Effects of Alterations in Peripheral Resistance on Left Ventricular Function.* (30441)

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The influence of alterations in peripheral resistance on the function of the left heart is incompletely understood. Previous studies in the heart-lung preparation indicate a marked sensitivity to an increase in outflow resistance(1). A sudden increase in outflow resistance results in an immediate decrease in stroke volume, peak ventricular power, and stroke work. However, if the increased resistance is maintained, there is, within a very few beats, an increase in peak power and stroke work to levels exceeding control values (2). Although of less magnitude, partial ventricular compensation also occurred when diastolic ventricular dimensions and pressures were not permitted to change, indicating an intrinsic adaptation to increased resistance, despite lack of diastolic stretch. Other studies in the open-chest animal(3) indicate that if carotid sinus pressure is allowed to increase, an increase in outflow resistance will result in a decrease in stroke volume without an appreciable change in peak power and stroke work.

When peripheral resistance is decreased, as in an arterio-venous fistula, previous workers (4-7) have usually obtained an increase in stroke volume and cardiac output, although the increase in cardiac output apparently may be produced by an increase in rate without a marked change in stroke volume(4). The corresponding changes in cardiac work and stroke work have not been directly studied in the intact animal. However, Guyton and Sagawa(5) found a 74% increase in left ventricular work in response to large fistulas, using a preparation in which the right ventricle was replaced by a pump.

Thus the left ventricular response to a change in peripheral resistance is to increase its output for a decrease in peripheral resistance and to decrease its output for an increase in peripheral resistance. Cardiac work, however, is primarily the product of cardiac output and aortic mean systolic pressure and may increase or decrease depending on the relative changes in pressure and flow. The previous studies indicate that work is increased, decreased, or unchanged when resistance is increased. These experiments were undertaken to follow the alterations in left ventricular responses to both increases and decreases in resistance in the anesthetized open-chest animal.

Methods. Thirteen mongrel dogs weighing from 11.5 to 19.5 kg were anesthetized with sodium pentobarbital (12 mg/kg i.v.) after premedication with morphine sulfate (3 mg/kg i.m.). The chest was opened by a right thoracotomy and an electromagnetic flowmeter probe placed around the root of the aorta, just distal to the origin of the coronary arteries. The flowmeter probe was connected to a square-wave electromagnetic flowmeter similar in design to that previously described(8,9). In the animals in which peripheral resistance was to be increased, a Blalock clamp was placed on the descending thoracic aorta. Polyethylene catheters were introduced into the right atrium and into the aorta, both proximal and distal to the clamp, *via* the right external jugular vein, left common carotid artery, and right femoral artery, respectively. These were connected to Statham transducers placed at the right atrial horizontal level. Where resistance was to be decreased, a bilateral fistula, consisting of Tygon tubing and glass cannulae, was inserted between the femoral arteries and femoral veins, and the animal appropriately heparinized. Fistula flow was monitored by a flo-thru type electromagnetic probe. Arterial pressures were then recorded from the proximal aorta and from the arterial side of the fistula.

Continuous recordings were thus obtained of stroke volume (minus coronary flow), cen-

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tral venous pressure, proximal and distal aortic pressure, and fistula flow. A control recording was taken for 10 minutes, the clamp partially or totally closed or the fistula opened for 10 minutes, followed by a repeat control observation for 10 minutes. Values were tabulated at 2 and 10 minutes during each 10-minute period in order to avoid transient phenomena. Stroke volumes were obtained by planimetering the areas of the aortic flow record which correspond to ventricular systole, leaving out the negative flow portion at the end of systole (which represents blood that has already passed through the probe on cardiac ejection). Coronary flow was not estimated. The results of 51 experiments are reported.

The flowmeter was calibrated either *in situ* by inserting a calibrated rotameter into the descending thoracic aorta and tying off the head vessels and the proximal intercostals, or by excising a segment of the ascending aorta and pumping blood through an artificial system with a Sigmamotor pump. The fistula flow probe was calibrated directly by allowing the animal to bleed through the probe into a graduated cylinder for timed intervals.

Peripheral systemic resistance was calculated by dividing the aortic to right atrial pressure drop by aortic flow. Stroke work was found by multiplying stroke volume by mean aortic pressure. Cardiac minute work was obtained from the product of stroke work and heart rate.

Results. Fig. 1 illustrates the type of response seen on opening a large fistula and on aortic clamping. Upon opening the fistula, heart rate increased moderately accompanied by a small drop in aortic pressure and a marked increase in aortic flow rate. Complete occlusion of the descending aorta resulted in a slight rise in pressure and decrease in heart rate, with a small increase in aortic flow.

Fig. 2 compares the percentage variations in cardiac output (minus coronary flow), stroke volume and heart rate with the experimentally induced changes in systemic peripheral resistance. Cardiac output showed a decrease from very high values at low resistances to about 60% of the control value at very high resistances. Several attempts were made to obtain further data for resistance increased by 200% or more. Such large increases in resistance were seldom seen, however, even when the descending aorta was completely occluded. Maximal fistula flows represented aproximately 130% of control cardiac output.

No attempt was made to hold the heart rate constant. The corresponding changes in heart rate and stroke volume are shown in the figure. Stroke volume followed the cardiac output curve roughly but with considerably more variation. Heart rate remained relatively constant in the fistula animals but decreased in the animals with their aorta constricted, presumably due to increased pressure in the baroreceptors. Right atrial pressure remained relatively constant in the clamp experiments, but increased by 25.6%, from $3.24 \pm .38$ to $4.07 \pm .42$ cm of H_2O (mean and standard error), in the fistula group ($P \leqq .005$).

It appeared that the constricted animals could establish their cardiac output by varying either stroke volume or heart rate. Some animals maintained a high stroke volume and decreased their heart rate (for example the group of 3 at a resistance of 180% in Fig. 2), whereas others had a lower stroke volume but a faster rate. (The Figure is so arranged that each experiment may be followed vertically up and down to compare the factors producing a given change in cardiac output.)

Fig. 3 shows the percentage variations in mean aortic pressure, stroke work and cardiac work *vs* peripheral resistance. As with heart rate, most of the changes in pressure occurred as a result of clamping the aorta, whereas the fistula produced little change. Cardiac work tended to be similar to the cardiac output curve but with much more variability. Stroke work was even more variable but showed a definite increase in the large fistulas.

Discussion. The response to lowering the peripheral resistance was a definite increase in stroke volume and cardiac output accompanied by small changes in rate. This is similar to the results obtained by others with

arteriovenous fistulas(4-7), although Murphy *et al*(4) found no consistent change in stroke volume, but definite increases in rate. Cardiac work and stroke work increased in large fistulas, but were much more variable in small fistulas, even decreasing in some animals. Aortic pressure decreased slightly.

Increasing the peripheral resistance increased aortic pressure, but decreased heart rate and cardiac output. Stroke volume varied, increasing in some cases and decreasing in others, accompanied by a corresponding directional change in stroke work. In general, others(1-3) have found decreases in stroke volume when the heart rate remains constant. Of 27 experiments with aortic clamping presented here, 14 showed an increase and 13 a decrease in stroke volume. The reason for this is not apparent from our experiments. It seems unlikely, however, that statistical variation alone could account for these changes, since the scatter of data about the corresponding cardiac output curve is much smaller.

No attempts were made to hold heart rate or venous return constant. The changes in stroke volume may be due to changes in end systolic or end diastolic volume, or both, and may be associated with changes in venous return or cardiac contractility. In the animals subjected to aortic clamping, when the rise in aortic pressure was accompanied by a marked decrease in heart rate, there was a corresponding increase in stroke volume. The

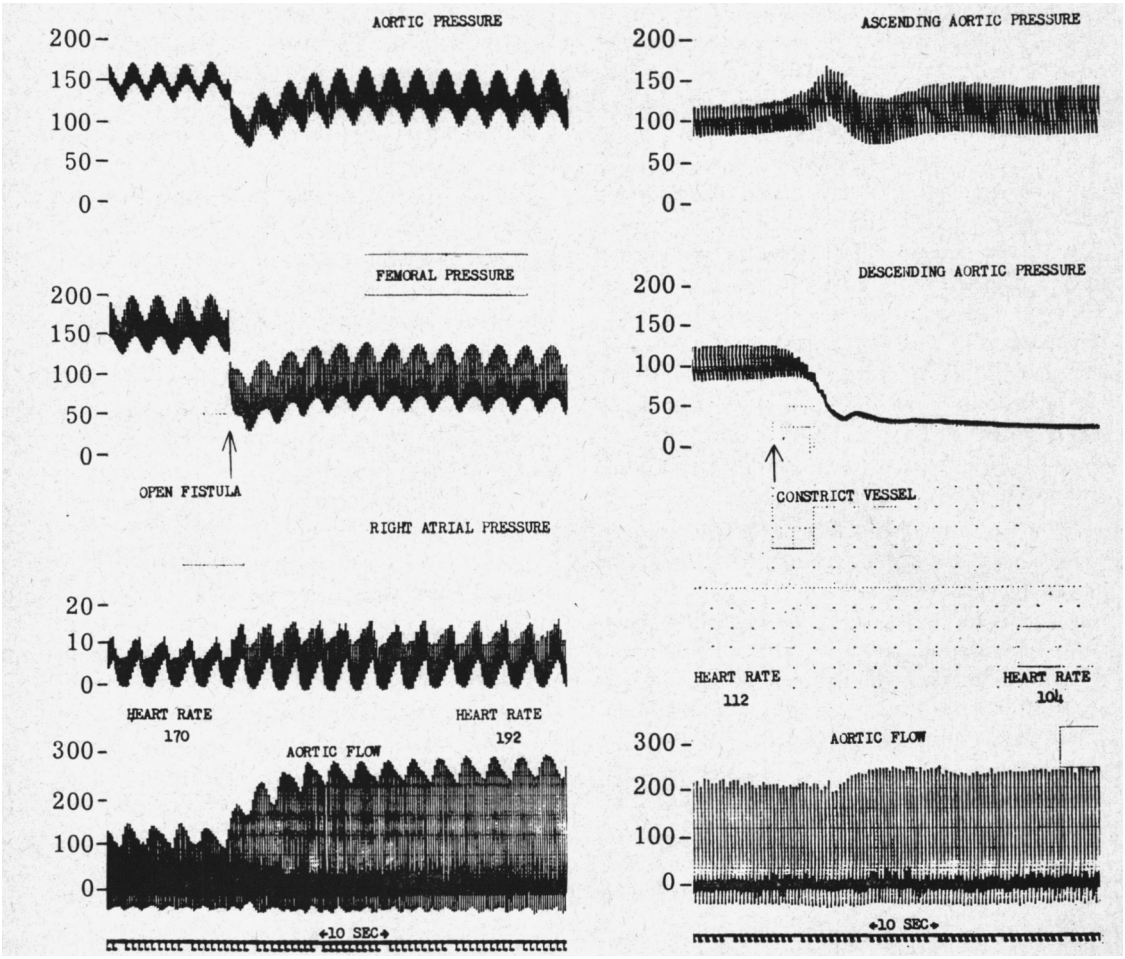
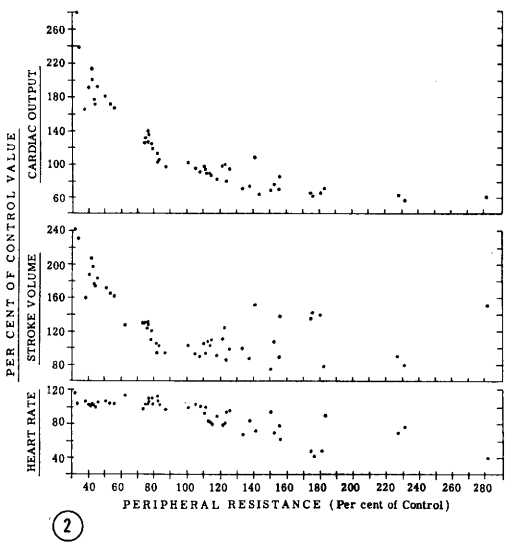


FIG. 1. Typical responses to opening a large femoral arteriovenous fistula (left panel) and to aortic clamping (right panel). Arterial pressure in mm Hg, right atrial pressure in cm H_2O. Heart rate in beats per min. Flow in cm^3/sec.

latter may be due to increased filling time, intrinsic adaptation to the increased resistance(2), or to a positive inotropic reflex associated with baroreceptor stimulation. Such a reflex appears unlikely, however, since stimulation by *lowering* carotid sinus pressure has been associated with positive inotropic effects(10) and raising carotid sinus pressure with negative inotropic action(10, 11).



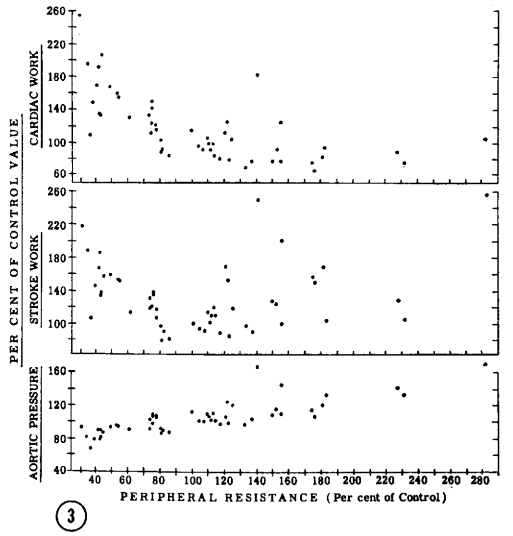


FIG. 2. Cardiac output, stroke volume (minus coronary flow), and heart rate plotted as per cent of control value produced by the experimental procedure *vs* the corresponding alterations in peripheral resistance.

FIG. 3. Cardiac work, stroke work, and aortic pressure *vs* peripheral resistance. Units are per cent of control values.

Two comments on limitations of method are appropriate. Our experiments were carried out in open-chest anesthetized animals with consequent possible alterations in the pressure relationships between the heart and its inflow-outflow vessels, and any additional changes produced by artificial respiration and anesthesia. A fair amount of manipulation was necessary in order to place the flow probe around the aorta. Coronary flow was not measured and probably represents a larger percentage of the cardiac output than normal in the clamp experiments.

Finally, the method of obtaining stroke work was to multiply mean aortic pressure by stroke volume. This is not equivalent to the more accurate method wherein a computer is used to multiply instantaneous pressure by instantaneous flow and integrate over the time of ejection. In the final analysis, however, the data were considered in terms of the percentage variation of experimentals *vs* controls, which should make this error less significant.

Summary. The effects of increasing or decreasing peripheral resistance on heart rate, left ventricular stroke volume, cardiac output, stroke work, cardiac work and aortic pressure were investigated in 51 open-chest acute experiments. The results show a decrease in cardiac output, heart rate, and cardiac work with an increase in systemic resistance. Aortic pressure increased, but stroke work showed no consistent relationship to an increase in resistance. Stroke volume increased in approximately one-half of the animals when resistance was increased, accompanied by a decrease in heart rate. Cardiac output, stroke volume, cardiac work and stroke work all increased in response to a decrease in systemic resistance, accompanied by smaller changes in heart rate and aortic pressure. Right atrial pressure also increased significantly when resistance was decreased.

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Zoster-Like Lesions from Herpes Simplex Virus in Newborn Rats.* (30442)

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This paper reports that intradermal inoculation of herpes simplex virus into newborn rats causes a vesicular skin lesion with a segmental distribution. Teague and Goodpasture(1) reported a similar eruption in the skin of rabbits and guinea pigs when herpes simplex virus was inoculated by application to the scarified skin. The appearance of those lesions was very similar to that found in the present studies in rats. We are not aware of any other report of an experimental virus lesion that has a distribution corresponding to sensory branches of the spinal nerves. Because of the similarity of this lesion to herpes zoster of man, it may have value as an experimental model for the study of that skin eruption, in spite of the fact that herpes simplex and herpes zoster are caused by antigenically unrelated viruses.

This study also provides an new example of increasing natural resistance to virus infection with increasing age. This prenomenon was systematically explored in mice by Lennette and Koprowski(2) using herpes simplex and several arboviruses. Recent studies with arboviruses in this laboratory have demonstrated that the phenomenon also occurs in rats(3).

Methods. The virus was the HF strain(4) of herpes simplex (herpes virus hominis) originally obtained from Rockefeller Institute but maintained in this Institute for several years through an unrecorded number of intracerebral passages in adult mice. Its identity was confirmed during the course of these studies by neutralization tests with 2 commercial antisera, and by the production of characteristic lesions on the corneas of rabbits and on the chorioallantoic membranes of embryonated hens' eggs.

Virus stock for these experiments was prepared as the supernate from a 20% homogenate of infected adult mouse brain and stored in sealed glass ampules in a dry-ice (solid CO_2) box until use. The suspending fluid for virus preparations was 0.85% sodium chloride containing 0.75% bovine serum albumin and penicillin (200 U/ml) and streptomycin (0.2 mg/ml).

Control mouse brain preparations were made in the same manner from healthy uninoculated mice from the same source.

Virus infectivity was titrated simultaneously with every rat experiment by intracerebral inoculation of young (16 to 18 g) male Swiss white mice (Millerton Farms, Millerton, N. Y.) with 0.03 ml volumes of 10-fold serial dilutions of the virus preparation. All virus titers are expressed as that

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