Hemodynamic Basis of Norepinephrine Shock.* (29153)

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It has been known for some time that the infusion of norepinephrine(1) or epinephrine (2), can produce shock in dogs. The arterial pressure becomes increasingly refractory to the pressor effect, and the animal may die after several hours of infusion. It is not clear whether this loss of pressor effect is due to (a) a decrease in peripheral resistance, perhaps because of the appearance of dilator substances(3,4), (b) to a decreased cardiac output, or (c) to both events occurring together. The output could fall because of either myocardial weakness of a decreased venous return(5). The explanation is of interest not only because of the role of catecholamines in the pathogenesis and treatment of experimental and clinical shock, but also because a clinical counterpart of this form of shock may occur in subjects with pheochromocytoma(6). The present study shows that norepinephrine refractoriness in dogs is associated with declining myocardial function.

Methods. All studies were carried out in mongrel dogs weighing from 10 to 16 kg, and anesthetized with intravenous sodium pentobarbital. Pressures were measured through polyethylene catheters leading to Statham transducers and recorded on a direct writing oscillograph. Arterial pressure was measured at the femoral artery. Central venous pressure (CVP) was measured through a catheter passed down the external jugular vein to the superior vena cava or right atrium. This catheter was also used for injection of indocyanine green dye from a calibrated syringe, so that cardiac output (CO) could be determined by the indicator dilution method. For this purpose, blood was withdrawn through a Colson densitometer at a constant rate from a catheter inserted down the common carotid to about the aortic arch. In some experiments, pulmonary artery and left atrial pressures were measured with catheters inserted after thoracotomy. Hematocrits were measured in Wintrobe tubes spun at 3,000 RPM for 30 min and pH was determined anaerobically on arterial blood in the Cambridge research model pH meter.

Norepinephrine, freshly made up in 5% dextrose and water, was infused with a constant flow pump into a femoral vein. After control observations, the infusion was carried out for 120 minutes, in amounts which at first sufficed to raise mean arterial pressure by about 50 mm Hg. The infusion rate was increased during the experiment, but rarely was the initial pressure increment maintained. Cardiac output was measured at regular intervals during the infusion.

In 3 experiments, the venous return was followed during norepinephrine infusion using a preparation similar to that described by Weil *et al*(7). The azygos vein was ligated and the venous return from the cannulated superior and inferior venae cavae and right atrium was directed into a reservoir, where the level was followed, and whence the blood was returned at a constant rate of flow (58-85 ml/kg) by a Sigmamotor pump to the pulmonary artery. The level of blood in the reservoir thus rose or fell in relation to a rise or fall in venous return. Ignoring transients, arterial pressure also varied in accord with total peripheral resistance (TPR), since return to the right heart was constant. Care was taken to ensure that pressure in the cavae was held at 0-1 mm Hg to prevent passive distention of veins. Blood loss was measured and venous return values corrected accordingly.

Results. The course of the blood pressure

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in 9 experiments is shown in Fig. 1. Despite manipulation of the infusion rate, there was considerable variation in levels of pressure maintained. The average norepinephrine infusion rate was 8 μg/kg/min (2-18 μg/kg/min) at beginning of the experiment, and 18 μg/kg/min at the end. By 10 minutes, a loss of pressor response was evident. Two animals died with low arterial pressure and low CO's before the end of the 2-hour infusion. The CO (Fig. 2) usually rose at first, but then fell so that by 100 minutes, it was below control levels in all instances. TPR changes, as shown in Fig. 3, were highly variable. The average TPR remained somewhat above control value throughout the infusion. Of particular interest, CVP, except in 2 instances, tended to rise. In Fig. 4, the change in CVP

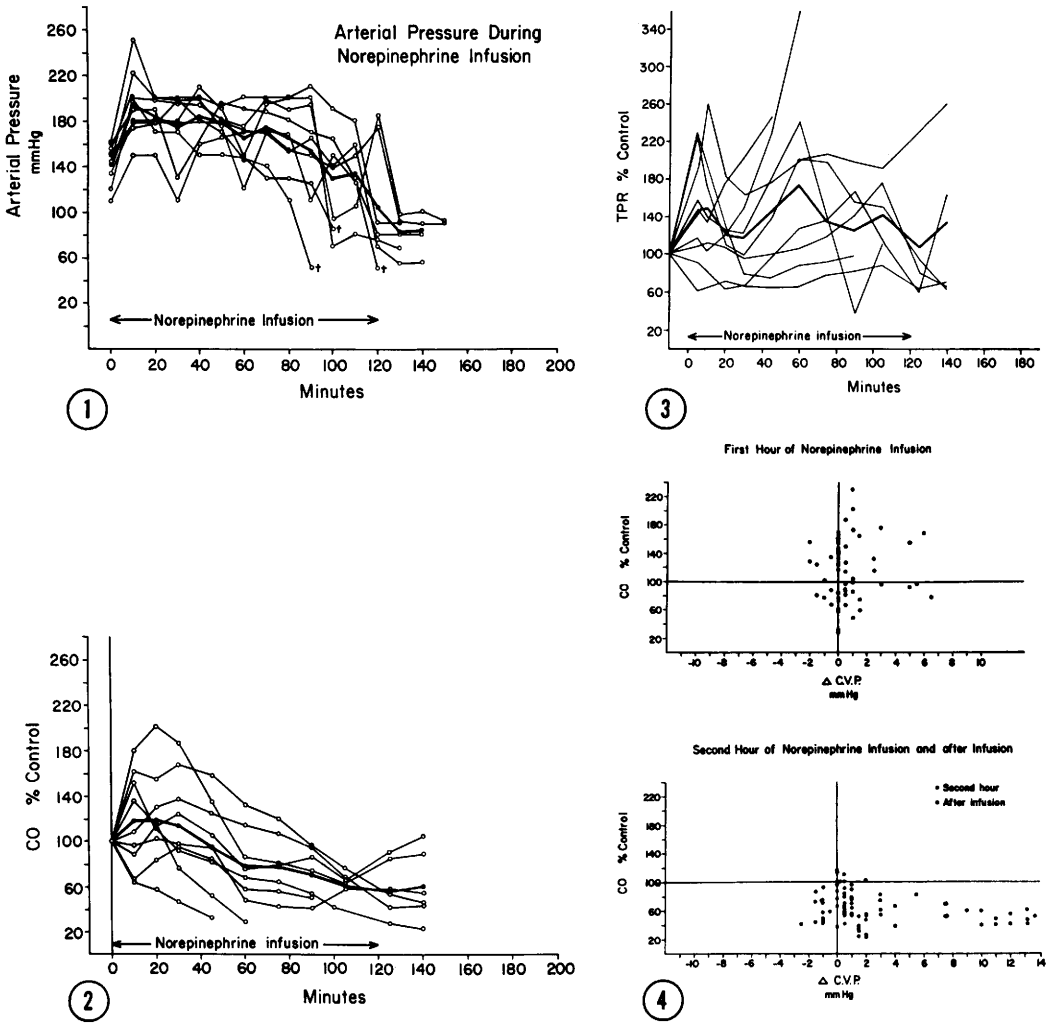

FIG. 1. Arterial pressure changes in individual experiments during norepinephrine infusion. Heavy line represents mean of 9 experiments.

FIG. 2. Cardiac output (CO) as percent of control value. Heavy line represents mean of 9 experiments.

FIG. 3. Total peripheral resistance (TPR) changes. Heavy line represents mean of 9 experiments.

FIG. 4. Percent change of cardiac output (CO) from control level, plotted against change from control central venous pressure (CVP). Upper graph shows changes during first hour; lower graph shows changes during and after second hour of infusion.

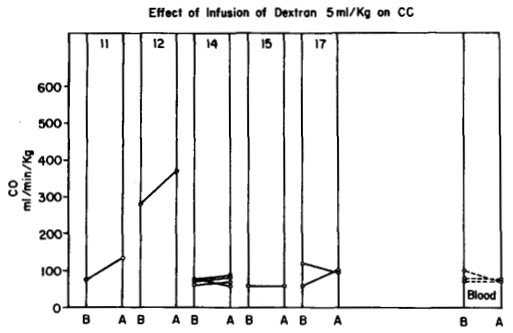

FIG. 5. Effect of dextran infusion (5 ml/kg) on cardiac output (CO) during norepinephrine infusion. B = before dextran; A = after dextran. Numbers at top correspond to specific experiments.

is graphed against the percent change in CO. The top graph shows changes during the first part of the infusion; the lower part, during and after the second hour. By the second hour, the CVP's are higher and the CO's lower. Furthermore, in only 3 of 12 trials during the later phase of 6 additional experiments did efforts to raise the CO by increasing the blood volume prove successful (Fig. 5). This was despite an increase of CVP. However, 7 of these 12 trials were in 2 dogs. The hematocrit rose from an average of 42 to an average of 51.

In one of 5 open chest experiments, the pulmonary artery pressure rose by 20-30 mm Hg, though the animal lived through the infusion period. In the other 4, there was an early rise of only 5-6 mm Hg followed by a return toward control levels after the first hour. Except for the animal whose pulmonary artery pressure rose excessively, left atrial pressure changes were slight, and resembled the CVP changes. The average rise was 1.7 mm Hg (range 1.5 to 3.0), although a late rise to 19 mm Hg was seen in one animal.

Two of the 3 venous return experiments showed an initial loss of blood volume to the reservoir, followed by a fall in reservoir level and a gain in the animal's weight past control levels (pooling). In the third animal, norepinephrine caused immediate pooling, sustained through each of 2 infusion periods.

Discussion. The cardiac output has been said to fall after the prolonged infusion of norepinephrine in dogs(8), though only an increase in output and myocardial contractility was observed with a 10-minute infusion (9). The decreasing response seen in the present experiments was associated with a falling CO, and not with a falling TPR.

Because of (1) the steady or elevated CVP, and (2) the poor output response to increasing the blood volume by infusion, it is probable that the decreasing CO is due to deteriorating myocardial function. Although the 3 venous return experiments show, in addition, a falling venous return or pooling of blood (cf. hematocrit rise) at constant CO and CVP, this does not suffice to explain the declining cardiac output of the intact animal with steady or elevated CVP. There was no evidence of a decreasing TPR, such as might result from elicitation of a dilator substance, like histamine(4). Dilatation of certain vascular beds may, of course, still occur(10).

The present study offers no explanation for this apparent decrease in myocardial function. When measured in 3 of these experiments, arterial pH fell to an average of 7.06 after 90-120 min of infusion. Arterial oxygen saturation was not determined, but in only one of 4 open chest experiments was there a rise of pulmonary artery and left atrial pressure of such degree as to cause pulmonary edema. Ecchymoses were commonly noted in the myocardium and under the epicardium and endocardium. Striking myocardial histological changes have been described from norepinephrine(11,12).

Summary. During prolonged (2-hour) norepinephrine infusion in the dog, the pressor response became less, cardiac output fell, and central venous pressure tended to rise. The loss of pressor responsiveness probably resulted from decreasing myocardial function.

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Effect of Hemolytic Streptococci on Tissue Cells.* (29154)

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The etiologic relationship of certain infections of the upper respiratory tract to group A hemolytic streptococci is well established and the further relationship of these infections to rheumatic fever and acute glomerulonephritis is highly probable, hence it seems important to learn more about host-parasite relations. Host-parasite relations at the cellular level are difficult to study in the patient and although tissue culture techniques at best are not a true counterpart of what happens in the patient, these techniques have some application in the study of these relationships. In this paper are reported experiments designed to study the spacial relationship and effect of group A streptococci on human tissue cells growing in tissue culture, and the effect of the tissue cells on the bacteria.

Methods and materials. Tissue cells.† Human tonsils were the source of lymphocytes. The tonsils were cut into fine pieces within 60 minutes of removal. The fibrous tissue was separated and the lymphoid tissue minced as fine as possible with scissors. The mince was filtered through sterile gauze. The filtrate, which contained the lymphocytes suspended in about 20 ml of medium, was composed of equal parts of mixture 199 and Eagle's basal medium containing 5% human serum, 40 μg of neomycin/ml, 1000 units of mycostatin/ml, and 100 units each of penicillin and streptomycin/ml. The cells were separated by centrifuging at 2500 r.p.m. for 15 minutes, resuspended in 3 ml of the above medium, then incubated for 2 hours at 37°C. Two-tenths to 0.3 ml of packed lymphocytes were the usual yield from each pair of tonsils. The lymphocytes were usually bacteriologically sterile after this treatment. They then were washed 3 times in the culture medium, taken up in 3 ml of medium without antibiotics and distributed in tubes, 1 ml per tube.

Cell preparations of human tonsil,‡ human liver and human monocytes were made by sub-culturing cells in antibiotic-free medium in Leighton tubes containing coverslips of No. 1 thickness. Each tube contained 0.8 ml

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† Cell lines used in these experiments and growth medium for each type of cell were human tonsil epithelial-like cells and mixture 199 + 10% calf serum; human liver cells and Eagle's Basal medium + 10 % calf serum + 0.01 mg L-glutamine/ml; human monocytes and Eagle's Basal medium + 10% calf serum + 0.01 mg L-glutamine/ml; monkey heart and minimal essential medium + 10% calf serum; monkey kidney and mixture 199 + 10% calf serum; human heart (Girardi) and minimal essential medium + 10% human serum + 0.01 mg L-glutamine/ml; human lymphocytes and equal parts of mixture 199 and Eagle's Basal medium + 5% human serum. Unless antibiotic-free medium was required, 1 mg each of penicillin and streptomycin was added to each 10 ml of medium.

‡ The tonsil cells were from a line of human tonsil epithelial-like cells obtained from Dr. Alfred S. Evans, Dept. of Preventive Med., Univ. of Wisconsin School of Med., Madison.