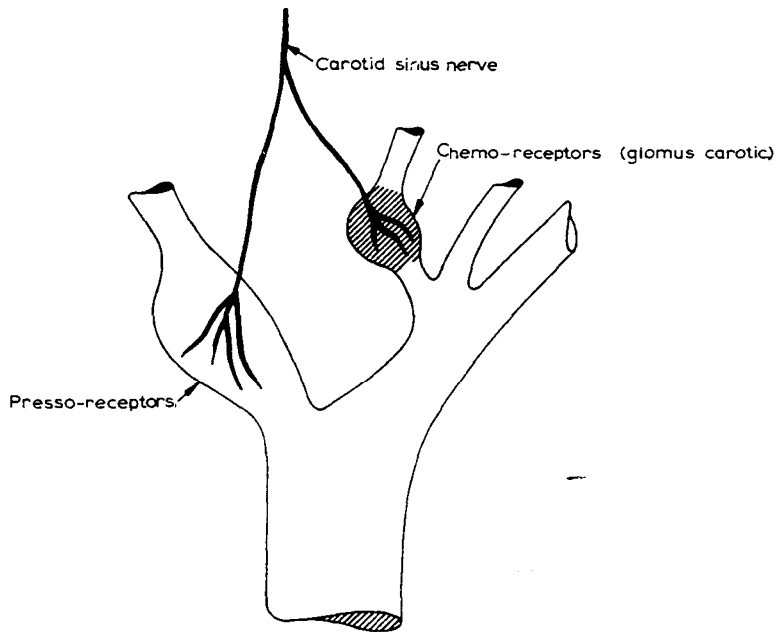


Fig. 17. Diagram showing the site of the reflexogenic presso- and chemo-receptors in the carotid sinus.

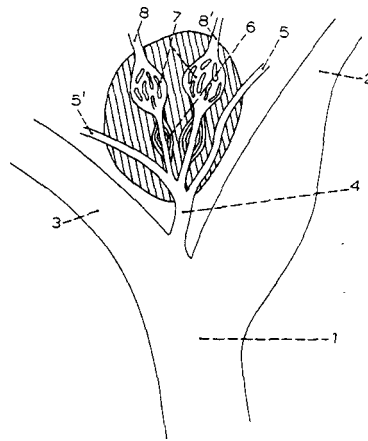


Fig. 18. Diagram of the carotid sinus and glomus caroticum.

(1) common carotid artery; (2) internal carotid artery; (3) external carotid artery; (4) occipital artery, branch irrigating the glomus caroticum; (5) occipital artery sub-branches; (6) afibrillar muscle cells on the afferent glomus arteries; (7) glomus tissue; (8) efferent glomus vessels.

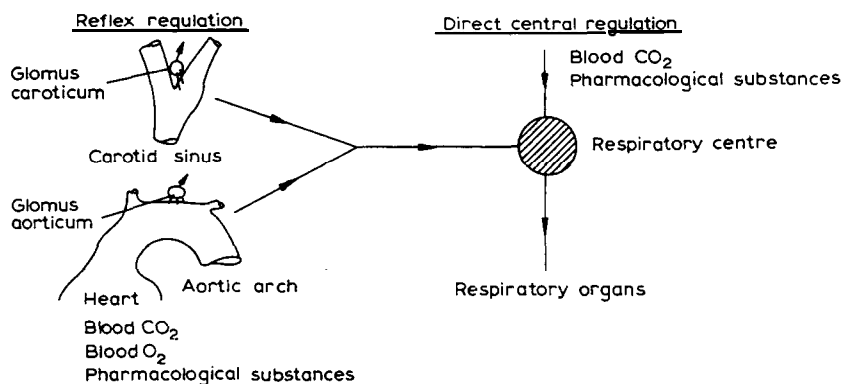


Fig. 19. Diagram of the reflex regulation of the respiratory centre by the presso- and chemo-receptors in the cardio-aortic and carotid sinus areas, and of the direct central control exerted on the respiratory centre.

The glomus caroticum, which contains the carotid sinus chemo-receptors, presents an interesting anatomical structure (Fig. 18).

Histological studies, by J. F. Nonidez in particular, and J. H. Cornroe's experiments have led to the location of the cardio-aortic chemo-receptors in the-aortic glomus tissue, whereas the presso-receptors are mainly located in the wall of the aortic arch.

The various experimental findings summarized in this lecture have thus brought to light a new physiological, physiopathological, and pharmacological mechanism which, by regulating the activity of the respiratory centre through the vascular presso- and chemo-sensitive reflexes (Fig. 19), establishes, thus, an even closer functional correlation between the blood circulation, the metabolism, and the pulmonary respiratory exchanges.