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Blood Flow and Peripheral Resistance in Normotensive and Hypertensive Dogs* (32995)

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The level of the peripheral resistance is frequently used in the estimation of the severity of hypertension or the response to drugs affecting the peripheral circulation. Yet when measurements of resistance are followed from day to day in normal or hypertensive dogs, there are unexplained variations. In particular the hypertensive animal will frequently show levels of resistance well within the normal range, suggesting that the condition may be undergoing variations in severity. Observing the behavior of the circulation over periods of time, it was noted that level of resistance appeared to vary inversely with the cardiac output. The present study investigated this relationship in dogs before and after the development of hypertension and as it is influenced by drugs.

Material and Methods. Trained conscious dogs with chronically implanted catheters in the aorta and right heart have been used. Blood pressure and cardiac output measurements were made at intervals of 3–5 days in the fasting state without restraint or premedication using methods previously described in detail (1). Five dogs were studied repeatedly in the normotensive state and then again 3 weeks after the application of a Goldblatt clamp to one renal artery with a contralateral nephrectomy. Two other dogs were studied repeatedly in the normotensive state and at each session, measurements were repeated after ganglion blockage with pentolinium (25 mg i.v. and 2.5 mg s.c.). This dose was chosen as it produced paralysis of the pupillary light reflex. After these measurements had been made, an infusion of norepinephrine (0.3 μg/kg per min) was administered through a third catheter in the ascending aorta for 5 min with a cardiac output and blood pressure measurement being made in the final minute. The pupillary light reflex remained paralyzed at the completion of the infusion.

Results. From one day to another, the cardiac output, both in the normotensive or hypertensive state, showed considerable variation (Fig. 1). The mean blood pressure also showed some fluctuation and varied from 90 to 126 mm Hg in the normotensive and from 136 to 187 mm Hg in the hypertensive state. There was, however, no tendency for it to change with cardiac output (Fig. 2). The peripheral resistance, however, clearly fell in an exponential fashion as cardiac output increased. With the development of hypertension, the curve shifted to the right to give a higher level of resistance for any given level of cardiac output (Fig. 1).

Since it was thought that these findings

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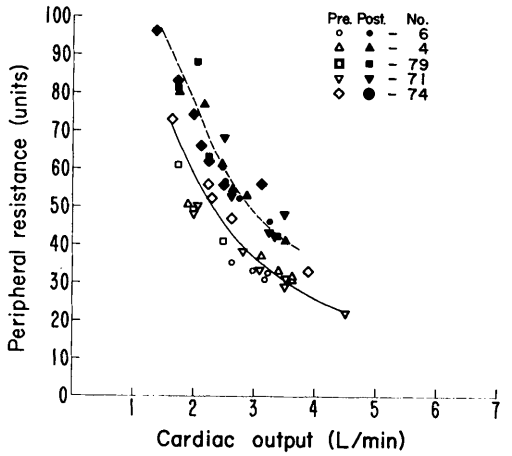

FIG. 1. Relationship between resting cardiac output and total peripheral resistance measured on different days in five dogs before (open symbols) and after (solid symbols) the production of renal hypertension.

might be the result of reflex control of blood pressure in the presence of the fluctuation in cardiac output, two further dogs were studied before and after autonomic blockade. These animals had smaller spontaneous fluctuations in cardiac output than the previous group, but the relationship between cardiac output and resistance was similar; furthermore, ganglionic blockade did not affect this relationship (Fig. 3). An infusion of norepinephrine then displaced the curve to the right,

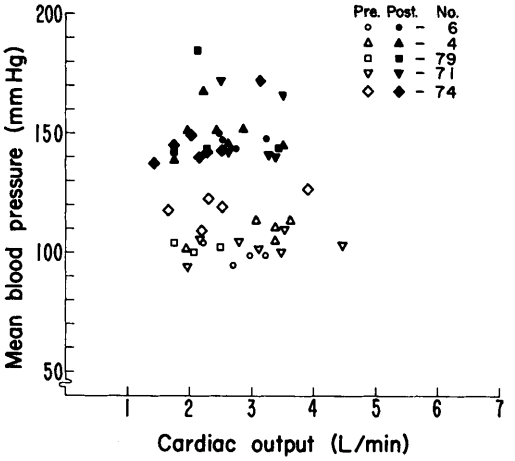

FIG. 2. Relationship between cardiac output and blood pressure. The animals studied and the symbols used are identical to those in Fig. 1.

and, as cardiac output fell, the rise in resistance tended to become steeper.

Discussion. In the normal and hypertensive states unpredictable day to day fluctuations in cardiac output and less so in blood pressure render the determination of peripheral resistance of doubtful value, if not frankly misleading. Nevertheless, there does appear to be a predictable relationship between cardiac output and peripheral resistance which can be used to follow changes in the vascular bed. Two explanations for these findings are possible. Either blood pressure is closely controlled irrespective of cardiac output, or output increases whenever peripheral resistance fails.

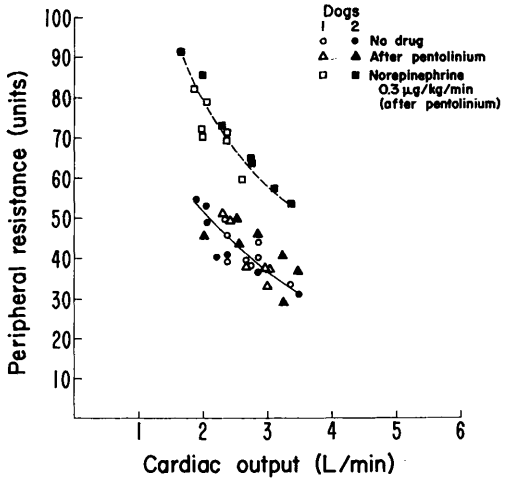

FIG. 3. Relationship between cardiac output and peripheral resistance in two dogs measured on different days before and after the administration of pentolinium. During ganglionic blockade, the effect of an infusion of norepinephrine was also determined.

The spontaneous increase in resistance with reduction in cardiac output demonstrated in these experiments is probably not due to activity of reflexes concerned with blood pressure regulation since it was uninfluenced by autonomic blockade. Cardiac output or vascular resistance are readily affected by other influences, for example: variations in metabolic activity would readily decrease resistance and increase cardiac output, and, in man, resting cardiac output is closely related to oxygen consumption (2). Such fluctuations, however, make it impossible to follow the

course of hypertension from peripheral resistance measurements. If the curve relating cardiac output to peripheral resistance is known, then the resistance value for a given cardiac output is meaningful and the difference in resistance produced by hypertension or, for example, by norepinephrine is seen clearly. These findings have clinical application since patients with mild hypertension have been reported as having an increased cardiac output with a resistance within the normal range (3). The seemingly normal levels of resistance may, in fact, be elevated at that cardiac output.

Summary. Peripheral resistance has been found to fall exponentially as cardiac output increases in dogs. A similar curve with a higher peripheral resistance at all levels of cardiac output is observed in hypertensive animals. The measurement, therefore, of peripheral resistance alone, or its changes, to indicate the state of the peripheral vascular bed is of little value unless level of blood flow is held constant or the relationship between blood flow and peripheral resistance have already been determined.

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The Effect of RES Blockade on Cellular Antibody Formation to Sheep Erythrocytes* (32996)

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Processing of particulate antigens by cells of the reticuloendothelial system (RES) is considered to be an important step in the "afferent limb" of antibody formation (1–4). Circulating and fixed macrophages have been shown to "digest" particulate antigens such as foreign erythrocytes or bacteria following their inoculation into experimental animals (4,5). Results by a number of investigators have suggested that, as a consequence of such phagocytosis, a product of the macrophage, possibly an informational nucleic acid product or a processed antigenic determinant, probably associated with RNA, is released and may act directly in stimulating antibody formation by lymphoid cells (6–11).

Blockade of the RES is regarded as a classic method of profoundly influencing the immune capability of animals toward a variety of antigens (2–4). In a number of such experiments, treatment of experimental animals with agents such as carbon, colloidal iron, or oil emulsion interfered with production of specific serum antibody, or development of protective immunity against challenge infection with a microorganism. Some investigators have reported an inhibitory effect of RES activity by blockading agents, others have observed no effect, and yet others have observed stimulation of RES activity by blockading agents (12–18). Many of these diverging observations have been related to the dependence of dosage and timing for either stimulation or depression of RES activities by large particulate matter and to the variations in phagocytic activities of individual animals.

In general, the role of phagocytic cells as related to antibody formation has been studied only on the humoral antibody level. In the present study, experiments were performed concerning the effect of RES blockading agents on the cellular immune response of

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