Carotid and Aortic Regulation of Arterial Blood Pressure

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SUMMARY The major purpose of this presentation has been to indicate that in a very classical area of cardiovascular physiology, which has fundamental importance and which has been studied for many years, there are still major unanswered questions. These include the gain or sensitivity, and perhaps even the ultimate function, of baroreceptors in the carotid sinus and aortic arch and in the cardiopulmonary region. In addition, the function of these receptors in hypertension, their role in body fluid regulation, as well as the role of body fluids in the maintenance of arterial pressure, need further clarification.

It is surprising that despite the many excellent studies in this area there are so many things to learn about the "oldest" and "best-known" cardiovascular reflexes. It is heartening that these problems are under intensive study.

This presentation concerns the arterial baroreceptor reflex, the earliest recognized and most powerful reflex controlling the cardiovascular system. It is my intention to re-examine and evaluate some aspects of this reflex. The anatomical units involved in the reflex are diagrammed in figure 1. Pressoreceptors in the walls of the carotid artery at the carotid sinus and in the region of the aortic arch increase their firing frequency with increased pressure, and decrease their frequency with decreased pressure. Impulses from these sensory receptors travel centrally to the medulla in the carotid sinus nerve and in the vagus nerve. Some sensory fibers from the aortic pressoreceptors make up a separate "depressor" nerve, which often parallels the vagus nerve bilaterally in the rabbit. The depressor nerve is often separate in the cat and often runs as a separate branch between the vagus and the cervical sympathetic fibers in the neck of the dog. The depressor nerve is thus at times separate and at times inextricably mixed with the vagus, depending on the species. Even when there is a separate depressor nerve, it does not contain all aortic pressoreceptor fibers. The neural output of the medullary control centers appears in the motor vagus and sympathetic nerves.

Increased arterial pressure, as indicated, increases the rate of receptor firing. The resultant reflex increase in vagal activity slows the heart. A reflex decrease of sympathetic motor activity to the heart further slows cardiac slowing and may decrease stroke volume by decreasing myocardial contractility. Decreased sympathetic vasomotor discharge also lowers peripheral resistance. All of these effects lower the blood pressure. With hemorrhage and a fall in blood pressure, decreased baroreceptor firing reflexly produces increased sympathetic and decreased vagal motor activity, leading to an increase in heart rate, a possible increase in myocardial contractility, and an increase in peripheral vascular resistance, all tending to restore the normal pressure. Maintenance of normal arterial pressure in the face of disturbances tending to lower or to raise pressure is thus dependent on the baroreceptor reflex.

The pressoreceptors are sensitive to mean pressure and to rate of change of pressure.\(^1\) The normal arterial pressure pulsations are important in receptor discharge. Decreased pulsation has the same reflex effect as a decrease in mean arterial pressure.\(^4\) With a normal arterial pressure pulse, firing of the receptors is greatest during the rising phase of arterial pressure, as shown in the classical study by Bronk and Stella\(^1\) (fig. 2) and elsewhere. Attempts to relate reflex responses to mean pressure at the baroreceptors may thus be in error in cases where the pressure pulsations change.

Figure 3 diagrams the reflex as a control system. Changes in pressure lead to changes in receptor firing. The resultant reflex changes in heart rate and stroke volume are determined by the central nervous system and tend to restore the pressure to its initial level. This is the traditional picture of this reflex as described in classical reports.\(^5\)\(^,\)\(^6\)

Carotid and Aortic Receptors: Range and Sensitivity

In the traditional picture, both the carotid and aortic receptors are viewed as normally operative. The data in figure 4, from the work of Donald and Edis,\(^7\) indicate that the aortic receptors have a higher threshold, a higher operating range, and a lower sensitivity than the carotid receptors. These and other data\(^8\)\(^,\)\(^10\) pose the question: Do the aortic receptors contribute to the control of arterial pressure near the normal physiological range, or do they function only or mostly when arterial pressure is elevated? Figure 5, from the work of Kumada and Sagawa,\(^11\) indicates that the electrical activity of the aortic arch receptors is not confined to pressure above normal. In this study, small decreases in blood volume decreased aortic nerve firing as arterial pressure fell. This result has been seen in several laboratories, although some data indicate that the sensitivity of the aortic receptors is lower than that of the carotid receptors when both receptors are exposed to nonpulsatile pressure. Angell James and Daly\(^12\) have produced evidence that in the dog the decreased sensitivity of the aortic receptors is seen when the receptors are exposed to nonpulsatile pressure, but disappears if the pressure is pulsatile.

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normal animals (fig. 6). These dogs who have only aortic receptors maintain the same normal arterial pressure as when both aortic and carotid receptors are present. These animals show a very mild hypertension immediately following denervation, but there is no significant increase in arterial pressure a week following surgery. Results in awake animals thus conflict with expected results from experiments in anesthetized animals.

**Baroreflex Sensitivity or “Gain”**

An important unanswered (or, at best, controversial) question concerns the sensitivity or “gain” of the baroreceptor reflexes. Gain is most easily defined as a change in systemic pressure for a given change in baroreceptor pressure. It is usually studied in animal experiments in which the carotid sinuses are isolated from the systemic circulation and carotid pressure is altered. These are called “open-loop” experiments as distinguished from “closed-loop” experiments, in which carotid and systemic arterial pressures are equal. For a linear control system, the relationship between open-loop and closed-loop gain is:

\[ G_c = G_o / (1 + G_o) \]

where \( G_c \) is closed-loop gain and \( G_o \) is open-loop gain. This simple formulation neglects the pulsatile pressure sensitivity of arterial baroreceptors, but it is useful in thinking about the reflex. The aortic receptors must be eliminated from such experiments, usually by vagotomy. If the aortic receptors are operative, they will initiate a counterreflex as they respond to changes in arterial pressure. Such experiments are, of course, performed under anesthesia, and as described, test only carotid receptors.

In denervation experiments conducted by Dr. Cyril Ito and me, we find that awake, unanesthetized dogs without carotid receptors have the same mean arterial pressure as do
The gain indicates the relative power of the reflex to control pressure. If the open-loop gain of the reflex is low, a perturbation which would alter pressure (hemorrhage, hyperperfusion, administration of cardioactive or vasoactive drugs) will have a large effect. If the reflex gain is high, the change will be much more completely corrected. If the open-loop gain of the reflex is 1, a perturbation will be only 50% corrected, i.e., the change will be half as big as if there were no reflex at all. If the gain is 9, the perturbation will be about 90% corrected. Complete correction of a perturbation indicates an infinite open-loop gain and a closed-loop gain of 1.0.

In most of the classical experiments, the apparent open-loop gain is about 1. However, in our early experiments we found higher gain in cats and dogs. Recently, McRitchie and Vatner et al. compared blood pressure responses to vasoactive drugs in dogs before and after sino-depressor denervation (the carotid sinus nerve and the cervical aortic [depressor] nerve were cut in the neck) (fig. 7). From the results they calculate a gain which is quite low. We have found that animals subjected to the denervation procedures which they used have remaining aortic baroreceptor fibers and have clear reflex responses to the application of negative pressure to the lower body, a procedure which simulates hemorrhage. Thus, these animals are not completely denervated. The gain observed in McRitchie and Vatner's experiments may be lower than
Vagal and Sympathetic Heart Rate Control

As shown by Warner and Cox (fig. 8), the heart rate response to stimulation of the vagus nerve occurs very rapidly in dogs, so that a maximal change in heart rate is usually seen on the first beat following the start of stimulation. Sympathetic responses, however, are slower, so that several beats are required for a sympathetic effect to be completed. A related finding, by Glick and Braunwald (fig. 9), in humans and dogs was seen when vasoconstrictors (or vasodilators) were used to alter pressure and blocking agents were used to detect the participation of sympathetic and parasympathetic nerves in reflex heart rate responses. Contrary to the traditional picture of regulation, motor responses to increased pressure appear to be predominantly vagal and responses to decreased pressure predominantly sympathetic. This picture has been slightly modified in later

Figure 8. The lower record shows the duration of stimulation of the sympathetic (solid line) and parasympathetic (dotted line) fibers to the heart. The upper curves show the effects on heart rate of the stimulations. The curves have been superimposed to facilitate comparison. Note that the cardiac slowing in response to vagal stimulation is accomplished very rapidly — less than 1 sec is required for the response to be virtually complete. The "off" response when vagal stimulation ceases is slightly slower. In contrast, the heart rate increase in response to sympathetic stimulation may not be fully complete in 20 sec, and the slowing of the rate when sympathetic stimulation ceases is even slower. (After Warner and Cox, J Appl Physiol 17: 349, 1962)

Figure 9. The traditional concept of heart rate regulation, shown on the left, postulates an increasing parasympathetic and decreasing sympathetic activity as a compensation for increases in blood pressure, and opposite effects for a fall in blood pressure. The work of Glick and Braunwald, shown on the right, postulates predominantly vagal correction for pressures above the normal and predominantly sympathetic correction for pressures below normal, with virtually no synergistic activity of the two systems. (From Glick and Braunwald, Circ Res 16: 363, 1965)
experiments from the same laboratory, and the partition of control seems to depend in part on the relative level of the existing vagal or sympathetic activity. However, the predominance of vagal or sympathetic control in different conditions appears real.

Our own studies, as shown in figure 10, indicate that for increased pressure the responses in the dog are mostly vagal, with no time or phase lag between the change in systolic pressure and the resultant change in beat duration. The chairing baboon, on the other hand, shows a greater phase lag, probably indicating more sympathetic activity. Human responses are intermediate between those of the dog and baboon. For decreases in pressure, all three show greater lags in pressure than for increases, and the species differences are preserved, i.e., the baboon's responses are slower than the human's, which in turn are slower than the dog's. In a similar vein, the results of Van Citters and Franklin indicate that the dog does most of his regulation of blood pressure during exercise with vagal heart rate changes, and does not show the strong vasomotor responses that are obvious in the awake human. Thus, there appear to be species and pressure-dependent modifications of our traditional picture of complementary sympathetic and parasympathetic regulation in the control of blood pressure.

**Nonarterial Baroreceptors**

A third question concerning regulation involves nonarterial baroreceptors. Such receptors are found in the atria, the ventricles, and the pulmonary veins. In general, they respond to pressure changes in these vessels or chambers as do the arterial receptors. These are referred to as cardiopulmonary baroreceptors. Reflex effects considered to arise from these are shown in figure 11 from the work of Mancia and Donald.

In dogs with carotid sinuses denervated and the cervical depressor (aortic) nerve cut in the neck, vagal block causes a marked increase in blood pressure. This increase can be decreased by removal of the receptor sites listed above. It appears from these studies that cardiopulmonary receptors can markedly change blood pressure.

Our experiments on this topic were, in part, neurophysiological. Dr. Ito and examined the depressor portion of the canine cervical vagus. This portion of the vagus is not cut in the denervation procedure used by Mancia and Donald. We found that there were baroreceptor fibers active at normal arterial pressures in this nerve and we were able to elicit reflexes from these fibers (fig. 12). Thus, sectioning of the depressor nerve does not denervate all aortic receptors. In other experiments in our laboratory, we studied dogs in which the arterial receptors were intact, and we altered arterial pressure by decreasing the venous return. This was done before and after anesthetizing the cardiopulmonary baroreceptors with intrapericardial procaine. The control animals were studied under atropine and propranolol so that we could study control and experimental animals at the high heart rates which are found after intrapericardial procaine.

Figure 13 shows a steep change in descending aortic blood flow as arterial pressure decreases. There is a threefold increase in resistance. The curve is the same with and without the cardiopulmonary baroreceptors. With arterial receptors active, we found no effects from cardiopulmonary receptors except for some effects, apparently from ventricular receptors; with very large increases in intraventricular pressure, a bradycardia was seen. We conclude that cardiopulmonary receptors may play some role in regulation when no arterial pressure receptors are present. Their integrated role remains to be elucidated. Their long-accepted function in the regulation of blood volume has recently been questioned.

Some teleological questions seem in order here. Is it reasonable to place receptors in a low pressure area to control arterial blood pressure? As an extreme example, this is like placing the thermostat in the barn while the furnace is in the house. One may further ask if this "reflex" is like other reflexes and has the property that the output response returns the regulated variable toward normal, thus canceling the "error" signal at the receptors. Would a tachycardia and

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**Figure 10.** Phase shift between heart rate and arterial pressure in response to sinusoidally altered pressure in the dog, monkey, and man for pressure increases. Note that the dog shows a pure vagal response (little phase lag) to increased pressure, while the monkey shows a marked phase lag, indicating a sympathetic response, and the human is intermediate. (From Scher et al., Fed Proc 31: 1219, 1972)

**Figure 11.** Left) Increase in aortic blood pressure during vagal block with only the atria in situ (ventricles removed). Right) Absence of the increase after removal of the atria. Original tracings from a dog with its carotid sinuses denervated, its aortic nerves cut, its vagi divided at the diaphragm, and its lungs removed. The temperature record (T) was obtained from a thermistor at the surface of one vagus. (From Mancia and Donald, Circ Res 36: 310, 1975)
vasoconstriction, caused by a fall in pressure at the low pressure receptors, reflexly increase the (venous) pressure at the low pressure receptors? Since storage of blood in arterial vessels would be increased, venous pressure would probably fall!

This reflex response appears to be present in humans subjected to low levels of lower body negative pressure (LBNP), a procedure which probably simulates mild hemorrhage. In these experiments, forearm and splanchic vasoconstriction follow the application of LBNP, although mean arterial pressure and pulse pressure do not appear to fall. The vasoconstriction occurs without any increase in heart rate. The effective stimulus appears to be from the cardiopulmonary receptors, since arterial pressure and rate of change of pressure and pulse pressure do not change.

If arterial pressure is the regulated pressure in these studies, the effective closed-loop gain would appear to be 1.0 and the open-loop gain infinite, since only with this high a gain does an output variable remain completely unaltered by a perturbation. It is even more surprising that the regulation is so perfect since the receptors apparently do not “see” the regulated pressure. To put the question another way, can cardiopulmonary receptors regulate arterial pressure perfectly if they do not “know” what it is?

**Long-Range Control of Blood Pressure**

Traditionally, a large hemorrhage and attendant fall in blood pressure should cause a cessation of arterial baroreceptor firing if arterial pressure is very low. A marked cardiac acceleration and vasoconstriction should ensue. Similar cardiac and vasomotor responses should be seen with arterial baroreceptor denervation. Neurogenic hypertension should ensue. The literature contains many denervation studies. In some experiments in dogs, hypertension followed arterial baroreceptor denervation; in others it did not. Some animals were studied under anesthesia and some were not, and in many cases, animals were examined for only a short time during each recording session. Recently, Cowley in Guyton's department has examined awake, unanesthetized dogs before and after chronic denervation of the carotid sinus. The animals were studied over a 24-hour recording period. Normal animals, shown on the left side of figure 14, kept their pressure within a narrow range, whereas the denervated animals studied seemed to divide into two groups: 1) The majority of the denervated animals, as seen in the figure, had hypertension (mean pressure about 150 mm Hg); 2) others were normotensive or even hypotensive. The average increase in pressure was about 10 mm Hg. The conclusion of this study was that the arterial baroreceptors are not responsible for long-term control of arterial pressure. This conclusion had earlier been reached by Guyton on other information.

Dr. Ito and I repeated the above study, expecting to find more hypertension than was found by Cowley. Our dogs were studied over many 75-min recording periods at 1-week
intervals before (1+ month) and following a nearly complete baroreceptor denervation. Following denervation, the animals were hypertensive for about a week, but the pressure returned to normal over two and one-half weeks. The standard deviation of pressure after denervation is larger than in control animals, indicating that the animals do not control their pressure as well, but the mean pressure is not elevated. Note that these animals were studied over a long period after chronic denervation.

I here insert a *caveat* about denervation. As indicated previously, in dogs in which denervation is confined to the carotid sinus and to the depressor nerve in the neck, denervation is definitely not complete. In our studies (fig. 7), we denervated on the right by cutting the entire vagus below the junction with the superior laryngeal nerve and by cutting all branches to the right subclavian artery. On the left, we stripped all branches which join the vagus in the thorax down to and including the junction of the vagus and the left laryngeal nerve. This denervation is more extensive than any other with which we are familiar. If we cut a few more vagal branches below the left laryngeal nerve, the esophagus becomes grossly dilated and the animals die in achalasia. Nevertheless, even with this very extensive denervation, the dogs have measurable reflex responses to several stimuli. This leaves us with a dilemma: Are the remaining small reflex responses sufficient to prevent these animals from becoming hypertensive, or are they so negligible that one would expect hypertension in these animals? Prior studies by Thomas and Nowak in awake animals indicated that hypertension followed a denervation less extensive than was seen in ours, but the experimental conditions differed.*

It is extremely puzzling that animals with virtually no arterial baroreceptor control can nevertheless maintain a normal arterial blood pressure. How can the animals maintain a normal blood pressure if they have no way of sensing the pressure? It has been claimed that regulation of blood pressure over the long term, and thus in these animals, is dependent on body fluid volume. This interesting theory needs to be further explored. The relationship between blood volume and arterial pressure is not clear. We have been unable to alter the pressure markedly in our denervated dogs by large infusions of fluid.

*In studies conducted since this lecture was delivered, we have tentative evidence that we can produce hypertensive dogs if we impose more extensive denervation.

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References

5. Heymans C: Le Sinus Carotidien. London, HK Lewis, 1929
20. Glick G, Braunwald E: Relative roles of the sympathetic and parasym-
Comparative Hemodynamic Effects of Inotropic and Vasodilator Drugs in Severe Heart Failure

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SUMMARY In 12 patients with severe congestive heart failure (CHF) due to ischemic heart disease or nonischemic cardiomyopathy the hemodynamic response to intravenous infusion of sodium nitroprusside (N) was compared to that of dobutamine (D) 10 μg/kg/min. D and N produced comparable increases in cardiac output (CO) (2.8 to 5.8 L/min and 2.9 to 5.0 L/min, respectively), but, compared to N, D caused a higher arterial pressure (99.3 vs 86.2 mm Hg, P < 0.01) and heart rate (102.5 vs 95.3, P < 0.05) and less reduction in pulmonary wedge pressure (PWP) (28.9 to 20.2 mm Hg vs 29.1 to 16.6 mm Hg, P < 0.05). In five additional patients N and D were studied separately and then were infused together. The combination resulted in a higher CO, lower PWP and greater reduction in systemic and pulmonary vascular resistances than either drug alone. Brachial arterial infusion of nitroprusside produced prominent foreand vasodilation in a dose less than 10% of the systemic dose, whereas vasodilation with dobutamine was only modest even when 50% of the systemic dose was infused. Therefore, potent inotropic and vasodilator drugs produce similar and additive augmentation of left ventricular performance in heart failure. Reduction in vascular resistance with dobutamine probably is largely of reflex origin, but the vasodilation itself may be an important determinant of the rise in cardiac output.

RECENT STUDIES from this and other laboratories have revealed that infusion of a vasodilator drug can result in significant improvement in left ventricular pump function in patients with heart failure. This functional improvement, which is characterized by a reduction in left ventricular filling pressure, an increase in stroke volume and no change in heart rate or in indices of left ventricular contractility, has been attributed to a reduction in impedance to left ventricular outflow. The traditional means of improving left ventricular performance in the failing heart has been by administration of an inotropic drug. Since previously available inotropic agents exerted considerable effect on the peripheral circulation or heart rate, it has not been possible to evaluate in the intact circulation the effects of a pure inotropic intervention. Furthermore, a direct comparison of the relative effectiveness of vasodilator and inotropic therapy on the failing heart has not been reported previously.

The purpose of the present study was to compare in a group of patients with severe congestive heart failure the functional response of the left ventricle to infusion of sodium nitroprusside, a potent vasodilator with no direct cardiac effect, and dobutamine, an inotropic agent that is relatively devoid of peripheral vascular and chronotropic effects.

Materials and Methods

Studies were performed in 21 hospitalized patients with class III or IV congestive heart failure as defined by the New York Heart Association. In eleven patients the heart failure was thought to be on the basis of nonischemic myocardial disease due in some cases to excessive alcohol ingestion and in others to unknown cause. The absence of significant coronary artery disease was documented by angiography in nine of these patients. The other ten patients had severe ischemic heart disease with previous myocardial infarctions or documented multiple vessel coronary artery disease. All patients had had symptomatic heart failure for at least six months and had been treated with digitalis and diuretics without complete relief of symptoms. Digitalis therapy was continued on a daily basis throughout the study period, but diuretics were withheld on the day of study. Patients gave informed, written consent for performance of the studies.

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