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The Hemodynamic Adjustments in the Carotid Sinus Pressor Reflex

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THE HEMODYNAMIC ADJUSTMENTS IN THE CAROTID SINUS PRESSOR REFLEX

by

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LIFE

Harry John Pappas was born in Buffalo, New York, January 5, 1927.

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INTRODUCTION

The everyday use of the carotid sinus reflex by the body is a controlling factor in the maintenance of normal blood pressure. It is now known that upon inducing a hypotension in the carotid sinus area, a pressor response in the arterial systemic blood pressure is elicited. This reflex pattern has been shown experimentally. The hypotension causes a decrease in the stimulation of the carotid sinus pressoreceptors. The decrease of impulses along the carotid sinus and glossopharyngeal nerves to the medulla creates a situation which results in the activation of the vasoconstrictor center and depression of the vasodilator center. The resulting efferent impulses travel by way of the sympathetic nervous system. According to many descriptions this reflex also involves the cardioaccelerator and cardioinhibitor centers.

The effect of this reflex on such factors as cardiac output and right ventricular pressures, is not clear. If there is an increase of peripheral vasoconstriction and if the cardiac output remains unchanged or rises, as a result of this reflex, then we can postulate that the heart will work harder. However, the diversity of results obtained by various investigators precludes conclusions regarding cardiac work. There has been agreement only regarding evidence of peripheral vasoconstriction.

To better evaluate this problem, a study of the circulatory hemodynamics resulting from the elicitation of the carotid sinus pressor reflex has

been done. The studies included determinations of the femoral artery and right ventricular cardiac pressures, the cardiac output, and other related factors.

Anatomy of The Carotid Sinus Reflex. The carotid sinus nerve arises from the carotid sinus area. This is a specially innervated part of the vessels and tissues in the neighborhood of the bifurcation of the common carotid artery and its branches. In man, and many other mammals, the common carotid artery divides into internal and external carotids, and a bulbous expansion, the carotid sinus or carotid bulb, is seen at the root of the internal branch. A nerve twig runs from the carotid sinus to the glossopharyngeal nerve (see figure 1).

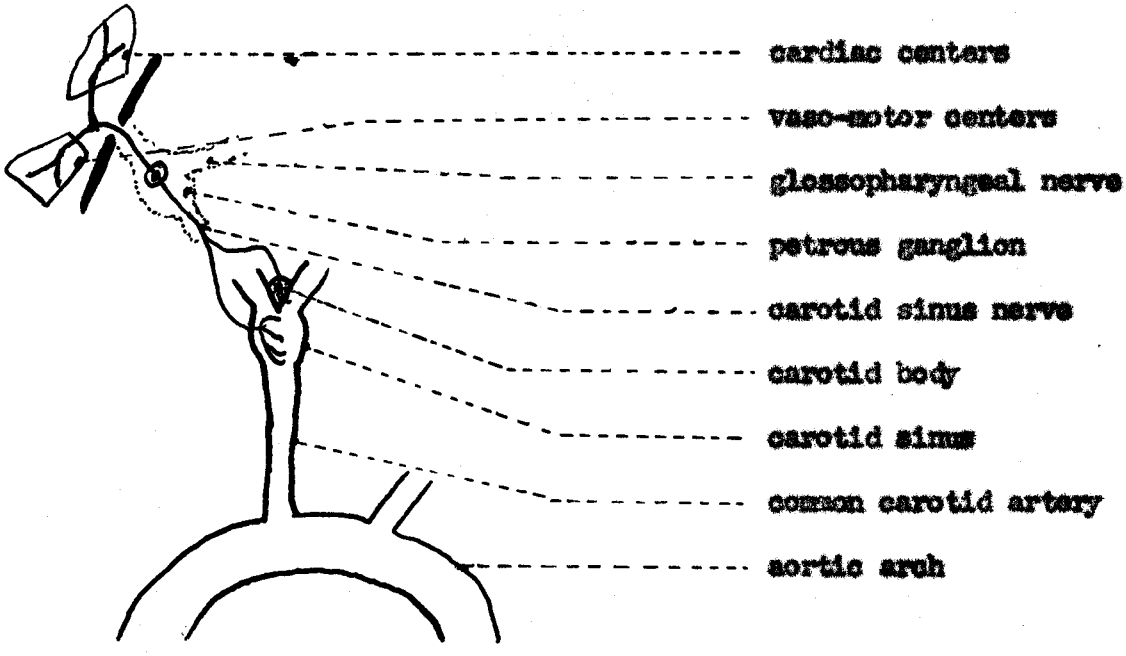

Figure 1. AFFERENT INNERVATION OF THE CAROTID SINUS REGION. (FROM STARLING, 1945)

All the principal nerves in the region of the carotid sinus have been mentioned in the literature as supplying fibers to the sinus. Hering (1923) in his original publications first mentioned that the sinus reflex was transmitted through nerves which pass from the carotid sinus to the superior cervical ganglion of the sympathetic nervous system. He (1924) later described a branch from the glossopharyngeal nerve, which he named the sinus nerve. On the basis of his experiments, Hering believed that the reflex from the carotid sinus was transmitted by the sinus nerve.

De Castro (1928) has attacked the problem from the morphologic standpoint. Because the branch from the glossopharyngeal nerve supplies fibers to both the carotid sinus and the carotid body, De Castro preferred to call it the intercarotid nerve. He had found that after section of the glossopharyngeal nerves, including its intercarotid branch, the specialized receptors are still found in the carotid sinus. In his experiments the specialized nerve endings in the carotid sinus remained unaltered after removal of the superior cervical ganglion. He has emphasized the importance of branches from the vagus nerve and from the ganglion nodosum. He was of the opinion that afferent impulses liberated from the carotid sinus reach the medullary centers partly through the glossopharyngeal nerve but more particularly by way of the vagus nerve.

Danielopolu and his co-workers (1927) have postulated a threefold nerve supply; namely, a branch from the glossopharyngeal nerve, a branch from the vagus, and a branch from the superior cervical ganglion of the sympathetic nervous system. They state that all three nerves take part in the transmission of the reflexes of the carotid sinus.

Code, Dingle, and Moorhouse (1936) studied the anatomy of the carotid region of the dog in order to determine the nerves ending in the carotid sinus. The physiologic function of the nerves supplying the sinus was investigated. They found that anatomically, the carotid sinus possesses three sources of nerve supply; a branch from the posterior division of the glossopharyngeal nerve, a branch from the superior cervical ganglion, and a small nerve which accompanies the internal carotid artery. Electric stimulation indicates that the nerve accompanying the internal carotid artery is not concerned in the carotid sinus reflex. A study of the comparative responses of the sympathetic nerve and the sinus nerve to electric stimulation clearly indicates the greater importance of the sinus nerve. Therefore, they conclude that the cardiovascular components of the sinus reflexes are conducted solely through the sinus nerve.

Ray and Stewart (1948), however, found that there are four nerves which contribute to the innervation of the carotid sinus and adjacent carotid body, namely, the glossopharyngeal, vagus, cervical sympathetic, and hypoglossal. The branch to the hypoglossal is inconstant and the part played by this nerve is probably not important. The other three nerves show considerable variation in their gross anatomic arrangements, but great constancy in their connections to the carotid sinus and the intercarotid plexus. From anatomic dissection (Sheehan, et.al., 1941), it has been shown that a distinct and constant branch of the glossopharyngeal nerve connects with the sinus and intercarotid plexus. The importance of this nerve is supported by its striking constancy in all species of animals. Ray and Stewart, in their observations, conclude that the glossopharyngeal nerve transmits the afferent im-

pulses of the carotid sinus reflex induced by pressure on the carotid sinus. They showed, in man, that intracranial division of the nerve permanently abolishes the effects of pressure on the homolateral carotid sinus. The chemically induced part of the carotid sinus reflex probably remains intact after intracranial division of the glossopharyngeal nerve.

Effects of the Carotid Sinus Reflex on the Cardiovascular System. The discovery of the carotid sinus and its nerve by Hering, in 1923, originated a large number of experiments and clinical observations, many of them contradictory, yet many proving of great importance. The carotid sinus nerve together with the afferent nerves which come from the aorta, i.e. the aortic nerves, make up the two important buffer nerves which affect the heart reflexly, thereby controling the arterial blood pressure and, therefore, tending to maintain a normal circulation to the brain.

Since the days of Czermak, pressure over the vagus trunk as it lies behind the carotid artery in the neck has been known to produce cardiac slowing of varying degree in a proportion of normal men. The effect was originally attributed to mechanical exitation of the vagus trunk, but has been ascribed by Hering to reflex vagal exitation arising from stimulation of the carotid sinus. This conclusion was based on the comparative inexcitability of the vagus to mechanical stimulation, on the known response of the carotid sinus to mechanical stimulation in animals and man, and on frequently opposite effects produced in man by pressure applied at different levels in the neck of the same patient. In Hering's view (1923) these contradictory effects have been explained in the following manner. Pressure applied over the sinus by mechanical stimulation of the receptors in its walls, produces reflexly bradycardia

and peripheral vasodilation. On the other hand, pressure applied below the carotid sinus, by occluding the carotid artery, causes hypotension in the sinus, and produces reflexly tachycardia and peripheral vasoconstriction. Bradycardia is sometimes produced, however, by pressure low in the neck, and this has been explained by incidental traction upon the common carotid artery and consequent stimulation of the sinus.

The existence of these reflexes arising from the region of the bifurcation of the common carotid artery, first described by Hering, has been amply confirmed by later workers. The nature of these reflexes and their great complexity have been widely demonstrated through the experimental work of Moissejeff (1926), Hering (1927), Heymans (1930) and Koch (1931), and many others, and their clinical implications have been subject of much research.

Anrep and Segall (1926) showed that there was a distinct gap between the lowest arterial pressure at which the depressor mechanism begins to act, and the highest arterial pressure at which the pressor reflex comes into play. Anrep and Segall found in three experiments, that changes in arterial pressure between 80 to 120 millimeters of mercury had no effect on the circulation in the head, a rise above 120 millimeters of mercury caused a vasodilation, while a fall of pressure below 80 millimeters of mercury was accompanied by vaso-constriction.

A similar pressor reflex has been advocated for the carotid sinus by Heymans (1929). To show its existence he clamped both carotids in an anesthetized and vagotomized dog. The general hypertension produced by the fall of pressure in the carotid sinuses thus brought about showed a distinct diminution as soon as both carotid sinus nerves were cut. The existence of a pressor

reflex from the carotid sinus seems also confirmed by observations of Danielopolu et. al. (1927) according to whom it is possible, in the monkey, to obtain an increase of arterial pressure by suitable stimulation of the region of the carotid sinus.

That the pressosensitivity of the carotid sinus is very great has been shown by Heymans (1929). In the carotid sinus of the dog, a deviation in either direction of even one millimeter of mercury from the normal arterial pressure is sufficient to produce reflex compensatory changes in the general blood pressure.

Another group of experiments by Heymans et. al. (1929) has shown that the cardiovascular centers are not directly sensitive to variations in the blood pressure. The reactions of the cardiovascular centers to changes in cephalic blood pressure are entirely of carotid sinus origin. Only extreme anemia, they state, has a direct stimulating influence on the cardiovascular centers. The regulation of heart frequency depends mainly on changes in the vagus tone and to a slight degree on changes in the sympathetic activity.

Gesmill and his co-workers (1933), upon occluding the common carotid arteries in intact, unanesthetized dogs, noted that in these animals the pulse rate rose substantially. This rise was abolished, in three dogs, by denervation of the carotid sinus. In one dog the rise persisted after denervation.

Bouckaert and Heymans (1933) found that 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 occlusion of the

denervated common carotid arteries, or by occlusion of the vertebral arteries, do not directly stimulate the vasomotor, cardioregulatory, or the respiratory centers. Therefore, at low carotid sinus pressure, the vaso-tonic and respiratory centers are stimulated reflexly by way of the carotid sinus nerves, although the cerebral pressure and the cerebral blood flow are both increased by these vasomotor reflexes. Conversely, at high carotid sinus pressure, the vaso-tonic and respiratory centers 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.

The vascular reflex was found to be a very constant and definite entity by Winder (1937) in his experiments on the carotid sinus reflex. Its response to ordinary fluctuations in pressure was of striking sensitivity. Its maximal stimulation appeared capable of causing maximal and maintained vascular relaxation in the dog. Normally, impulses from the carotid sinus receptors were seen to cause inhibition of cardiac activity. Upon inducing hypotension in the sinus area, a peripheral vasoconstriction and a tachycardia were observed. Conversely when the pressure in the sinus was raised, usually by perfusion, the heart rate was seen to slow down, and a general vasodilation with lowered blood pressure was elicited.

With a technic developed in the laboratory of Heymans (1938), one or both carotid sinuses of a dog were isolated <u>in situ</u> from the circulation care being taken not to injure their innervation. These carotid sinuses were perfused with blood either by means of another dog, or with a Dale-Schuster pump. If the pressure inside the carotid sinuses was increased this rise of intracarotid sinus pressure was associated with a fall of the blood pressure in the

general circulation. With the fall of arterial pressure there was a slowing of the heart. Conversely, if the pressure was lowered in the isolated carotid sinus, the general blood pressure rose and the heart accelerated. These experimental observations, in addition to many others, demonstrated that the general arterial blood pressure is automatically controlled by means of the endovascular pressure itself, acting on the presseceptive nerve endings of the carotid sinus.

According to Heymans (1938) an increase in the carotid sinus pressure produced reflex arterial, venous and capillary dilatation, and a reduction in the caliber of the arterio-venous anastomoses, and a decrease in the cardiac output. A lowered carotid sinus pressure produced, on the other hand, according to this author, a reflex vascular constriction, an opening of the arterio-venous anastomoses, an increase in the circulating blood volume, and thus an increase in the cardiac output.

The arterial vascular tone is regulated, not only reflexly by means of neural influences, but also by reflex alteration in the adrenalin output. Heymans et. al. (1925, 1929) showed that the arterial blood pressure, by acting on the pressoreceptors of the carotid sinus, regulated reflexly the secretion and discharge of adrenaline, and thus controlled further, in a humoral way, the vascular tone, the heart rate, the circulatory blood volume and probably also the caliber of the arterio-venous anastomoses. It was pointed out, however, that this suprarenal hormonal regulation of the circulation by the carotid sinus was only an accessory regulating mechanism.

Heymans and co-workers (1951), using dogs as their experimental animals, found that small amounts of adrenaline or noradrenaline applied to

the arterial wall of the carotid sinus areas induced a stimulation of the pressoreceptors and thus a marked and prolonged reflex fall of the systemic arterial pressure and a decrease or suppression of the hypertensive reflexes normally provoked by a decrease of pressure inside of the carotid sinus. Section of the carotid sinus nerves when the systemic arterial pressure has been lowered by the local application of adrenaline or noradrenaline on the carotid sinus areas was noticed to cause an immediate and very marked rise of the systemic arterial pressure. These experiments showed that the state of contraction and thus the resistance to stretch of the arterial wall where the pressoreceptors are located are the primary factors affecting these receptors which regulate and moderate reflexly the systemic arterial blood pressure.

Effects of the Carotid Sinus Reflex on Respiration. The evidence for the part played by the carotid sinus in the control of respiration is somewhat conflicting.

Heymans and Bouckaert (1930) observed that occlusion of the common carotid arteries leads to a rise in arterial pressure and to an increase in the respiration. They showed that this effect is due to the reduction of pressure in the carotid sinus, since it disappears if the sinuses are denervated.

Bilateral denervation of that region has given variable results to different observers. Thus it was followed by great increases in depth and rate of breathing in the experiments of Heymans, Bouckaert and Dautrebande (1930), and of Koch and Mark (1931). However, Halladuraï and Wright (1932) found that the respiration was either unchanged in rate or slightly decreased, while as a rule the depth and the pulmonary ventilation were diminished,

sometimes by as much as fifty per cent.

An even more pronounced depression of respiration was described by Witt, Katz and Kohn (1932) according to whom denervation of the carotid sinus in the dog, sometimes of one side only, as a rule led to death of the animal from respiratory failure.

Schmidt (1932) was of the opinion that respiratory activity of an animal is very little, if at all, affected by the operation, of carotid sinus denervation, usually in the sense of transitory stimulation which only lasted a few minutes. He states further that the respiratory effects of occlusion of the common carotid arteries of dogs and cats, while generally comparable with the circulatory effects, were less constant and less persistent than the circulatory. They were usually but not always purely reflex in origin because sinus denervation did not always abolish them, although it made them much more capricious in their occurence. Endosinusal pressure was reduced by about 36 per cent at first, but as a result of collateral circulation, it rose during the occlusion until it was less than 20 per cent below normal; hyperpnea disappeared as the endosinusal pressure rose, but hypertension persisted, so that both effects can scarcely be due entirely to inactivation of the same sinus reflex mechanism. Bilateral carotid occlusion reduced cerebral blood flow by about 45 per cent in dogs, while vertebral occlusion reduced it only by about 25 per cent: the greater effect of the former upon respiration may therefore be partly due to its greater influence upon blood supply of the center. According to Schmidt the respiratory effects elicited by changes in endosinusal pressure probably arose from structures that are distinct from those concerned in circulatory reflexes because the intensities of the two

effects were often entirely independent; because the respiratory effects were less persistent than the circulatory and less proportional to the actual level of endosinusal pressure than to the level from which the pressure was changed; and because occasionally there may be definite reflex respiratory effects without any circulatory response whatever. The respiratory mechanism appeared to be relatively more sensitive to changes in pulsation than to changes in mean pressure, although it was influenced by both.

Gemmill et. al. (1933) found that clamping the common carotid arteries in the intact unanesthetised animal produced no definite change in the respiratory rate either before or after denervation of the carotid sinus.

Wright (1934) attempted to repeat, in the rabbit, the observation of Selladurai and Wright (1932) in the cat, but could come to no definite conclusion as to the importance of the carotid sinus in regulating the respiration in the former animal.

Stimulation of respiration as a consequence of denervation of the carotid sinus has been interpreted as being due to the removal of the inhibitory influence of impulses elicited by the action of the endosinal pressure. (Hering, 1927; Danielopolu, Aslan, Marcu, Proca, and Manescu, 1927; Moissejeff, 1927; Heymans and Bouckaert, 1930; Koch and Mark, 1931, and others). On the other hand, depression of the respiratory activity, as described by Selladurai and Wright (1932), and by Witt, Katz and Kohn (1934), has been adduced as evidence for the operation under normal conditions, of the same mechanism as is responsible for the stimulation of respiration when the isolated and innervated carotid sinus is perfused with hypercapnic fluid, i.e., the chemoreceptor mechanism (Heymans, Bouckaert, and Dautrebande, 1930).

This mechanism is considered to contribute, together with the direct excitability of the respiratory centers, to maintaining the magnitude of the animals' ventilation adjusted to the respiratory conditions of its arterial blood.

Stella (1935), in his experiments on the effect of bilateral denervation of the carotid sinus pressoreceptors on respiration found that, in the dog, this procedure was followed by alterations in the character of respiration, the latter becoming, as a rule, less deep and its rhythm being often accelerated. He also observed that the effect upon the magnitude of the pulmonary ventilation per unit of time was found to be variable. A decrease of the pulmonary ventilation was obtained whenever the inhibitory effect of the endosinal pressure upon respiration was weak, i.e., when the occlusion of the carotids caused little or no augmentation of breathing.

The type of anesthesia utilized was considered to have taken no significant part in the respiratory changes observed.

Effect of the Carotid Sinus Pressor Reflex on Cardiac Output. There is no agreement in the literature about the influence of the carotid sinus 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.

Rinl (1929) used seven rabbits anesthetized with urethane as his experimental animals. The cardiac output was determined by the Fick method on giving pure oxygen. The venous blood was collected with the aid of a cannula placed in the right auricle. Rinl concluded that the bilateral occlusion of the carotid arteries produced two opposing results, the reaction

depending solely on the animal: a) an augmentation, in four animals concominant with a notable drop of the arterial-venous blood oxygen difference; b) in three animals, a fall in the cardiac output together with an increase of the A-V blood oxygen difference.

Heymans et. al. (1931), applying the Fick principle to carbon dioxide 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 and Zander (1928).

$$\text{Cardiac output} = \frac{\text{Pulse pressure} \times \text{heart rate}}{\text{Mean arterial blood pressure}}$$

Holt et. al. (1946), employing Stewart's (1921) method, found an average reduction of cardiac output of seven per cent when they stimulated the carotid sinus nerve in dogs.

Charlier and Philippot (1947), using dogs anesthetized with chloralose, reported results which were different than other observations. Upon occlusion of the common carotid arteries they observed an increase of cardiac output ranging from 17.5 per cent to 77.9 per cent over the normal animal. An even greater increase was produced when the vagi were sectioned. These investigators determined the cardiac output according to the Fick formula. The analysis of the oxygen consumed was determined by the Haldane method. Room air was inspired during the entire experiment. The oxygen content was determined by collecting a sample of expired air and analyzing for the gas content. The arterial blood was collected from the femoral artery and mixed venous blood from the right auricle. The blood was collected in syringes

coated with paraffin containing a trace of sodium oxalate. Only one arterial blood sample was taken during the experiment and this was used for the arterial oxygen content in the calculation of all the cardiac outputs. In all animals the stroke volume and heart rate participated simultaneously in the increased cardiac output. Even when the heart rate increased notably, the stroke volume was capable of increasing simultaneously, despite the tachycardia present. The femoral artery and right auricular pressures, respiration, oxygen consumption and cardiac work all increased with the increased cardiac output.

Having observed that the right auricular pressure increased during the temporary occlusion of the carotid arteries, Charliar and Philippot (1947), investigated the effect of this procedure on the right ventricular pressure. A similar procedure as in their previous paper was performed, with the exception that the catheter was introduced into the right ventricle. The cardiac output again increased substantially anywhere from 20 to 72 per cent over the normal upon occlusion of the carotid arteries. The A-V blood oxygen difference decreased because the venous blood oxygen increased. The oxygen consumed and the intra-auricular pressure again were increased. The right ventricular pressure showed a rapid and often substantial rise upon bilateral carotid artery occlusion. The pressure attained its maximum when the arterial pressure reached its maximum. It maintained this peak for some time but slowly decreased as the occlusion was prolonged. When the carotids were opened the pressure of the right ventricle fell slowly. Both the right auricular and the right ventricular pressures were recorded in centimeters of water. The right ventricular pressure showed, on carotid artery occlusion, an

increase in the range of twice of the normal pressure.

Hoe et. al. (1949) using the Henderson cardiometer for cardiac output determinations were unable to confirm the results of Charlier and Philippot. They state that carotid artery occlusion causes little or no alteration in the cardiac output.

De Vleeschhouwer et. al. (1950), working in this field, employed a procedure quite similar to that used by Charlier and Philippot. The Fick principle was used to determine the cardiac output. The Haldane method for analysis of blood gases was utilized. The mixed blood was collected from the right auricle. Their results show that after common carotid artery occlusion the general arterial blood pressure rose between 20 to 42 per cent. During the occlusion, the cardiac output was augmented in seven dogs and diminished in three dogs. The augmentation of the output varied between 14 to 148 per cent, the diminution between 5 to 43 per cent. Of the seven animals, which presented an augmented cardiac output during the carotid artery occlusion, three showed a progressive diminution of the output during the first minutes following the release of the occlusion. In the four other animals, the output continued to increase for several minutes after the release of the occluded arteries but at the same time the blood pressure was returning to its normal value. Finally no correlation was found between the increase of blood pressure and the increase of cardiac output.

Kenney, et. al. (1951) performed several experiments on this problem with the idea of, at least, producing a better understanding of the effects of carotid artery occlusion. Dogs anesthetized with chloralose or with sodium pentobarbital were used. Respiration and oxygen usage were recorded

in most experiments by the closed circuit method. However, in three experiments respiration was recorded by the open circuit method of Douglas the animals, therefore, breathing room air. The oxygen content of the arterial and venous blood samples taken during the experiment was determined by using the Van Slyke manometer apparatus. From the arterio-venous oxygen differences and the simultaneous oxygen usage cardiac output was calculated according to the Fick equation. Experiments were performed on five dogs in which oxygen usage was determined by closed circuit spirometry. There was no significant change in cardiac output during bilateral carotid artery occlusion in two experiments. One experiment showed a fall in cardiac output of approximately 11.5 per cent. In one experiment carotid occlusion apparently caused a rise in cardiac output, of the order of 20 per cent 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 per cent, but once more the release of occlusion did not restore the original value of cardiac output. In another experiment two results were obtained in successive carotid occlusion experiments. One result showed a reduction of cardiac output of 10 per cent. The estimation , however, showed no change in cardiac output after release of the carotid clamps. In the second experiment when both carotids were occluded there occurred a further fall in cardiac output of about 10 per cent. 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. In every experiment carotid occlusion raised the mean right atrial pressure. This rise in atrial pressure was of the order of 0.5 centimeters of water and was unrelated to the

effect of carotid occlusion on cardiac output. Finally, in the experiments conducted in which the oxygen usage of the animal was determined by the open-circuit method, the animal breathing room air, it was found that 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.

Methods used for determination of cardiac output. The first reasonable accurate attempt to determine the blood flow in man was undertaken by Adolf Fick (1870, 1944). He was particularly interested in hemodynamics and he created numerous ingenious apparatus and procedures in his extensive investigation. In 1870, Fick demonstrated the fact that the quantity of blood extruded from either ventricle in the course of a minute, namely the minute output of blood, could be determined by the adaptation of a formula based on the quantity of oxygen absorbed by the venous blood in the lungs in the same period. The formula used is as follows:

$$\text{Minute volume of blood flow in cc.} = \frac{\text{cc. of oxygen consumed in lungs/min. X 100}}{\text{difference in volumes per cent of the oxygen content of arterial and venous blood}}$$

In this method of examination numerous difficulties were encountered, but the basic ingenious principle of Fick's discovery continues to be used with modifications.

Starr and Schroeder (1940), utilized an approximate method for the determination of the minute output of the heart. The instrument, known as the ballistocardiograph, was composed of a sensitive balanced table on which the subject reclined. The unit recorded the recoil of the body when the blood was

propelled by the ventricles into the aorta and pulmonary artery. The graph thus secured was termed the ballistogram. The results of this method have been compared to those obtained by more direct and accurate methods have been found to correspond within a certain range.

Forssmann (1929), demonstrated the feasibility of introducing a small catheter from a vein of the right arm into the cavities of the right side of the heart. His investigation was motivated by a desire to secure a rapid and direct method of introducing stimulant drugs into the heart in instances of abrupt heart failure, in collapse during anesthesia, and in the circulatory collapse of accidental poisoning. He called attention to dangers attending intracardiac injection of drugs. Forssmann first devised his technic on cadavers and after attempting the procedure on a patient without complete success, had the method performed on himself. He did not realise the full potentialities of the procedure as adapted today, but stated it could be used for securing samples of blood for oxygen and carbon dioxide saturation studies.

Cournand and Ranges (1941) utilized the method to obtain samples of mixed venous blood and thus in a direct method apply the principle of Fick already discussed. Since then the method of cardiac catheterization has been extensively used and has added great precision in specific identification of certain solitary and multiple congenital cardiac defects. It has also proved to be an ideal method for the introduction of radiopaque substances such as diodrast. The limits of this method have as yet not been completely explored. Many workers have contributed to the refinements of cardiac catheterization and its extension in association with roentgenography is evident.

METHODS AND MATERIALS

Dogs of both sexes were used in these experiments. Three types of anesthesia were employed. Pentabarbital sodium (1 cc. of a 6.5 per cent solution per five pounds of animal weight or 30 mg/Kg. body weight injected intraperitoneally) was used on seven dogs and chloralose, injected intravascularly or chloralose with morphine was used on the other seven dogs. The chloralose concentration used was in the range of 80 to 100 milligrams per kilo of body weight. The morphine (one milligram per kilo) was injected intramuscularly about one half hour before any chloralose was given. This procedure proved very satisfactory.

The animal was placed in the supine position on a dog board and the extremities tied securely. An incision was made down the mid-line of the neck. The trachea was exposed, opened, and a cannula was passed through and tied securely. The cannula was then attached to the oxygen consumption measuring apparatus. The apparatus for the measurement of oxygen consumption in dogs consisted of a spirometer, of about 1500 cubic centimeters capacity, suspended in a water jacket, connected to the intra-tracheal cannula by rubber tubing. Levers were used to record the excursions of the spirometer on a revolving kymograph.

Through the midline incision, the two common carotid arteries were also exposed, and a silk ligature was placed around each vessel. The arteries, were, therefore, ready and accessible for easy occlusion during the experiment.

A cut-down was now made over the left external jugular vein, and the vein was isolated for approximately four centimeters. Two silk ligatires were placed under the vein and the distal ligature was tied securely, so as to prevent bleeding, when the vein was opened. The proximal ligature was held taut when the vein was opened so as to prevent back bleeding or any air from entering the vein. A transverse incision was made in the vein wall and the proximal lip of the opening was caught in a fine hemostat so that the lumen could be held open while the catheter tip was being introduced.

The venous catheter used was a modified uretheral type made of nylon, with a smooth non-wettable plastic covering, flexible and radiopaque. The catheter was fifty centimeters long, with only one opening at the tip and an air tight adapter at the proximal end. For convenience in manipulation, a slight curve was provided in the distal three or four centimeters. A number eight French catheter was preferable in dogs, since pressure tracings were more satisfactory with this than with a larger size catheter, and as a rule, the withdrawal of blood samples was easy.

The proximal end of the catheter was attached to a three way stopcock to which, at one outlet, was connected a plastic tube leading from an elevated reservoir of physiological saline solution, to which had been added one cubic centimeter of sodium heparin (Abbott) per liter of saline. The other outlet was connected, by vinyl plastic tubing, to the Sanborn electromanometer. Before introducing the catheter any great distance, it was wiped with saline solution enabling it to slip along inside the vein with greater ease. Once the catheter was introduced a constant drip from the reservoir bottle was allowed to pass through the catheter at a rate of ten to fifteen drops a minute, and only when

blood samples and pressure readings were being taken was this allowed to be stopped.

After the catheter was successfully introduced a cut-down was made over the left femoral artery, and the arterial indwelling needle was inserted, threaded up the artery, and left in place until subsequent blood samples and pressure recordings were made. At this time the needle was attached to a three way stopcock, to one arm was attached the tubing to the electromanometer, and to the other outlet was attached a syringe to collect the blood samples.

The indwelling arterial needle used for insertion into the femoral artery was a modified Lindemann type in which a medium bevel # 22 needle fits into a # 19 outer sleeve with a blunt tip. The syringe adapter was soldered about one and a half centimeters down the shaft of the # 19 sleeve, the base of the shaft being allowed to project past the adapter. When a Luer-lock syringe was attached for sampling, this free segment fitted directly into the end of the syringe and an air tight connection, preventing air seepage and blood clotting, was thus established.

Six to eight 10 cubic centimeter syringes with Luer-lock adapters used in blood sampling were prepared, before the experiment, by lightly greasing the surface of the barrel of the syringe with a silicone lubricant to avoid leaks and accumulation of air bubbles during sampling. The sides of the syringes were then moistened with 0.2 cubic centimeters of the following solution: 100 milligrams of sodium fluoride in ten cubic centimeters of sodium heparin (Abbott). The excess was expelled from the syringe.

The apparatus for recording blood pressures was the Sanborn electromanometer, based on the principle of the strain gauge unit, which permits the

recording of variations of pressure with a controlled amplification. The Sanborn poly-viso electrocardiograph machine was employed for the transcription of the tracings. Three tracings, the two pressure recordings and an electrocardiogram, were recorded on the animal simulatneously.

After the catheter had been advanced fifteen to twenty centimeters, further manipulation was done under fluroscopic control. This consisted in advancing, rotating, and withdrawing the catheter until its tip was placed in the desired location. The electrocardiograph was connected to the animal during this procedure, and was used to watch for cardiac irregularities caused by the catheter touching the heart wall. To reach the right auricle, the catheter tip was advanced until it lay about two to four centimeters above the level of the diaphram. To enter the right ventricle, the tip was rotated to point toward the left and then advanced. On one such effort it would easily cross the midline. Passage into the ventricle was checked by noting the pressure recorded by the electromanometer.

In passing the catheter, it was never advanced against resistance, and caution was exercised to avoid buckling, or the formation of a "U". Only when the catheter was pointing in the desired direction was it advanced rapidly.

The experiments that were performed made it necessary to collect blood samples and record blood pressures in the heart and large blood vessels in rapid sequence.

Blood samples were taken from the apex region of the right ventricle and the femoral artery simultaneously. During the blood sampling the animals' oxygen consumption was likewise measured for a period of approximately three

to five minutes.

In the collection and handling of the blood samples the following procedures were used: a syringe containing three or four centimeters of physiological saline and heparin and no air bubbles was attached to the three way stopcock connecting the catheter to the saline reservoir. Through proper manipulation of the stopcock and the syringe it was made certain that the circuit was free from any air bubbles and that the flow from the catheter was free. Then suction was applied gently until blood flowed back easily into the syringe. No forceful suction was used while sampling in the right ventricle, since it would often cause ectopic beats. Then the Luer-lock syringe used for sampling, and prepared as described previously, was adapted to the three way stopcock and a blood sample of seven cubic centimeters was obtained. The sampling syringe was disconnected and the three way stopcock and catheter were immediately flushed with several cubic centimeters of saline solution, and the continuous drip started again. Meanwhile, the syringe was then stoppered with air-tight caps, and rotated in the hands to force any air bubbles that may be present to the top of the syringe. This air was expelled forcefully. Then a few drops of mercury were drawn into the syringe, which was then rotated, stoppered again, and placed in a container of ice cold water until gas analysis was carried out on the sample. A similar procedure in regards to drawing blood from the femoral artery, was done concurrently with that done on the right ventricle.

Occasionally, some difficulty in drawing blood from the right ventricle was encountered and a bad sample would be taken. If this was the case, then both right ventricle and femoral artery blood samples were discarded and

repeat samples were taken.

Before blood was removed from a chilled syringe, for gas analysis, it was rotated to thoroughly mix the blood constituents. The blood was transferred under pressure into an Ostwold-Van Slyke pipette from the syringe by means of a short piece of rubber tubing connecting the two openings. The pipette was then fitted with a special-made rubber tip so that the transfer of blood would be airtight. The analysis of blood oxygen content, capacity, and saturation was in accordance with the methods of Van Slyke and Neill (1924), and Peters and Van Slyke (1943).

Three and sometimes four blood samples were taken in the course of the experiment. The control samples were taken immediately before the common carotid arteries were clamped. Right ventricular and femoral artery pressures were subsequently taken. An electrocardiogram was taken to check the heart rate. Oxygen consumption was measured simultaneously by the closed circuit method, i.e. while the animal was breathing 100 per cent oxygen.

The common carotid arteries were now clamped while the poly-viso was running and a record was taken at the time of clamping and during the four or five minute period of carotid artery occlusion. Blood samples were again taken before pressure readings were recorded. Usually two pressure recordings were taken during the occlusion period. The clamped carotids were then released and pressure readings were taken at five, ten, and twenty minute intervals following. The femoral artery and right ventricular blood samples were taken immediately before the twenty minute interval.

In this manner blood samples were taken in this sequence: control before clamping, during occlusion, and a control twenty minutes after releasing

the clamped carotid arteries. This procedure seemed to work most satisfactory. From the arterio-venous oxygen differences and the simultaneous oxygen usage cardiac output was calculated according to the Fick equation.

The pressure recordings were taken from the right ventricle through the catheter, and from the indwelling arterial needle in the femoral artery. In setting up the apparatus for taking the pressure recordings, the free end of the vinyl plastic tubing connected to the manometer was fixed near the animal at a level corresponding to the plane of the heart, which in the dog was approximately one third in the distance of the chest depth, measured from the spine, or at the level of the peripheral artery for the intra-arterial pressure recordings. The free side arm of the three way stopcock connecting the catheter and the saline reservoir was flushed with fluid from the reservoir and then attached to the plastic tubing. The animal was sacrificed at the end of the procedure. (Cournand and Ranges, 1941; Cournand and Riley, 1945; Dexter, Haynes, and Seibel, 1946; Dexter, 1947; Sosman, 1947; and Burchell and Wood, 1950).

The stroke volume of the heart was determined by dividing the cardiac output in cubic centimeters per minute, by the heart rate per minute. The cardiac index was determined by dividing the cardiac output, in liters per minute, by the surface area of the dog in square meters. Meeh's formula using Rubner's constant (Benedict, 1938) for the dog was applied in finding body surface area:

$$\text{Surface area} = \frac{11.2\ W^{0.677}}{10{,}000}$$ where W is weight in grams.

RESULTS

The effects of bilateral carotid artery occlusion on certain hemodynamic aspects of the dog are presented in Table I. Experiments were performed on a total of fourteen dogs weighing 9 to 17.6 kilograms. All the experiments were done under closed circuit spirometry using pure oxygen. In seven experiments, sodium pentabarbital, was used as the anesthesia; in four experiments chloralose was used, and in three experiments chloralose and morphine anesthesia was utilized.

Cardiac Output - During the occlusion of the carotid arteries, twelve of the fourteen experiments did not show a significant change in the output. Of these, the cardiac outputs in six of the experiments showed decreases from that of the control value. These included experiments one, a decrease of 4 per cent; two, a decrease of 11.3 per cent; six, a decrease of 6.6 per cent; seven, a decrease of 11.4 per cent; nine, a decrease of 8.7 per cent; and twelve, a decrease of 5.3 per cent. The remainder of the experiments in this category showed slightly increased outputs during the occlusion of the arteries. These included experiments three, an increase of 8 per cent; four, an increase of 6 per cent; five, an increase of 9.8 per cent; eight, an increase of 13.7 per cent; ten, an increase of 12.3 per cent, and eleven, an increase of 5.1 per cent. In experiment ten, showing an increased cardiac output of 12.3 per cent, the control output after the carotid artery clamps were removed dropped only 4 per cent and

not to the original control value. The remaining two experiments showed substantial increases in the cardiac output between the control and occlusion values. One (exp. 13), produced an increase of 34.5 percent, the other (exp. 14) showed an increase of 44 per cent. However, in both cases the control outputs after the occluded carotids had been released did not return to normal but instead remained near the occlusion output values. There was no apparent correlation between the cardiac changes and the various anesthesias employed.

Oxygen consumption. - In eight dogs (# 2, 3, 5, 6, 11, 12, 13, 14) the consumption increased, usually slightly during the latter part of the occlusion period, but more noticeable during the post-occlusion control period. This change in oxygen consumption ranged from an increase of 12.5 per cent (exp. 3) to an increase of approximately 55 per cent (exp. 13). In six experiments (# 1, 4, 7, 8, 9, 10) no change in oxygen consumption during the entire experiment was noted.

Respiratory rate. - In ten experiments (# 3, 4, 5, 7, 9, 10, 11, 12, 13, 14) practically no change in the rate was noted during the entire procedure. In one experiment (# 8), a slight increase in the rate was observed. Another experiment (# 2) showed a moderate increase in the respiratory rate. Finally, considerable increase in respiration was seen in experiment six. The respiratory rate was not determined in experiment one, due to its irregularity and rapidity.

Heart rate. - In ten experiments (# 2, 4, 5, 6, 7, 8, 9, 12, 13, 14) moderate to large increases in the heart rate were observed during the carotid artery occlusion. In five of these experiments (# 4, 6, 7, 9, 13) the post-occlusion heart rate returned close to the control or to lower levels. In four experi-

ments (# 1, 3, 10, 11) there was no change in the heart rate during the occlusion.

Stroke volume. - For the most part the stroke volumes did not show any significant changes. In eleven experiments (# 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 14) it mirrored the change in cardiac output. However, in three experiments (# 4, 5, 13) this did not apply. In experiment four while the cardiac output was rising, the stroke volume showed no change. In experiment five, the stroke volume decreased slightly when the cardiac output increased. In experiment thirteen, again the stroke volume decreased when the cardiac output increased.

Right ventricular pressures. - The following results were observed in the end-diastolic pressures of the right ventricle: in eleven dogs (Exp. 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14) the end-diastolic pressures increased immediately after the carotid occlusion. In three dogs (Exp. 1, 7, 13) practically no change was recorded in the end-diastolic pressures. The mean right ventricular pressure showed an increase during the occlusion, in eight dogs (Exp. 2, 3, 5, 6, 9, 10, 12, 14). In six dogs (Exp. 1, 4, 7, 8, 11, 13) there was almost no change of the mean pressure during this period. The systolic pressures of the right ventricle showed small increases in all the experiments.

Femoral artery pressures. - The arterial pressure increased in every case during the carotid occlusion. The mean arterial pressure showed a range of increase from ten to sixty millimeters of mercury over that of the resting control, with an average increase of about thirty-five millimeters of mercury. The pulse pressure, during the occlusion, in all cases, increased over that of the normal resting stage.

Left ventricular pressures. - A small group of experiments (four) was done in which the left ventricular pressures were recorded during carotid occlusion, (see figure 2). In every case there was a rise in the systolic and end-diastolic pressures.

Cardiac work. - As a result of carotid artery occlusion, the work of the heart increased in every experiment. The average rise was approximately 38 per cent (Table II).

TABLE I

EFFECTS OF BILATERAL CAROTID ARTERY OCCLUSION IN THE DOG

Exp. # Weight (Kg) Surface Area (m^2)	O_2 Vol.% Art.	O_2 Vol.% Ven.	O_2 A-V Diff.	Oxygen Usage cc/min	Rates (per min) Resp	Heart	Cardiac Output Per Min (cc)	Per Stroke (cc)	Cardiac Index $l/min/m^2$	Pressures (mm Hg) Fem Art S	D	M	RT Heart S	D	M	Conditions
	12.50	9.54	2.96	74	—	150	2500	16.6	4.43	135	75	100	30	2	12	Cont
1 N* 11.3 0.564	11.26	8.05	3.21	77	—	150	2400	16.0	4.25	200	130	150	32	2	13	Occlud
	10.91	7.86	3.05	70	—	134	2300	17.2	4.08	125	80	100	30	0	11	Cont
	21.63	14.63	6.99	151	11	166	2160	13.0	2.89	155	122	125	42	1	21	Cont
2 N* 17.2 0.746	21.66	14.03	7.63	146	11	188	1914	10.2	2.57	190	135	150	43	4	23	Occlud
	22.20	13.45	8.75	207	25	188	2366	12.6	3.17	155	110	125	41	3	15	Cont
	21.69	15.90	5.79	57	21	188	984	5.2	1.79	165	125	140	30	2	12	Cont
3 N* 10.8 0.548	23.44	17.69	5.75	61	21	188	1060	5.6	1.93	185	135	155	32	8	23	Occlud
	22.52	17.03	5.49	64	24	188	1165	6.2	2.13	170	125	140	35	-2	15	Cont

N* = Nembutal

TABLE I (Cont.)

Exp. # / Weight (Kg) / Surface Area (m^2)	O_2 Vol.% Art.	O_2 Vol.% Ven.	O_2 A-V diff.	Oxygen Usage cc/min	Rates (per min) Resp	Rates (per min) Heart	Cardiac Output Per Min (cc)	Cardiac Output Per Stroke (cc)	Cardiac Index $l/min/m^2$	Pressures (mm Hg) Pem Art S	D	M	Rt Heart S	D	M	Conditions
	20.69	16.42	4.27	46	6	142	1077	7.6	1.99	170	115	140	24	2	14	Cont
4 N* 10.6 0.541	19.77	15.74	4.03	47	7	150	1141	7.6	2.11	190	130	150	25	4	15	Occl
	19.88	15.71	4.17	47	7	150	1127	7.6	2.08	190	130	150	25	4	15	Occl
	19.77	15.66	4.11	45	6	120	1095	7.5	2.02	165	115	135	21	2	12	Cont
	17.39	13.40	3.99	52	16	125	1304	10.4	2.70	160	105	120	48	3	16	Cont
5 N* 9.0 0.485	17.84	13.72	4.12	59	21	143	1432	10.0	2.95	210	140	168	49	6	20	Occl
	17.86	13.70	4.16	59	21	143	1418	9.9	2.92	210	140	168	49	6	20	Occl
	18.21	12.94	5.27	67	17	138	1271	9.5	2.62	162	120	135	47	3	14	Cont
	16.91	11.83	5.08	90	40	200	1772	8.9	3.32	225	163	188	38	2	14	Cont
6 N* 10.4 0.533	17.52	11.54	5.98	99	76	214	1655	7.7	3.10	260	190	215	42	5	20	Occl
	16.68	11.03	5.65	107	56	193	1894	9.8	3.55	195	140	155	34	2	10	Cont

N * = Nembutal

TABLE I (Cont.)

Exp. # Weight (Kg) Surface Area (m^2)	O_2 Vol.% Art.	O_2 Vol.% Ven.	O_2 A-V Diff.	Oxygen Usage cc/min	Rates (per min) Resp	Rates (per min) Heart	Cardiac Output Per Min (cc)	Cardiac Output Per Stroke (cc)	Cardiac Index l/min/m^2	Pressures (mm Hg) S	D	M	S	D	M	Conditions
	15.35	11.84	3.51	64	16	162	1823	10.8	2.40	220	155	178	30	2	9	Cont
7 N* 17.6 0.758	15.57	11.17	4.40	71	22	174	1614	9.3	2.13	265	189	210	32	3	9	Occl
	15.41	11.97	3.44	65	22	158	1890	11.9	2.50	162	112	132	28	2	10	Cont
	18.71	15.09	3.62	84	17	157	2320	14.0	3.29	175	115	135	42	1	12	Cont
8 C* 15.8 0.706	19.34	15.39	3.95	104	25	176	2633	14.9	3.73	250	150	195	44	4	10	Occl
	19.34	15.41	3.93	104	25	176	2646	15.0	3.74	250	150	195	44	4	10	Occl
	18.00	14.16	3.84	90	25	166	2344	14.3	3.32	175	100	125	35	1	9	Cont
9 C* 15.8 0.706	21.40	16.21	5.19	103	23	120	1984	16.5	2.81	200	140	160	82	3	30	Cont
	21.67	16.54	5.13	93	23	136	1812	13.3	2.56	240	160	185	100	5	45	Occl
	21.67	15.56	6.11	99	19	125	1620	13.0	2.30	190	140	150	65	5	35	Cont
	20.46	16.20	4.26	73	20	230	1713	7.5	3.21	155	105	120	47	1	13	Cont
10 C* 10.4 0.533	19.53	15.32	4.21	81	20	230	1926	8.4	3.61	200	138	155	48	4	15	Occl
	21.41	17.26	4.15	77	24	214	1855	8.7	3.48	155	112	130	44	3	13	Cont

* N = Nembutal
* C = Chloralose
CM = Chloralose and morphine

TABLE I (Cont.)

Exp. # Weight (Kg) Surface Area (m^2)	O_2 Vol.% Art.	O_2 Vol.% Ven.	O_2 A-V Diff.	Oxygen Usage cc/min	Rates (per min) Resp	Rates (per min) Heart	Cardiac Output Per Min (cc)	Cardiac Output Per Stroke (cc)	Cardiac Index l/min/m^2	Pressures (mm Hg) S	D	M	S	D	M	Conditions
11 C* 9.0 0.485	20.54	17.50	3.04	44	16	175	1447	8.3	3.00	165	110	125	35	0	9	Cont
	20.52	17.30	3.22	49	13	177	1522	8.6	3.14	207	140	160	40	4	10	Occl
	20.62	16.60	3.96	56	13	150	1414	9.4	2.92	182	118	135	34	0	8	Cont
12 CH* 16.2 0.717	20.29	16.41	3.88	75	10	82	1933	23.6	2.70	165	100	108	33	1	9	Cont
	20.99	16.29	4.70	86	13	94	1830	19.5	2.55	223	150	170	38	6	11	Occl
	20.27	15.85	4.42	88	13	111	1990	18.0	2.78	175	120	140	37	2	10	Cont
13 CH* 11.3 0.564	20.91	16.30	4.61	55	6	50	1193	23.8	2.11	195	120	130	33	4	10	Cont
	20.94	16.52	4.42	71	8	75	1606	21.4	2.85	220	140	180	49	4	11	Occl
	21.30	15.53	5.77	85	7	58	1473	25.8	2.61	200	120	135	41	1	10	Cont
14 CH* 11.3 0.564	20.74	14.57	6.17	58	5	120	940	7.8	1.67	160	105	115	33	0	10	Cont
	21.00	15.76	5.24	71	6	125	1355	10.6	2.40	240	145	160	41	2	13	Occl
	20.73	14.31	6.42	83	9	188	1292	6.8	2.29	135	85	100	38	1	17	Cont

* C = Chloralose

CH = Chloralose and morphine

TABLE II

THE EFFECTS OF CAROTID ARTERY OCCLUSION ON CARDIAC WORK

Exp. #	Control	Artery Occluded	% increase
1.	250,000	360,100	44
2.	270,000	287,000	6
3.	137,760	164,300	20
4.	150,780	171,000	13
5.	156,480	243,100	54
6.	332,760	355,830	7
7.	324,500	338,940	4
8.	313,200	515,970	64
9.	317,440	335,220	5
10.	205,560	298,530	45
11.	180,875	243,520	34
12.	212,300	311,100	45
13.	155,190	288,000	85
14.	108,100	216,800	100
			av. 38 ± 8 %

CW = M.B.P. x C.O.*

* C.W. = cardiac work

MBP = mean arterial blood pressure

C.O. = cardiac output

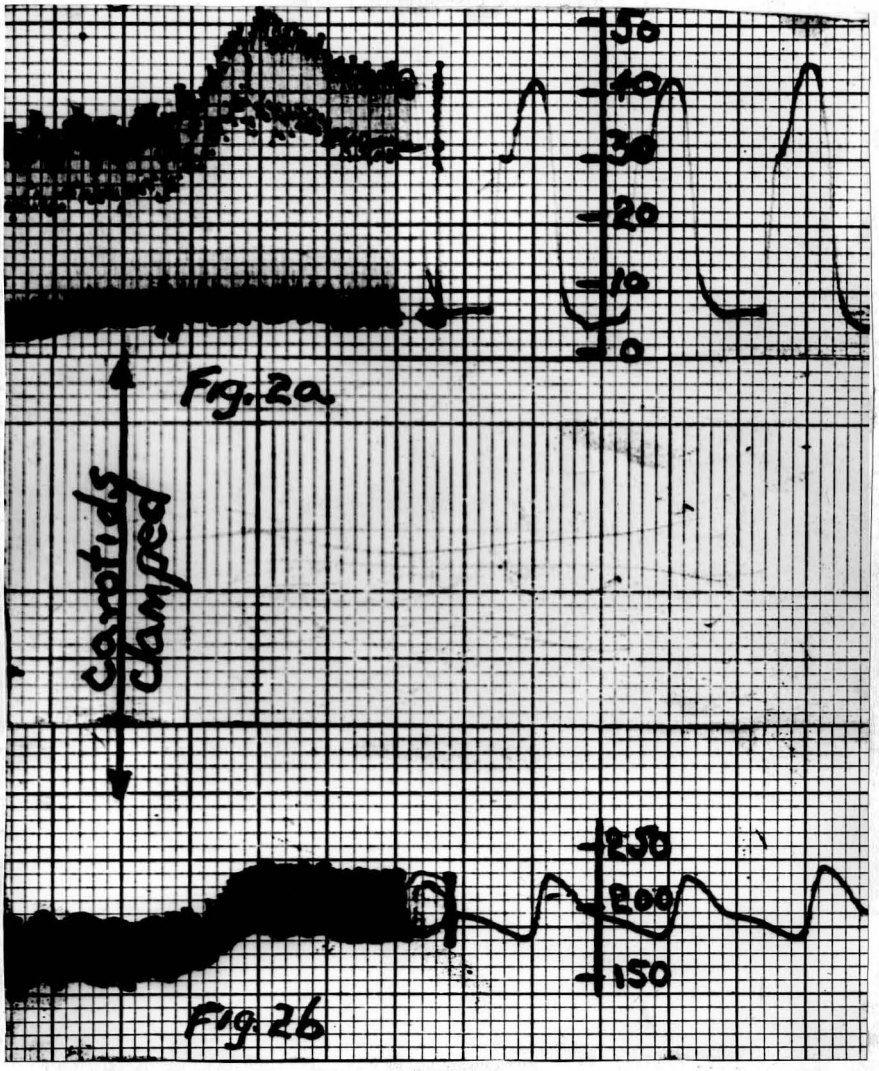

Figure 2. PRESSURE CHANGES UPON OCCLUSION OF THE COMMON CAROTID ARTERIES (MILLIMETERS OF MERCURY): a) RIGHT VENTRICULAR PRESSURE, b) FEMORAL ARTERY PRESSURE.

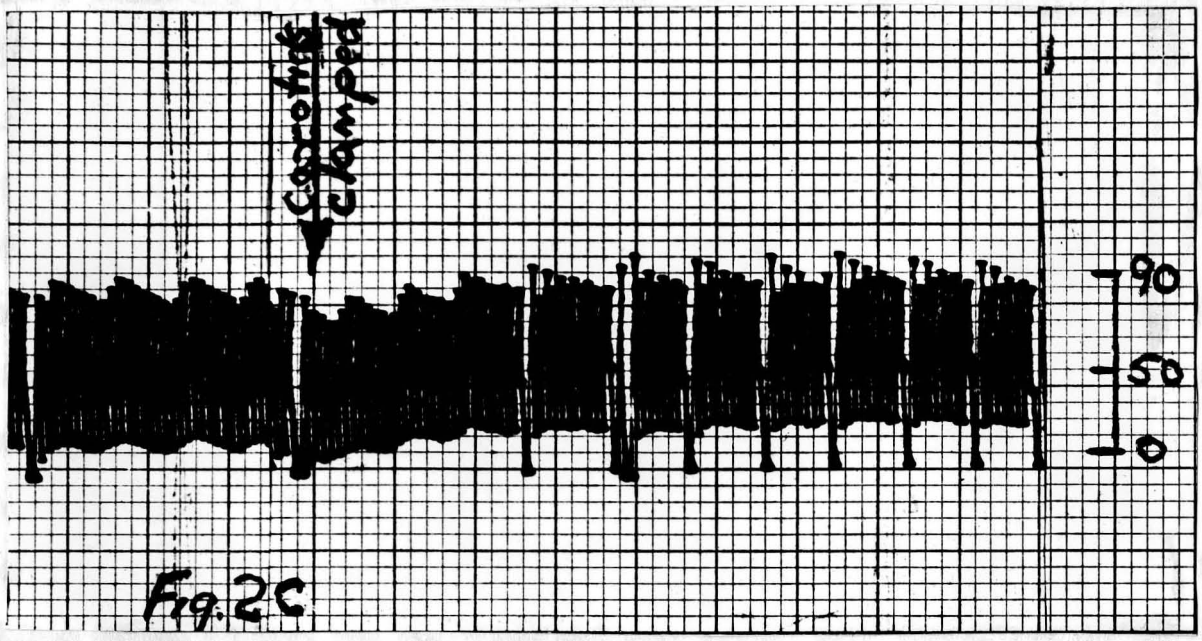

Figure 2c. LEFT VENTRICULAR PRESSURE CHANGES.

DISCUSSION

Cardiac Output - No significant changes were observed in the cardiac output of our animals, after occlusion of the two common carotid arteries. Our results are not in agreement with those of Charlier and Philippot (1947) who under similar experimental conditions noted that the cardiac output invariably increased during carotid artery occlusion. They recorded a mean rise of cardiac output of 54.6 per cent (range 17.5 to 77.9) in their dogs. On the other hand Kenney and his co-workers (1951) showed results, again in similar experiments, in agreement with ours in that they observed no significant changes in cardiac outputs. The results in the experiments of Charlier and Philippot, in which open circuit spirometry was utilised, were based on single control samples of expired air during each experiment assuming that this value and hence the oxygen consumption value, would not vary significantly during the post-occlusion period. Also, only one determination of the arterial blood oxygen content was performed and that result used throughout the experiment for both control and carotid occlusion values. Kenney and co-workers believe that the latter assumption is less dangerous than the first since increased respiratory activity, they state, causes only minor changes in the amount of oxygen dissolved in the blood. This appears certainly to be a valid criticism in that many factors such as pulmonary ventilation, pulmonary blood flow, and pulmonary blood content may have affected expired air oxygen content

in the manner that would change the computed cardiac output had samples been taken for the post-occlusion control. Also in regard to the second criticism of taking only one arterial oxygen sample, in our experiments, significant changes in arterial oxygen content during the time of the experiment were noted in most instances. These changes, slight as they may seem, appear more significant when applied to the determination of cardiac outputs. As an example we may use experiment three, in which the cardiac output increment during the occlusion was only eight per cent based on the measured A-V oxygen difference of 5.75 volumes per cent. However, if we were to substitute the pre-occlusion control value of arterial oxygen content for the occlusion value as was done in the experiments of Charlier and Philippot, the resulting A-V oxygen difference would be only 4.0 volumes per cent. This smaller A-V oxygen difference produces a significant change in the cardiac output determined by using the Fick formula, the cardiac output now showing a 55 per cent increase over the control value. Thus, the determination of the oxygen content of the arterial blood during each step of the experiment appears to be crucial.

Another reason for the discrepancies between results obtained by Charlier and Philippot and those obtained in our experiments as well as those of Kenney et. al. lies in the observation by Charlier and Philippot of increased venous oxygen content during carotid occlusion. Such an alteration was noted neither by us nor by Kenney et. al. The reason for this discrepancy is not apparent.

Chemoreceptor response to carotid artery occlusion has been suggested (Von Euler and Liljestrand, 1943; Neil et. al., 1949) to take some part in the

hemodynamic changes. This evidence is not substantiated in our experiments. Significant changes in the respiratory rate which should be the primary response in such a condition did not result from carotid artery occlusion. Moreover, Kenney and his co-workers have shown that in animals breathing room air, there was no significant change in the cardiac output during carotid occlusion, as compared to animals breathing pure oxygen in which similar results were obtained.

Arterial blood pressure. - The increase in the systemic blood pressure, upon occlusion of the carotid arteries is a well-known phenomenon. Several investigators (Hering,1927; Heymans, 1929; Danielopolu et. al., 1927 and others) have proven this substantially in many species of animal. Likewise in our dogs there was an average increase in the mean arterial blood pressure of approximately 35 per cent. Presumably, during occlusion the change in carotid endovascular pressure affects the presoceptive nerve endings of the sinus. The inhibitory impulses normally present from the carotid sinus and reflexly affecting the vasomotor center (Winder, 1937; and others) are now depressed resulting in vasoconstriction and a blood pressure increase. An increased secretion of adrenalin at this time may also affect the caliber of the blood vessels (Heymans et. al., 1925, 1929).

Should the cardiac output be considered to rise markedly as has been suggested by some (Charlier and Philippot) it would appear that a vasoconstrictor response to carotid occlusion need not be of primary importance; a marked cardiac output increase in itself would explain a blood pressure increase without a change in the peripheral resistance as represented by vasoconstriction. In the experiments of Charlier and Philippot, there would need be even a

decreased peripheral resistance (Kenney et. al., 1951). In our experiments, in which the cardiac output remained unchanged, the increase in the blood pressure can be based only upon the increase in peripheral resistance due to vasoconstriction and to the procedure itself. This is in keeping with the numerous observations in which the vessels of the skin and viscera have been studied (Heymans, 1929; Malmejac, 1934). Also, it was observed by Heymans and Bouckaert (1933) that a sympathectomy changed the blood pressure response to carotid sinus occlusion so that there was no rise in blood pressure.

It is possible that local areas of vasodilatation could explain the diminution of peripheral resistance as must be postulated if cardiac output is said to increase markedly in the face of the already known areas of vasoconstriction. It has been suggested that an increased muscle blood flow would possible account for an increased cardiac output, however, according to experiments done by McDowall (1950), the muscle vessels and consequently the muscle blood flow are relatively insensitive to carotid artery occlusion.

Cardiac work.- The maintenance of the normal cardiac output during the time of vasoconstriction, as reflected in the rise of systemic blood pressure, indicates increased cardiac work. This is shown in Table II, where the average rise in the experiments was 38 per cent. Two methods are possible by which the myocardial work is increased: (1) by an increased rate of the heart beat and (2) by a greater force of contraction.

As has already been shown the heart rate although practically always increasing during occlusion, increases only slightly. If the rise in the heart rate were the sole factor in maintaining the output one would expect a decrease in the stroke volume, that is dependent only upon the fact that the

ventricular filling time is shorter. In such a case one would not expect a rise in left ventricular diastolic pressure during occlusion as found in our experiments since the diastolic volume should remain practically unchanged.

The fact that there is a rise in left ventricular diastolic pressures (with a diastolic volume increase) suggests the second possibility of a more forceful myocardial contraction. This intrinsic mechanism of increased myocardial work with increased diastolic stretch, other conditions remaining unchanged, has been described by Starling (1918).

Also to be considered is an increased force of myocardial contraction that may be secondary to neurogenic and hormonal factors (Heymans et. al., 1925, 1929).

Interrelationship of factors. - The observations in these experiments, in response to hypotension in the carotid sinus, included: (1) an unchanged cardiac output (2) a gradual increase in systemic blood pressure (3) a mild increase in heart rate (4) an immediate rise in the right ventricular systolic and end-diastolic pressures that retreated after a few minutes to a lower level but still higher than the control level, and (5) a gradual increase in the left ventricular systolic and diastolic pressures.

The actual sequence of events in this phenomenon could be ascribed to one of three possibilities: (1) an initial event of arterial-vasoconstriction (2) an initial increase in right-sided pressures or (3) a combination of both.

Firstly, if it is assumed that the sequence of events is initiated by an increased peripheral resistance, due to vasoconstriction, one would expect the first few heart beats following the carotid occlusion to be of a

lower than normal stroke volume. This decrease in ventricular emptying would result in an increased diastolic volume that would bring into play intrinsic myocardial mechanisms as described by Starling; i.e., the increasing left ventricular diastolic volume (with an accompanying increased diastolic pressure) stimulates the myocardium to greater work and after a period of compensation the output would equal the control output but at a higher level of diastolic stretch. The increased left ventricular diastolic pressure is reflected backward through the left atrium, pulmonary vascular system, and finally the right side of the heart where, similarly an intrinsic myocardial compensation occurs. Finally the right and left cardiac outputs are equalized at a level close to the control. This sequence of events would explain all the observed data except for an immediate rise in the right ventricular pressures which occur prior to the time that would be expected in the above interpretation. This can be seen in figure 2.

The explanation for the immediate transient rise in the right ventricular systolic and end-diastolic pressures hinges upon either (1) an increased resistance ahead, i.e., in the pulmonary circuit or (2) an increase in the venous or right cardiac tonus. There is as yet no good evidence favoring the pulmonary vasomotor mechanism. Likewise the factor of cardiac tonus is in a highly questionable status. However, there has been evidence presented for a venomotor mechanism and also for this mechanism as a factor during hypotension in the carotid sinus area. (Gollwitzer-Meier & Schulte, 1931; Gollwitzer-Meier, 1932).

Should the increase in venous tone with its resultant increase in the right heart inflow be considered as the initiating mechanism the sequence

could be as follows: first the increased venous tone would increase the right heart filling pressure and would increase the right ventricular diastolic volume. This results in an increased right ventricular output in response to the intrinsic myocardial mechanism of Starling. Pulmonary vascular volumes, as well as pressures, would rise and this ultimately would be reflected in a left ventricular diastolic volume increase. Such an increase would result in a greater left ventricular cardiac output with (assuming no changes in the peripheral resistance) an increase in the systemic arterial pressure. Again such an explanation is not completely in keeping with our findings in that it assumes an increased cardiac output maintaining an increased arterial blood pressure.

The third possibility of vaso- and veno-constriction occurring concomitantly on carotid artery occlusion explains completely the data observed. This would involve increased pressures forward to the heart in the arterial system and behind the heart in the venous system. The venomotor phenomenon appears to be transitory (Landis & Hortenstine, 1950). However, the overall picture would be represented by a shift of blood toward the heart and lungs.

SUMMARY

1) Certain hemodynamic changes as a result of bilateral common carotid artery occlusion were studied in fourteen dogs under pentabarbital or chloralose anaesthesia. Well-known techniques of cardiac catheterisation were utilised in the recording of right ventricular pressures. The Fick method was employed in the determination of cardiac outputs.

2) No significant alterations in the cardiac outputs were observed during the occlusion of the carotid arteries.

3) The respiratory rate was not increased substantially so that the chemoreceptor response to carotid artery occlusion was not considered to be of importance in these experiments.

4) In most of the experiments moderate to large increases in the heart rate resulted from the occlusion.

5) There was an immediate rise in the right ventricular end-diastolic pressures in eleven dogs following carotid occlusion. This increase dropped slightly later in the occlusion but was still higher than the control value. The right ventricular systolic pressures showed small increases. The left ventricular systolic and end-diastolic pressures showed small but definite increments.

6) On carotid artery occlusion the cardiac work, based on the product of the mean arterial blood pressure and the cardiac output, increased in all the experiments, with an average rise of 30 per cent.

7) The sequence of events following carotid artery occlusion were discussed. It was concluded that the observed data could not be explained assuming that either a vaso- or veno-constriction to be the sole initiating factor. However, the entire picture could be correlated if it were assumed that there was a concomitant vaso- and veno-constriction following carotid occlusion.

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APPROVAL SHEET

The Thesis submitted by Harry John Pappas has been read and approved by three members of the Department of Physiology.

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form, and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

August 31 1953 — Date

Albert Omachi — Signature of Adviser