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Adaptation of Cardiac Output to Peripheral Runoff Studied in Intact Dogs

Abstract. A pump with sinusoidal piston movement was connected to the abdominal aorta of intact anesthetized dogs, causing slow oscillations of arterial blood pressure. Evidence was found for the existence of a mechanism which enables the heart to adjust its output immediately to changes of peripheral outflow.

In previous publications (*1*) Wetterer and I described a method by which we produced slow, nearly sinusoidal oscillations of the arterial pressure in intact anesthetized dogs. At that time it became apparent that these oscillations do not cause any reflex activity in the cardiovascular system and that the vasomotor tone is unchanged. Since recent studies of the performance of the heart (*2*) emphasize the importance of experimentation in intact animals as compared to experimentation in preparations such as Starling's, it became obvious to us that this method would be most suitable for such studies.

Twelve experiments were performed on large dogs anesthetized with 30 mg of Nembutal, or 3 mg of morphine sulfate, plus 200 mg of sodium barbital per kilogram. A pump with a nearly sinusoidal piston movement (a specially adapted Harvard respiration pump) was connected to the abdominal aorta by way of a short polyethylene tube of 3.2-mm inside diameter via the right femoral artery. The volume displacement of the pump was variable within the range of 50 to 100 ml. The piston movement was continuously recorded by means of a linear differential transformer. The pump was operated with frequencies from 0.18 to 0.30 cy/sec and in operation caused a slow oscillation of the mean arterial pressure by alternatingly taking out and reinjecting blood. Arterial blood pressure was measured in the aortic arch by means of a miniaturized catheter tip manometer with a natural frequency of 500 cy/sec (*3*). The manometer was introduced through the left femoral artery. A catheter tip flowmeter with a natural frequency of 160 cy/sec (*4*) was placed in the ascending aorta close to the aortic valves by way of the left carotid artery. Clotting was prevented by the injection of 5 mg of heparin per kilogram. Calibration of the flowmeter was accomplished *in situ* by taking simultaneous dye-dilution curves (*5*). Zero flow in the ascending aorta was obtained by arresting the heart for a few seconds by stimulation of the left vagus nerve.

Our recordings taken during operation of the pump show that the oscillation of the aortic pressure, while accompanied by significant changes of aortic flow, is not reflected in the pressure in the right atrium. They demonstrate further that operation of the pump does not cause any changes in heart rate. This, as well as the fact that the arterial pressure after the pump is stopped returns within 1 second to the level recorded before the pump was started, indicates that the pressure oscillation does not produce reflex changes in the circulatory system.

For the evaluation of the recordings the area under the curve of the aortic flow, which was taken as a measurement of cardiac output, was measured with a planimeter, and each stroke volume was calculated. The volume exchanges of the pump were derived from recording the piston movement.

It was found that for any given diastolic aortic pressure, the algebraic sum of cardiac output and volume injected or withdrawn by the pump during the same systole was a constant. This is shown in Fig. 1*A*, where stroke volume plus pump volume is plotted against diastolic aortic pressure P_d. It can be seen that values which were obtained with three different pump frequencies follow closely the same line. This shows that although the rate of inflow or outflow produced by the pump was greatly changed by changing the pump frequency, any variation of total systolic inflow into the arterial system was fully and immediately compensated by the heart. Since the effect of the pump represents in a sense a continuous change of the peripheral outflow such as would result from a change of the peripheral resistance, one must conclude that this mechanism adjusts cardiac output immediately to changes in peripheral outflow.

The constancy of the total systolic inflow for a given diastolic pressure must necessarily lead to a constancy of the aortic pressure pulse with respect to this diastolic pressure, since, as stated above, the vasomotor tone and therefore all other parameters, such as the systolic runoff and the elasticity coefficient of the arterial system, are unchanged by the operation of the pump. This is demonstrated in Fig. 1*B*, where systolic aortic pressure P_s is plotted against diastolic pressure P_d in order to show values obtained during injection as well as withdrawal of the pump. The ratio P_s/P_d was found to be changed only during the brief periods of respiration of the animal, where systolic pressure rose to relatively higher values. Therefore, only pressure cycles without respiratory activity were evaluated (*6*).

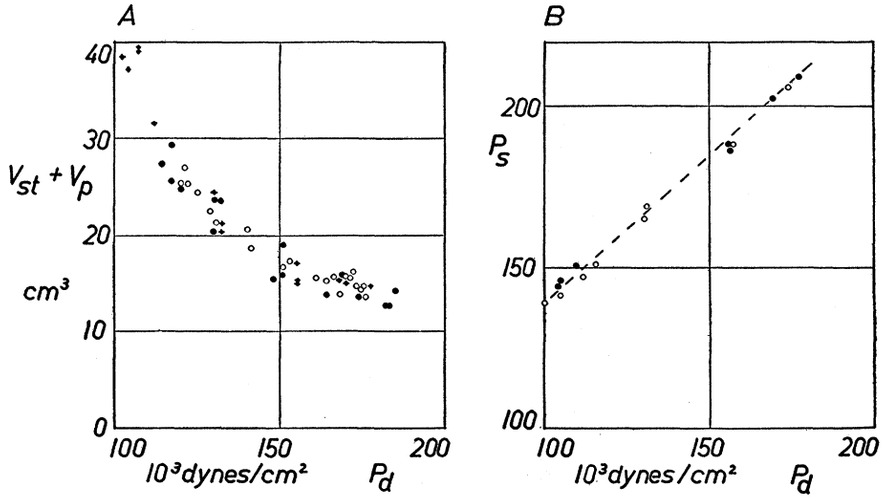

Fig. 1. (*A*) Stroke volume plus pump volume ($V_{st} + V_p$) plotted against diastolic aortic pressure P_d. Values for three different pump frequencies: +, 0.28 cy/sec; ●, 0.22 cy/sec; O, 0.16 cy/sec. (*B*) Systolic aortic pressure P_s plotted against diastolic aortic pressure P_d; O, during withdrawal; ●, during injection of pump.

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Primary Site of Gene Action in Anterior Pituitary Dwarf Mice

Abstract. The transplantation of anterior pituitary glands of normal mice into hypophysectomized dwarf littermates has resulted in mice that are normal in appearance and growth rate. In contrast, the anterior pituitary gland of dwarf animals, when placed in the sella of hypophysectomized normal littermates, failed to promote the growth of these animals. These results indicate that the primary site of gene action in dwarfism lies in the anterior pituitary itself rather than in the hypothalamus.

The dwarf mouse has been used extensively in a variety of endocrine studies. Snell (*1*) demonstrated that the dwarfism is the result of a single recessive gene that is not sex-linked. The immediate cause of dwarfism is the failure of the anterior pituitary gland to function in the production of growth hormone. Smith and MacDowell (*2*) were the first to suggest this cause after observing the hypoplastic nature of the anterior pituitary lobe, the sexual glands, and the adrenal cortex. These two investigators produced dwarf mice that were normal in growth and appearance following daily implants of normal rat pituitaries. Kemp and Marx (*3*) demonstrated normal growth and appearance of dwarf mice following daily injections of anterior pituitary extracts. Francis (*4*) studied the cytology of the pituitary of the hereditary dwarf in some detail and confirmed earlier studies which related the dwarfism to an absence of typical acidophiles and a deficiency of growth hormone. Current interest in hypothalamic-anterior pituitary interrelationships directed our attention to the possibility that the primary site of gene action might lie in the hypothalamus rather than in the anterior pituitary per se.

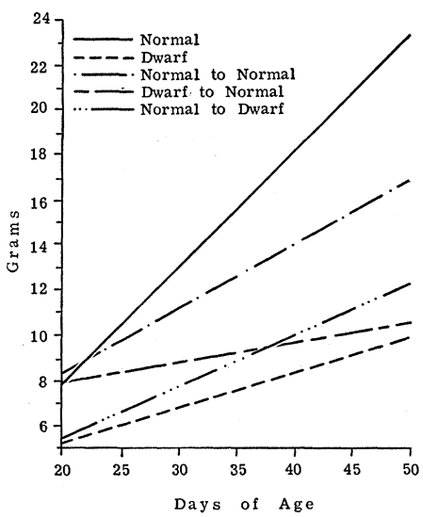

Fig. 1. Growth curves of intact and pituitary graft-bearing mice of the genetic dwarf strain. Each curve represents pooled data obtained from a group of five animals.

In order to answer this question we have transplanted anterior pituitary glands between normal and dwarf members of litters whose parents were heterozygous for the dwarf gene. Our experiments were so designed that the activity of the anterior pituitary homografts could be observed by daily weighings and resultant growth curves. Using littermates, we hypophysectomized normal mice (14 to 18 days old) by the parapharyngeal method. A dwarf littermate of like sex was killed, and its pituitary was placed immediately into the sella of the hypophysectomized normal littermate. The transplanted pituitaries were held in place against the hypothalamus by Gelfoam sponge (Upjohn), and the incision was closed with silk sutures. In this manner, transplants were made from dwarf mice to normal mice, from normal mice to dwarf mice, and from normal mice to normal mice. There were five animals in each of these groups. The growth of these animals and that of five unoperated dwarf and five unoperated normal mice was determined by daily weighings for a 30-day period (20th day through the 50th day). Growth curves representing these five groups of mice were then made.

Our observations were as follows (Fig. 1). (i) Unoperated normal mice gained 15.5 gm. (ii) Unoperated dwarf mice gained 4.4 gm. (iii) Hypophysectomized normal mice bearing transplants from normal mice gained 8.7 gm. (iv) Hypophysectomized normal mice bearing transplants from dwarf mice gained 2.8 gm. (v) Hypophysectomized dwarf mice bearing transplants from normal mice gained 6.7 gm.

More important than the total weight gain is the rate of weight gain. The rate of weight gain in hypophysectomized dwarf mice bearing pituitaries of normal mice was almost equal to the rate of growth of hypophysectomized normal mice bearing pituitary transplants from normal mice. On the other hand, the rate of weight gain of hypophysectomized normal mice bearing pituitaries of dwarf mice was even less than the rate of growth of unoperated dwarf mice.

These results indicate that the hypothalamus of the hereditary dwarf mouse is capable of stimulating a pituitary graft from a normal animal to function at a level comparable to that seen in normal animals bearing similar pituitary grafts. It is noteworthy that the dwarf mouse, when given a normal anterior pituitary as an intrasellar graft, comes to resemble a normal mouse in rate of growth and in physical appearance. Also, the evidence obtained indicates that the pituitary of the dwarf mouse is incapable of producing significant amounts of growth hormone, even when it is placed in contact with the hypothalamus of a normal animal. This shows rather clearly that the anterior lobe of the pituitary and not the hypothalamus is the primary site of gene action in the anterior pituitary dwarf mouse.

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Heterogeneity of Ion Exchange Resins

Abstract. The density gradient method of Linderström-Lang has been used to study density variations among swollen beads in batches of cation exchange resin. Solutions of salts such as sodium tungstate which have dense anions are used. Certain commercial resins appear to be very uniform in cross linking and sulfonation.

A report by Högfeldt (*1*) shows that individual beads in a batch of ion exchange resin can differ widely in their characteristics. Beads taken from a batch of sulfonated polystyrene resin with a nominal 4 percent of cross linking showed selectivities for silver ions against hydrogen ions which varied by a factor of more than 2. Parallel variations were found in the swelling. These could be due to differences in cross linking, sulfonation, or both.

In our laboratory we are studying the thermodynamics of ion exchange,