

## REFLEXES THAT CONTROL CARDIOVASCULAR FUNCTION

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*AM. J. PHYSIOL. 277 (ADV. PHYSIOL. EDUC. 22): S234-S243, 1999*

Realistically, most professional and general physiology courses will have only one or two lecture hours devoted to cardiovascular reflexes. Therefore, it is important to choose carefully the points you consider the most important and focus your lecture(s) to stress these points. In writing this article, I have tried to highlight the concepts that, in my opinion, are the most important. I have geared the discussion to a presentation of one to two lecture hours, and have indicated areas that may be covered in more depth if time is available.

When teaching autonomic reflexes that control the cardiovascular system, I focus on the arterial baroreflex. This topic should be presented after the students have learned about the autonomic nervous system and basic hemodynamics. As a brief introduction, it is helpful to review the autonomic innervation of the cardiovascular system (Fig. 1) and the relationships between mean arterial pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), heart rate (HR), and stroke volume (SV):  $MAP = CO \times TPR$  and  $CO = HR \times SV$ . The major point to make is that the sympathetic nervous system can rapidly increase MAP by constricting arterioles, or by increasing heart rate or stroke volume. The predominant effect of activation of the parasympathetic nervous system is a rapid decrease of heart rate, which will influence cardiac output. This review of the cardiovascular effects of activating the efferent limb of the autonomic nervous system sets the stage for discussing how efferent outflow is controlled by afferent input from sensory receptors.

### ARTERIAL BAROREFLEXES ARE A NEGATIVE FEEDBACK SYSTEM

Under a variety of environmental and physiological circumstances, arterial blood pressure is regulated around a narrow range and arterial baroreflexes are critically important for the beat-to-beat regulation of blood pressure. Figure 2 is a schematic that is useful in introducing the concept of a negative feedback system. Even with a limited amount of time, it is very useful to provide a concrete example of a negative feedback system (Fig. 2A). Students at almost any level can readily grasp the concept of a negative feedback system, which buffers changes in room temperature. Analogies can then be made to the arterial baroreflex, which is a negative feedback system that buffers fluctuations in arterial pressure (Fig. 2B). After this presentation, schematics showing the anatomic location of the arterial baroreceptors, the afferent nerves, the central pathways, and the efferent systems under the influence of the arterial baroreflexes can be discussed in more or less detail, as time allows. However, during this initial introduction of the arterial baroreflex, it is wise not to stray too far from the overall picture and the concept of a negative feedback system.

In presenting the arterial baroreflex, the determination of set point should be briefly discussed. In normal animals there is a narrow range of blood pressure that is ideal for the maintenance of adequate blood flow to the various vascular beds, and although the exact

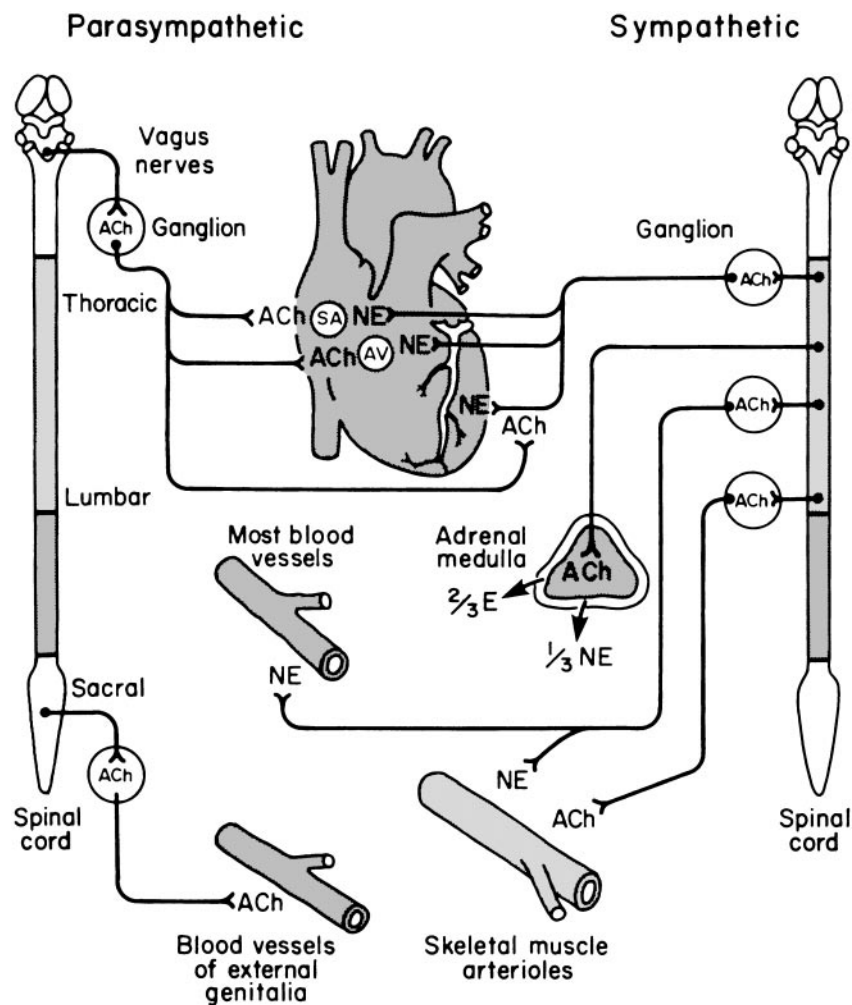


FIG. 1. Autonomic innervation of cardiovascular system. ACh, acetylcholine; NE, norepinephrine; E, epinephrine; SA, sinoatrial node; AV, atrioventricular node. [Reprinted from Sparks and Rooke (18) with permission.]

mechanism is not known, determination of this set point ultimately involves the central nervous system (central nervous system). Although arterial baroreceptor input to the central nervous system is critical for buffering deviations from the set point, the arterial baroreceptors are not the major determinant of set point. A figure from the classic study by Cowley et al. (3), which shows traces of blood pressure recordings from baroreceptor intact and chronically baroreceptor denervated conscious dogs, is an impressive graphical illustration of this (Fig. 3). Initially when arterial baroreceptor afferent nerves are severed, there is a profound rise in arterial pressure (not shown). How-

ever, over time mean arterial pressure returns to predenervation levels so that the average level of arterial pressure is not different between normal and baroreceptor-denervated animals. Also notice that variability around mean arterial pressure is much greater in baroreceptor-denervated animals because the moment-to-moment buffering system (arterial baroreflex) is no longer operative.

### CONCEPT OF BASELINE TONE

In my opinion, understanding the concept of baseline neural tone in both the afferent and efferent limbs of

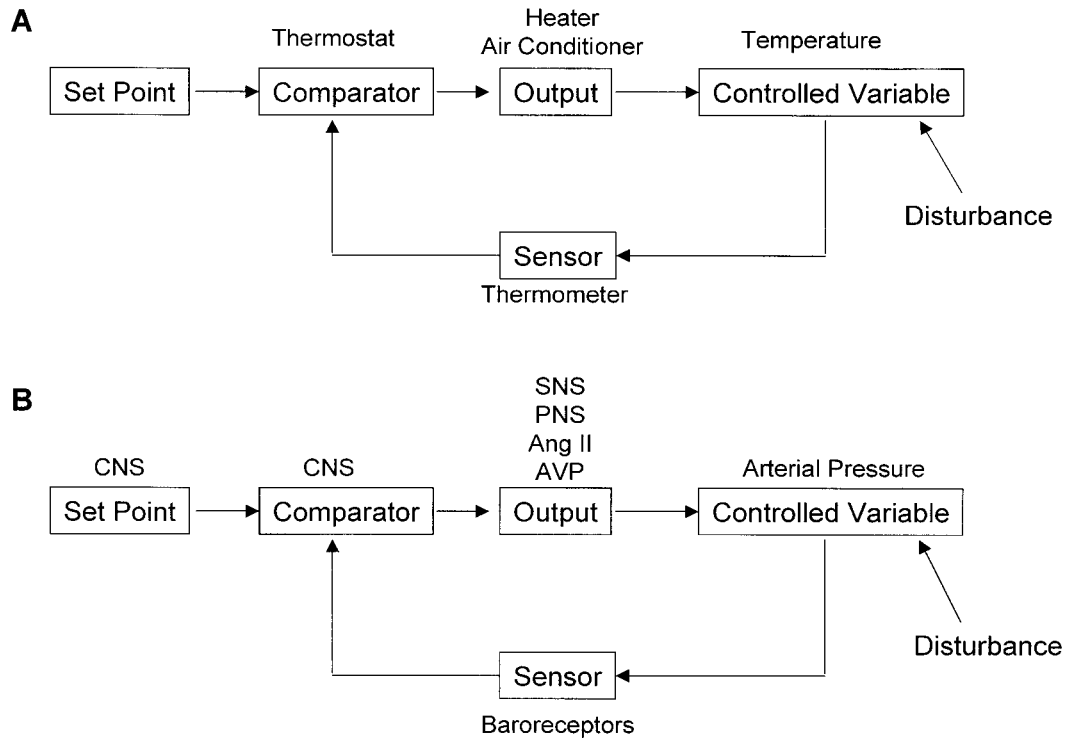


FIG. 2.

**Negative feedback systems. A:** negative feedback system for controlling room temperature. Thermostat (comparator) receives information about desired room temperature (set point) and actual room temperature (controlled variable), which is measured by a thermometer (sensor). If desired temperature and actual temperature differ, an appropriate output is generated to bring room temperature up or down to desired level. **B:** arterial baroreflex. If arterial pressure (controlled variable) deviates from desired arterial pressure (set point), arterial baroreceptors (sensors) change their firing rate and the central nervous system (CNS; comparator) changes neural and humoral output to bring arterial pressure back to desired level. SNS, sympathetic nervous system; PNS, parasympathetic nervous system; ANG II, angiotensin II; AVP, arginine vasopressin.

the arterial baroreflex is the single most important factor in understanding arterial baroreflex function. At normal resting blood pressures, the central nervous system is receiving information continuously from the afferent baroreceptor projections. At rest, the heart is receiving information from both the sympathetic and parasympathetic branches of the autonomic nervous system, and the balance between activity of these efferent systems will determine baseline heart rate. At rest, the vasculature is receiving tonic information from the sympathetic nervous system. This means that under normal resting conditions the arterial baroreceptors are serving as a “brake” to keep heart rate and arterial pressure lower than they would be in the absence of baroreceptor input. Although this may seem like a simple concept, it is not trivial and should

be emphasized. When students have trouble predicting reflex responses to a perturbation in resting blood pressure, usually it is because they do not truly understand the concept of baseline neural tone. Therefore, when the afferent and efferent responses to changes in arterial pressure are presented, the fact that there is neural activity at rest should be stressed.

#### AFFERENT BARORECEPTOR DISCHARGE

Baroreceptors do not actually sense pressure; rather, they sense stretch. Because of their arrangement in the vessel wall, when arterial pressure is increased, the sensory nerve endings (baroreceptors) are stretched and afferent nerve discharge is increased. Most textbooks of physiology have drawings showing

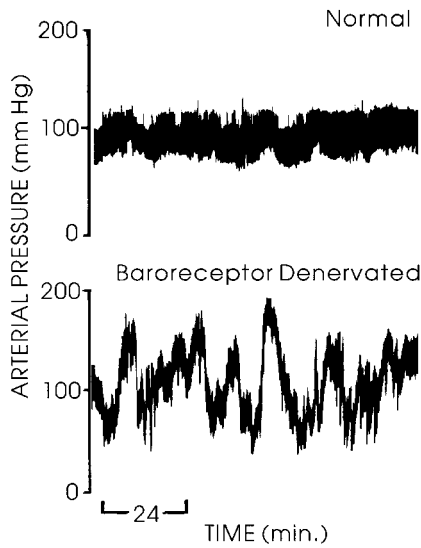


FIG. 3.

Recordings of pulsatile arterial pressure in a normal dog (*top*) and in same dog (*bottom*) several weeks after baroreceptors have been denevated. [Adapted from Cowley et.al. (3) with permission of American Heart Association.]

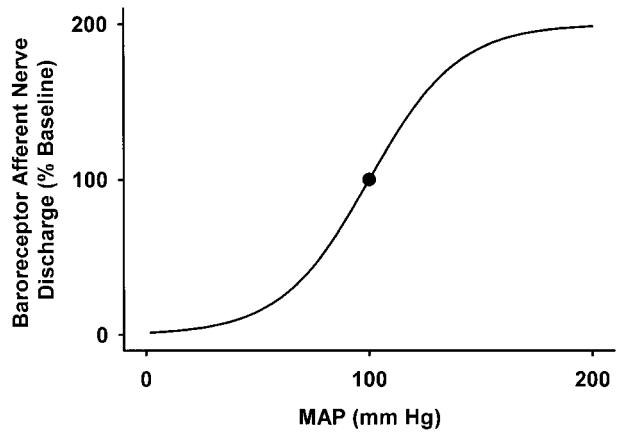


FIG. 5.

Baroreceptor afferent nerve discharge curve. ●, Baseline mean arterial blood pressure (MAP). Baroreceptor afferent nerve activity increases when MAP is increased above baseline level (●) and decreases when MAP is decreased below baseline level. Note that relationship between baroreceptor afferent nerve discharge and MAP is most steep (sensitive) on either side of baseline MAP.

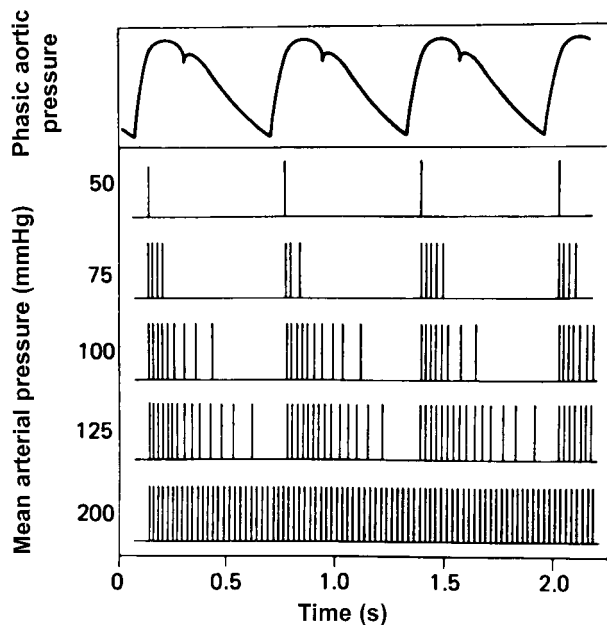


FIG. 4.

Relationship of phasic aortic blood pressure to firing of a single baroreceptor afferent nerve fiber at different levels of mean arterial pressure. [Adapted from Berne and Levy (1) with permission.]

the location of arterial baroreceptors in the vessel wall of the carotid sinus and the aortic arch and their afferent projections. Figure 4 demonstrates the pulse-synchronous nature of afferent baroreceptor discharge at rest and illustrates the fact that the baroreceptors are discharging at baseline mean arterial pressure (~100 mmHg). With each arterial pressure pulse, the highest rate of firing occurs when pressure is rapidly rising, demonstrating that the arterial baroreceptors are sensitive to the rate of stretch. When pressure is decreased, baroreceptor discharge decreases, and when pressure is increased, baroreceptor discharge increases. It is worthwhile to also point out that an increase in pulse pressure, even with the same mean arterial pressure, will increase arterial baroreceptor discharge. A simple schematic of a baroreceptor function curve similar to that shown in Fig. 5 demonstrates that baroreceptors send information about blood pressure to the central nervous system over a range of pressures, but the most sensitive part of this relationship is directly above and below resting blood pressure. Because the role of the baroreceptor reflex is to buffer fluctuations from baseline pressures, it is important that the most sensitive portion of the curve is around baseline pressure. Discussion of these diagrams will provide the most critical information on baroreceptor function. Discussion of baroreceptor

## Sympathetic Tone

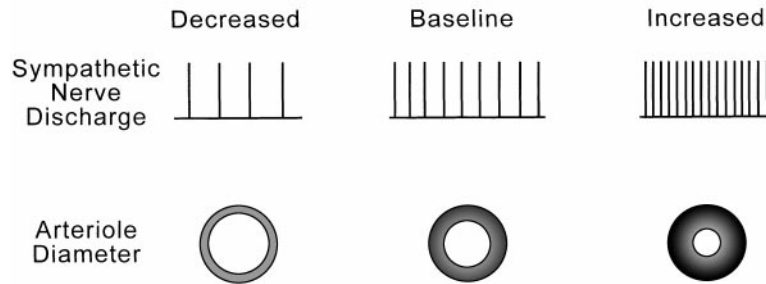


FIG. 6.

Sympathetic nerve discharge and arteriole diameter. Under baseline conditions (*middle*), there is tonic sympathetic activity to the vasculature and arterioles are partially constricted. If sympathetic activity increases (*right*), arterioles constrict further. If sympathetic activity decreases (*left*), arterioles dilate.

afferent fiber types and differences in discharge patterns and function between baroreceptors connected to myelinated and unmyelinated afferent fibers (see e.g., Refs. 5, 11, and 15) should be reserved for an advanced course.

### EFFERENT BAROREFLEX RESPONSES

Figure 6 illustrates the effects of changes in efferent sympathetic nerve activity on the diameter of resistance vessels. At baseline there is activity in sympathetic nerves providing neurogenic sympathetic tone to the arterioles, and therefore the vessels are partially constricted. This is the normal resting condition. If sympathetic nerve activity increases, the vessels constrict and arterial pressure will increase. If sympathetic nerve activity decreases, the vessels will dilate and arterial pressure will decrease.

Figure 7 summarizes arterial baroreflex control of sympathetic and parasympathetic outflow. At normal arterial pressures (Fig. 7, *middle*) there is activity from all neural components of the arterial baroreflex: both afferent and efferent limbs. Both resistance and capacitance vessels are partially constricted. With regard to determinants of heart rate, the sinoatrial and atrioventricular nodes receive sympathetic and parasympathetic innervation, and both efferent outflows are active at rest. Baseline heart rate is determined by the

balance between these two opposing influences and the relative contribution of the sympathetic and parasympathetic nervous systems varies among species. In conscious humans, basal parasympathetic nerve activity to the heart is the major determinant of baseline heart rate, whereas basal sympathetic nerve activity has small or negligible effects (14). In addition, variation in resting heart rate among individuals is caused mainly by differences in basal parasympathetic tone. For example, compared with sedentary individuals, the lower baseline heart rate seen in endurance exercise-trained humans is a result of augmented parasympathetic tone at rest (17). Stroke volume is influenced by venous return and cardiac contractility. Increases or decreases in sympathetic nerve activity to the capacitance vessels and the ventricles therefore will affect stroke volume. It is worth spending time on this diagram to discuss how a change in blood pressure, and thus baroreceptor afferent nerve discharge, will change efferent nerve activity and how each change in efferent nerve activity could act to buffer the initial perturbation. Figure 8 illustrates a simple arterial baroreflex function curve for control of sympathetic outflow, which is a major determinant of total peripheral resistance and arterial blood pressure. The inverse relationship between this and the arterial baroreceptor afferent nerve discharge curve (Fig. 5) should be briefly discussed. The point should be made that the baroreflex is operative over a range of arterial pressures

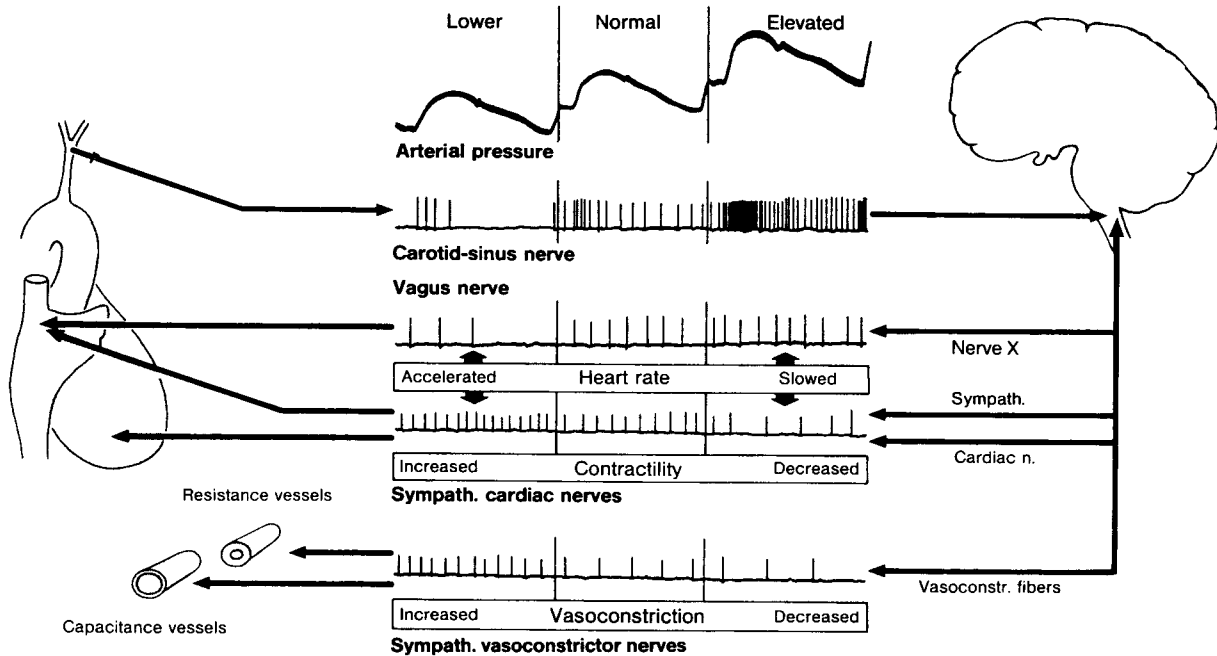


FIG. 7.

Baroreceptor reflex responses to changes in arterial pressure. When arterial pressure is elevated, afferent firing increases in carotid sinus nerve, which results in decreased sympathetic nerve activity to heart and blood vessels and increased parasympathetic nerve activity to heart, responses that will decrease arterial pressure. When arterial pressure is lowered, the opposite responses occur. [From Schmidt and Thews (16) with permission.]

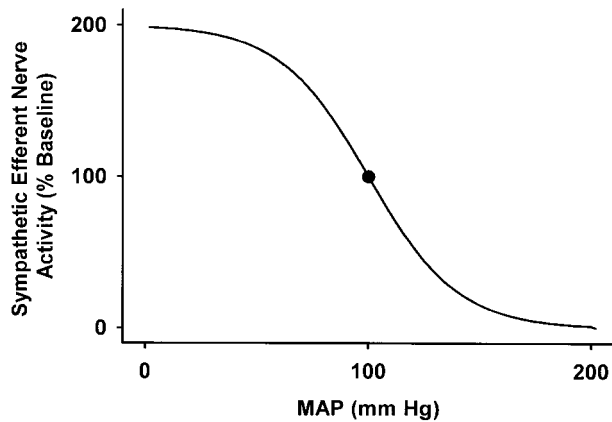


FIG. 8.

Baroreceptor reflex efferent nerve discharge curve. ●, Baseline MAP. Sympathetic efferent nerve activity decreases when MAP is increased above baseline level and increases when MAP is decreased below baseline level. Note that relationship between sympathetic nerve discharge and MAP is most steep (sensitive) on either side of baseline MAP.

but is most sensitive to changes in arterial pressure immediately above and below baseline blood pressure.

A laboratory experience or demonstration is extremely valuable in teaching arterial baroreflexes. Even in a course with only one and one-half hours dedicated to cardiovascular reflexes, I have played taped data for students where the arterial pressure pulse, afferent baroreceptor nerve discharge, and efferent sympathetic nerve activity scroll across the screen. This simple demonstration clearly shows the association of afferent baroreceptor discharge with the arterial pressure pulse. Students can see in real time the afferent and efferent nerve responses to increases and decreases in arterial pressure in a living animal, and it leaves a lasting impression. Laser disks and computer-assisted laboratory exercises and demonstrations are commercially available, and if time allows, they can be very useful. Another alternative would be to have these available to students in a common use area, where students could access them at their convenience.

### CENTRAL NERVOUS SYSTEM PATHWAYS

With limited time, the discussion of central nervous system integration of cardiovascular reflexes should be kept simple. The main point to be made in discussing the central nervous system pathways is to point out that, by virtue of the “wiring” and transmitters used, activation of baroreceptor afferent nerves can have opposite effects on the sympathetic versus the parasympathetic nervous system and can also affect humoral systems. Baroreceptor afferent fibers project to an area in the medulla in the brain stem that receives afferent sensory input from many sources. With regard to control of heart rate, increased afferent nerve activity leads to excitation of parasympathetic motor neurons and, through a different pathway, to inhibition of neurons that project to, and normally excite, sympathetic motor neurons in the spinal cord. With regard to control of vascular resistance, activation of baroreceptor afferent nerves ultimately results in inhibition of medullary neurons that normally excite sympathetic motor neurons in the spinal cord. Through a central pathway that projects to the hypothalamus, arterial baroreceptors influence the secretion of vasopressin such that activation of arterial baroreceptors inhibits the secretion of vasopressin. There are several good reviews of central baroreflex integration that are useful resources for the instructor

(e.g., Refs. 4, 6, and 19) and can serve as background reading for an advanced course.

### ARTERIAL BARORECEPTOR REFLEX RESETTING

As pointed out previously, the arterial baroreceptors are very important for the beat-to-beat regulation of arterial pressure and represent the most rapidly responding system of the regulatory systems for buffering fluctuations in blood pressure. However, they do not determine the absolute level of blood pressure for long-term regulation. If, for whatever reason, arterial pressure is changed for a period of time, the arterial baroreceptors will reset to operate around the new pressure to which they are exposed. This process begins within a matter of minutes and is virtually complete within a couple of days (9) to weeks (10, 11). Figure 9 shows that exposure to an elevated arterial pressure will result in a rightward shift in the baroreceptor and baroreflex function curves toward higher blood pressures, and exposure to decreased blood pressure will result in a leftward shift in the baroreceptor and baroreflex function curves toward lower blood pressures. Although the arterial baroreceptors do not strictly maintain blood pressure around one set point, this rather acute baroreceptor and baroreflex resetting may be viewed as functionally advantageous. Should there be an overriding influence

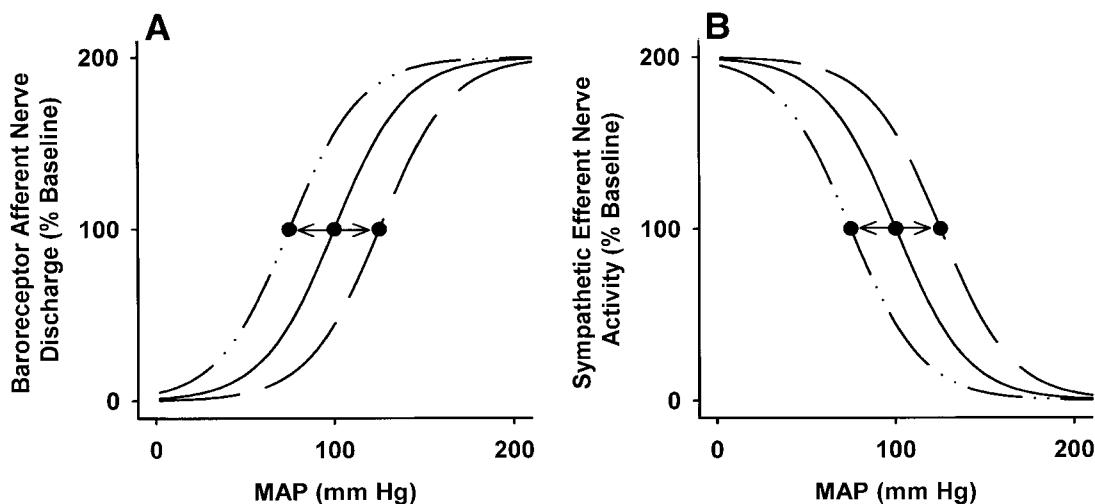


FIG. 9.

Short-term pressure-dependent baroreceptor reflex resetting. *A*: hypothetical curves showing baroreceptor afferent nerve discharge under control conditions (solid line) and after baseline arterial pressure (●) is elevated for several days (dashed line) or lowered for several days (dashed-dotted line). *B*: hypothetical curves showing predicted baroreflex responses under control conditions (solid line) and after an elevation (dashed line) or lowering (dashed-dotted line) of arterial pressure.

to increase or decrease baseline arterial pressure, the shift in the baroreceptor function curve in the direction of the prevailing pressure allows for a wider range of pressures over which the baroreceptors maintain high sensitivity to immediate (beat-to-beat) fluctuations in pressure.

It can be useful to provide examples of situations in which baroreflex resetting is evident. I have chosen the examples provided below because they are common occurrences that will be seen in the clinical setting. However, they are complicated by the fact that multiple mechanisms may contribute to changes in baroreflex sensitivity that accompany the shift in the function curve toward the prevailing arterial pressure. It is a judgment call for the instructor to determine whether these examples will enrich or confuse the particular group of students who are being taught.

### Hypertension

There are many proposed mechanisms for the etiology of hypertension, and it is not necessary to discuss them here. During the initial development of hypertension, when arterial pressure is elevated, the arterial baroreflex will shift to operate around the new elevated pressure with maintained sensitivity to increments in pressure (Fig. 9B). With time, if blood pressure remains elevated, the sensitivity to increments in pressure will be decreased (10, 11). Changes in the blood vessel wall, and thus baroreceptor afferent activity, and central nervous system mechanisms have been proposed to contribute to baroreflex resetting in chronic hypertension. The end result is that in established hypertension, the arterial baroreceptor reflex operates at higher pressures and is less able to correct for immediate fluctuations in blood pressure (Fig. 10). This chronic baroreflex resetting may contribute to the maintenance of established hypertension.

### Pregnancy

A physiological situation in which arterial blood pressure is decreased for a prolonged period of time is pregnancy. In pregnant animals, the baroreflex function curve shifts to operate at a lower arterial pressure range. Baroreflex responses to immediate increases in pressure are maintained or even potentiated, whereas

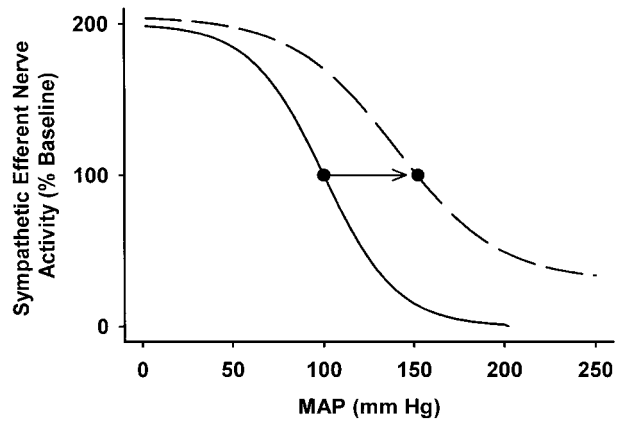


FIG. 10.

Long-term baroreflex resetting in hypertension. Solid line represents arterial baroreflex function curve for an animal with normal baseline MAP. Dashed line shows that baroreflex function curve is shifted to a higher operating pressure range with a reduced sensitivity to increments in pressure (decreased slope) in an animal with established hypertension. ●, baseline MAP.

responses to immediate decreases in pressure are attenuated (Fig. 11). The attenuated ability to compensate for a hypotensive challenge likely explains the increased incidence of orthostatic hypotension in pregnant women. Overall, the baroreflex resetting

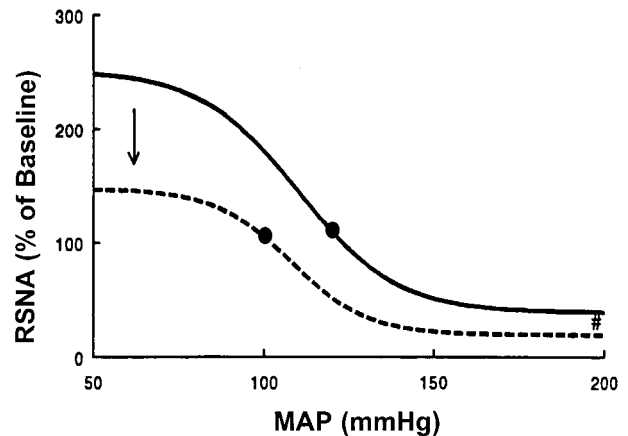


FIG. 11.

Baroreflex resetting in pregnancy. In pregnant animals (dashed line), baseline MAP is decreased and baroreflex function curve for control of efferent renal sympathetic nerve activity (RSNA) is shifted to a lower operating pressure range. Sympathoexcitatory responses are attenuated (arrow) and sympathoinhibitory responses are potentiated (#). ●, baseline MAP. [Adapted from Masilamani and Heesch (12).]



that occurs in pregnancy could be viewed as a protective mechanism to limit abrupt increases in sympathetic outflow in a hemodynamic state characterized by a substantial elevation of resting blood volume and cardiac output (12).

### **ARTERIAL BAROREFLEX CONTROL OF HUMORAL SYSTEMS**

In addition to controlling the autonomic efferent outflow to blood vessels and the heart, arterial baroreflexes modulate the secretion of vasoactive humoral agents. Increased arterial blood pressure results in an increase in afferent baroreceptor discharge and decreased circulating levels of adrenal catecholamines, vasopressin, and angiotensin II. The effects on catecholamine secretion are mediated through efferent sympathetic nerves to the adrenal medulla. The effects on vasopressin secretion are via a central pathway to the hypothalamus. Sympathetic efferent nerves to the kidney control secretion of the enzyme renin, and, through the renin-angiotensin system cascade, changes in renal sympathetic nerve activity will result in changes in circulating levels of angiotensin II. These humoral substances have vasoconstrictor properties and contribute to reflex adjustments in vascular resistance. However, the main effects of vasopressin (antidiuretic hormone) and angiotensin are on the kidney, and they influence arterial pressure primarily by regulating blood volume.

For later discussions, it is important to mention that these humoral systems are modulated by baroreflexes. However, this brief explanation is sufficient. In a general physiology course, avoid discussion of more complex interactions. For example, although there is ample evidence that both vasopressin (2, 8) and angiotensin (2, 13) have central nervous system effects on baroreflex function, discussion of the reciprocal relationship between neural and humoral systems belongs in an advanced course.

### **OTHER REFLEXES AFFECTING THE CARDIOVASCULAR SYSTEM**

#### **Cardiopulmonary Reflexes**

There are stretch receptors located in the atria, ventricles, and pulmonary vessels that are tonically

active under normal conditions and operate as a negative feedback system in much the same way as the arterial baroreceptors. Differently from the arterial baroreceptors, which are located on the high-pressure side of the circulation, these receptors are located on the low-pressure side of the circulation. Although cardiopulmonary reflexes can contribute to the overall regulation of arterial pressure similar to the arterial baroreflexes, they are involved mainly in volume regulation. The receptors are located in regions that will be stretched when blood volume is increased. Activation of these receptors has powerful effects on renal sympathetic nerve activity and secretion of vasopressin (antidiuretic hormone) such that an increase in blood volume is compensated for by a rapid loss of fluid into the urine.

#### **Arterial Chemoreflex**

The arterial chemoreceptors are collections of chemosensitive cells in the carotid and aortic bodies. They are located in the same general regions as the arterial baroreceptors. The chemoreceptor afferent nerves travel in the same nerve bundles as the arterial baroreceptors. The chemoreceptors receive a very high blood flow and are sensitive to changes in the  $PO_2$ ,  $PCO_2$ , and pH of arterial blood. They are mainly involved in control of respiration and serve to buffer changes in arterial blood gases. Discharge in afferent chemoreceptor nerves is increased when arterial  $PO_2$  or pH drops or when arterial  $PCO_2$  rises above normal. Reflex changes in alveolar ventilation serve to bring blood gases back to normal. Although arterial chemoreflexes are not a major mechanism for blood pressure regulation, arterial chemoreceptors are activated by blood pressures below the normal arterial pressure range, and chemoreceptor reflexes have an effect on arterial blood pressure. Increased chemoreceptor afferent nerve discharge stimulates central nervous system vasoconstrictor sites and results in increased sympathetic outflow to resistance and capacitance vessels, and thus an increase in arterial blood pressure. Heart rate responses to arterial chemoreceptor stimulation will vary depending on the respiratory effects.

In summary, most general physiology courses allow for only one to two lecture hours within which to cover reflexes that control the cardiovascular system. Therefore, it is very important to stress major points

and avoid unnecessary detail. I concentrate on the arterial baroreflex and stress the concepts of a negative feedback system and baseline tone. The textbooks edited by Berne and Levy (1) and Guyton and Hall (7) are often used in a general physiology course and are a good resource for the students and the instructor. Students appreciate examples of physiological and pathophysiological situations in which alterations in baroreflex function may be important. However, if time is short, examples such as those provided here (hypertension and pregnancy) could be eliminated without compromising the basic concepts.

I thank Drs. Eileen Hasser, Margaret Sullivan, James Schadt, and C. Michael Foley for helpful comments in review of this manuscript and Wesley Sechler and Charles Jorgenson for preparation of figures.

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