Regulation of the Heart's Functions

By Robert F. Rushmer, M.D.

The significance of cardiovascular regulation extends beyond considerations of normal function and control. Primary deregistrations of various cardiovascular control mechanisms represent an important and perplexing group of disease entities confronting the physician in his daily practice. The various types of regulating mechanisms being discussed in this symposium constitute a rational classification of those clinical problems that are produced by distortion or abnormalities of control. For example, abnormal control of heart rate is involved in the extravagant tachycardia that occurs with neurocirculatory asthenia and other manifestations of psychologic instability. Both primary and secondary systemic arterial hypertension involves abnormalities in blood pressure control. Orthostatic hypotension represents a failure of the normal peripheral vascular response to arising. A more specific defect in fine control of peripheral vasculature occurs in Raynaud's disease. The regulatory mechanisms that influence erythropoiesis may produce anemia at one extreme and polycythemia at the other.

The control of blood volume and of total body fluids must be deranged when patients with advanced cardiac disease develop peripheral vascular congestion and edema.

In addition to primary disturbances of control mechanisms, physicians must be alert to changes in control systems induced by various organic disease states. Consider a patient with severe aortic insufficiency. In spite of voluminous uncontrollable regurgitation of blood during each cardiac cycle, the net forward flow of blood through the arterial system is generally within the range of normal values so long as the heart remains compensated. Similarly, the cardiac output tends to be maintained even after large portions of the ventricular myocardium have been replaced by scar tissue after severe coronary occlusion. On the other hand, hyperthyroidism or emotional states may impose sustained loads on the hearts of patients that are unrelated to disease of the cardiovascular system. From this point of view it becomes imperative that the basic control mechanisms of the cardiovascular system be as fully understood as possible.

Cardiac Control

If we consider control of the heart in terms of the definition and example proposed by Dr. Peterson, many essential pieces of information are missing. Since the heart is a pump, its control must take the form of adjustments in the heart rate or stroke volume or both. If the cardiac output is regulated by a sensing element that provides an error signal whenever the cardiac output varies from some set value, we cannot at present identify the flow-sensing mechanism; we do not know the mechanism by which the resting levels are "set" nor can we describe in any detail the afferent pathways or coordinating centers for the appropriate reactions that maintain resting cardiac output. It is tempting to assume that the normal resting cardiac output represents the level to which heart rate and stroke volume would tend if all controls were removed. This concept does not appear applicable to the regulation of resting heart rate, which is the resultant of the mutually antagonistic effects of sympathetic and parasympathetic nerves to the pacemaker region. The parasympathetic effects are generally regarded as dominant, so that section of both sets of nerves leads to a faster heart rate than the normal resting value. Moreover, the cardiac index at rest

From the Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Wash.

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In a simple hydraulic system, the perfusion pressure can be maintained within narrow limits by a servo-control system that produces appropriate changes in pump output to balance any net changes in peripheral resistance or vice versa. The correspondence between this basic pattern and the pressoreceptor mechanism is illustrated.

tends to be about the same for subjects with either rapid or slow heart rates. In other words, a relatively slow heart rate is associated with a relatively large stroke volume and vice versa. If this is the case, the cardiac output may be regarded as "set" in terms of some other criteria, i.e., peripheral tissue requirements.

The flow of blood through peripheral tissues might be regulated to maintain a constant environment for the various cells. Such regulation might involve chemoreceptors in the systemic veins to monitor oxygen content of venous blood to provide sensing elements for proper adjustment of peripheral flow distribution and cardiac output. Such adjustments would be truly applicable only to those tissues in which blood flow is dependent upon metabolic rate and oxygen consumption, i.e., skeletal muscle. No chemoreceptors have been demonstrated in the various systemic veins thus far. Since skin serves an essential function in heat exchange, proper sensing elements to "set" blood flow through the subcutaneous tissues would be some form of temperature receptors. What would be the most appropriate sensory elements to monitor renal blood flow, gastrointestinal perfusion or circulation through glands? We have not found such receptors as might be required for these purposes. Indeed, in many instances we would not even know what to look for.

The traditional view of cardiac output regulation revolves about a mechanism for maintaining systemic arterial pressure to provide an effective balance between peripheral blood
Changes in left ventricular performance of a healthy dog (28 days postoperative) under various conditions are illustrated; A, startle reaction from a loud noise; B, eating response; C, confronted with the switch that actuates the motor driven treadmill; D, exercise at 3 m.p.h. on a 5 per cent grade; E, repeat exercise with a record at high paper speed (50 mm./sec.) interposed in the middle of the response. Note that under many different circumstances, elevated systolic ventricular pressure is accompanied by tachycardia.

flow and cardiac output. The basic principles of this regulation are illustrated in figure 1. If the perfusion pressure is maintained constant by means of servo-control, any net change in peripheral flow is promptly countered by the appropriate increase in cardiac output. The distortion receptors in the carotid sinus and aortic arch could serve as appropriate sensory elements to monitor systemic arterial pressure. Theoretically, changes in the discharge frequency along the nerves from the pressoreceptors influence medullary cardioregulator centers, so that any reduction in arterial pressure would be promptly countered by the proper degree of tachycardia and compensatory vasoconstriction in inactive tissues to maintain systemic arterial pressure within a narrow range. The pressoreceptor mechanism has received a great deal of attention, since it is the only neural feed-back loop for cardiovascular control that has been described in some detail. Whenever this mechanism plays a dominant regulatory role, tachycardia should be associated with any reduction in mean systemic arterial pressure. Elevated systemic arterial pressure should be accompanied by bradycardia. On the contrary, cardiovascular responses of intact dogs during spontaneous activity frequently display tachycardia during elevation of systolic ventricular pressure (fig. 2). Other studies have indicated that these conditions are also frequently characterized by increased mean arterial pressure. Apparently the sympathetic discharge to the
heart under these conditions overrides the pressoreceptor mechanism. Under these conditions, the arterial pressure controls cannot be regulating cardiac output. Dr. Peterson will present additional information regarding this important mechanism.

According to traditional concepts, a mechanism for adapting the stroke volume to the circulatory requirements was embodied in the length-tension relationships of the myocardium, and no external control need be postulated. This mechanism is clearly dominant in isolated or exposed hearts under experimental conditions. Similarly, increased stroke volume and stroke work accompany increased diastolic distention in intact animals during the transition from the standing to the recumbent position.\(^1\)\(^2\) However, other forms of cardiovascular adjustments appear to be initiated primarily by increased discharge of sympathetic nerves to the heart and peripheral vasculature. In a dog that is familiar with treadmill exercise, confronting him with the switch that turns on the motor-driven treadmill will characteristically induce changes in left ventricular performance that simulate those produced by the running at 3 m.p.h. on a 5 per cent grade (fig. 2C). The left ventricular response to this treadmill exercise generally involves a prompt elevation in left ventricular systolic pressure accompanied by an equally abrupt tachycardia.\(^3\)\(^4\) In the particular example presented in figure 2, the systolic ventricular pressure was elevated when the treadmill switch was presented but not during the exercise. Thus an inappropriate stimulus produced a more typical response in figure 2C than did the appropriate stimulus in figure 2D and 2E. The left ventricular response to treadmill exercise at 3 m.p.h. on a 5 per cent grade can also be quite precisely duplicated by electrical stimulation in 2 discretely localized sites in the dienecephalon (in the H\(_2\) field of Forel and the periventricular gray matter). The response can be elicited by very weak stimulation without movement by the animals with or without anesthesia.\(^3\)\(^4\)

The initiation of changes in circulatory pattern by increased discharge from the higher levels of the nervous system does not necessarily constitute a regulatory mechanism under the definition presented by Dr. Peterson, since no sensing mechanisms, setting mechanisms, or feed-back loops have been implicated. (This is analogous to the occupant of the house resetting the thermostat.) Adjustments in the cardiovascular system initiated voluntarily or from higher levels of the nervous system might more appropriately be regarded as control rather than regulation. When a dog exercises for the first time on the treadmill, virtually all the recorded parameters tend to display an overshoot for 10 or 15 seconds and then settle down to a fairly constant level. However, by the third or fourth bout of exercise, this tendency to overshoot largely or completely disappears. This looks like modulation of an excessive cardiovascular response by unknown regulatory mechanisms.

**Summary**

If a regulating system consists of a mechanism for sensing the essential parameters, detecting deviations from a "set" value, and initiating corrective action, then the arterial pressure-regulating mechanism is the only regulating system described for the circulation in any detail. This mechanism appears to be important in maintaining a level of mean arterial pressure within a narrow range. It does not appear, however, to play a dominant role in adjusting the level of the circulation to meet spontaneously changing circulatory demands under many circumstances. During spontaneous activity by intact dogs, an increase in systolic ventricular pressure (and mean arterial pressure) is frequently accompanied by tachycardia as though some other mechanism were overriding the pressoreceptor mechanism. Thus, it appears that the cardiovascular system as a whole is largely controlled by neural mechanisms, usually initiated by higher levels of the nervous system. Very little is known of the sensory limbs of reflex arcs that can serve to regulate the cardiovascular system as a whole.
Summario in Interlingua

Si un sistema regulatori pote esser definite como un mecanismo que percipe le parametres essential del processo a regular, que detege deviationes ab certe valores establite pro ille paramentros, e que initia actions corrective quando tales es indicate, alora le mecanismo del regulation de tension es le sol sistema regulatori in le complexo del circulation que ha essite describite in detalio. Iste mecanismo pare esser importante pro mantener le nivello medie del tension arterial intra strictissime limites. Tamen, illo non pare haber un rolo dominante in adjustar le nivello del circulation in responsa a spontaneamente alterate requirimentos circulatori sub varie circumstantias. Durante spontane activities per canes intacte, un augmento del tension ventricular systolie (e del tension arterial medie) es frequentemente accompaniate de tahecardia, de manera que on ha le impression que un altere mecanismo se impone con vigor superior super le mecanismo pressoreceptori. Assi il pare que le systema circulatori in su totalitate es regulate in grande mesura per mecanismos neural que es usualmente initiate per nivellos plus alte del systema nervose. Pauchissimo es cognoscite del circuitos sensori o del arcos reflexe que pote servir a regular le systema cardiovasceular in su totalitate.

References
