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Pulmonary Vascular Resistance and Right Ventricular Function in Canine Endotoxin Shock[1] (40107)

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The primary lethal factor in endotoxin shock has been thought to be inadequate venous return in the dog, which was ascribed to splanchnic pooling (1). In our studies of splanchnic pooling in canine endotoxin shock (2, 3), we found that the portal vein constricted early and remained constricted until death; the liver trapped blood early, but had returned to the control size by thirty minutes after endotoxin, whereas cardiac output and aortic pressure remained below 60% of the control levels.

In our 1970 study in the dog (2), we obtained arterial blood samples for lactate, pH, and gases at hourly intervals. There was a progressive increase in lactate and a progressive decrease in pH, and a corresponding decrease in PCO_2, except for the last sample before death which showed an increase in CO_2. Similarly, there were no consistent changes in PO_2 except for an abrupt but mild drop in the last sample. It seemed safe to conclude from the trends of lactate and gases that circulatory function was compromised rather than pulmonary function in endotoxin shock.

The same center that proposed splanchnic pooling as critical in the pathogenesis of shock (1) was also the first to report the response of the pulmonary vasculature to endotoxin (4). Kuida and colleagues found an average 43% increase in pulmonary arterial resistance. They discounted the pulmonary vascular changes as a major factor in producing fatal shock in dogs; they attributed the lethal outcome to an unchanged peripheral resistance (5) in the face of a cardiac output reduced by splanchnic pooling (4). In the cat, however, they accepted the pulmonary vascular changes as primary, leading to "gross pulmonary edema, right heart failure and sudden death." Similarly, Halmagyi and coworkers (6) found that the total pulmonary vascular resistance increased threefold in sheep, and this increase preceded the fall in cardiac output. Halmagyi explicitly blamed acute right ventricular failure for the fall in output. An editorial in LANCET even referred to the phenomenon in sheep as "cor pulmonale in endotoxin shock." The pathophysiology in sheep was distinguished from that in the dog because the cardiac output could be restored by transfusion in the latter (7), from which they concluded that inadequate circulating volume was the central disorder, in the dog.

At the time of Halmagyi's report in 1963 (6), most centers held that myocardial failure did not play a significant part in the early circulatory collapse (8, 9). More recently, Lefer and his colleagues (10), reported a myocardial depressant factor (MDF) which occurs later in endotoxin shock, and Hinshaw and co-workers also reported left ventricular depression in the dog. Myocardial depression in the presence of increased pulmonary vascular resistance, resulting in even moderate increases in right ventricular afterload, could produce acute right ventricular failure. We therefore have examined the pulmonary and systemic vascular resistances during endotoxin shock in the dog, the right ventricular performance, and the ability of dextran infusions to restore hemodynamic conditions to normal.

Material and methods. Twelve dogs of unselected sex and breed were used, weighing 18–24 kg. They were premedicated with morphine (2 mg/kg im), and anesthetized with sodium pentobarbital (15 mg/kg iv). Left

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ventricular pressure was obtained by retrograde catheterization from the carotid artery, and the aorta from the femoral artery. Cardiac output was determined by dye-dilution with indocyanine green; computation was performed on a PDP 11/45. A Swan–Ganz balloon-tipped catheter was advanced from the femoral vein to the pulmonary artery. A second venous catheter was advanced to the right atrium. After control recordings were made, an LD_{100} dose of endotoxin (5 mg/kg) from *E. coli* (Westphal extraction method, Difco Laboratories) was injected into the right atrium. Recordings were made at 5, 15, 30, and 60 min, and at hourly intervals for 4 hr. The data were reduced manually; the cardiac output, mean aortic pressure, mean pulmonary artery pressure, and vascular resistances were normalized for each animal, with the control value as 100%. For the low pressures, central venous pressure, pulmonary artery wedge pressure, and left ventricular diastolic pressure, the changes from the control value were calculated in mm Hg. Descriptive statistics were calculated for each variable at the intervals specified and will be presented as the mean and standard error of the mean.

To investigate the role of right ventricular failure in the declining cardiac output, we determined V_{max} (12) for the right ventricle during endotoxin shock, and compared this to V_{max} of the left ventricle. We believe that V_{max} is an index of contractility that is well-suited for following ventricular performance in endotoxin shock, since it is relatively insensitive to changes in afterload (13). The method does not require the determination of ventricular function curves, which requires interventions that may, *per se*, alter the target variable. For V_{max} determinations both right and left ventricle pressures were obtained in an additional 15 dogs. V_{max} was calculated from the isovolumic period of the respective ventricular pressure records, using a PDP 11/45. For the right ventricle, we used the same constants introduced for the left ventricle, 40 and 80 for K and C, respectively, in the formula V_{ce} (for the contractile element velocity of shortening) = $(dp/dt)/(KP + C)$. Normalization was performed for the values of V_{max} for each animal during the course of endotoxin shock before calculating the statistics, taking the control value as 100%.

To test the assumption that cardiac output in the dog could be restored by volume replacement, six animals were subjected to rapid infusions of low molecular weight Dextran, 25 ml/kg. The infusions were begun at five minutes after administration of endotoxin, and were completed prior to the fifteen-minute determination of cardiac output. (This would increase circulating volume during the interval of maximal hepatosplanchnic trapping) (2, 3). In addition, arterial PO_2 (PaO_2) was determined at the same intervals, using an Instrumentation Laboratories device. Comparison of mean values of these groups was done by unpaired *t* test.

Results. The hemodynamic course of early endotoxin shock is presented in Fig. 1. Cardiac output and mean pressures in the aorta, pulmonary artery, pulmonary artery wedge position, left ventricle, and central veins from twelve dogs are graphed for 4 hr. After endotoxin, there was a precipitous drop in cardiac output and aortic pressure, and a modest improvement by one hour. Thereafter, there

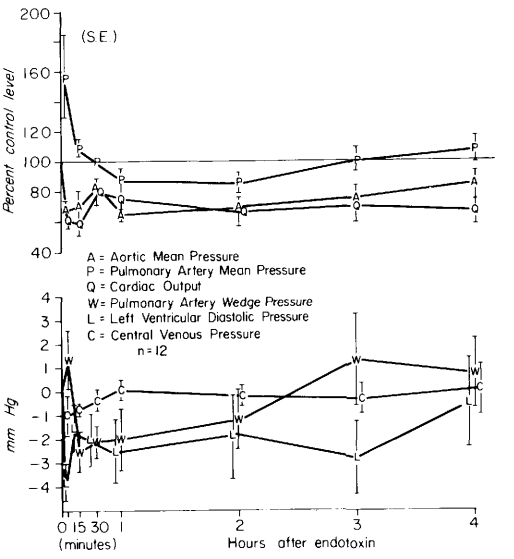

FIG. 1. Hemodynamic course in the first 4 hr of endotoxin shock in 12 dogs. The mean and SE of the mean are presented. Cardiac output (Q), aortic pressure (A), and pulmonary artery pressure (P) are presented as percentages of the control value. Pressures for pulmonary artery wedge (W), central venous pressure (C), and left ventricular diastolic pressure (L), are in mm Hg change from the control value for each animal.

was a gradual decline in output, but a gradual recovery of aortic pressure. In contrast to aortic pressure, the pulmonary artery pressure after endotoxin actually rose to over 150% of the control level; the pressure declined by one hour, and the two pressures paralleled each other after that with the normalized pulmonary pressures approximately 20% higher than the aortic. The pulmonary artery wedge pressure also rose in early endotoxin shock and fell by 15 min. It then commenced a very gradual recovery toward and above the control level by 4 hr. The left ventricular diastolic pressure had a prompt drop to a −3 mm Hg, recovered by 15 min to a −2 mm Hg, and remained at about that level until the 4-h determination. The central venous pressure fell less than 2 mm initially and recovered to almost control level for the entire experimental period.

The course of vascular resistance during endotoxin shock in the first 4 hr is presented in Fig. 2. The systemic vascular resistance is proportionately much lower than the pulmonary resistance, since the mean does not exceed 125% of control during the first 2 hr, whereas the peak pulmonary resistance is 450% greater than control.

Figure 3 presents the mean of V_{max} for the two ventricles and the cardiac output, normalized to the control value for each animal before averaging. The V_{max} for the left ven-

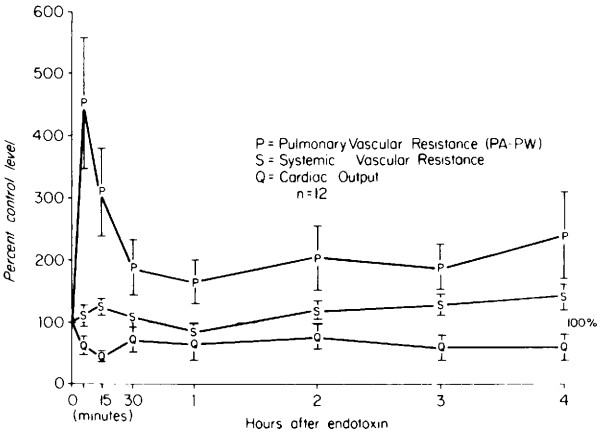

FIG. 2. Vascular resistances and cardiac output for the first 4 hr of endotoxin shock in 12 animals, presented as percentages of the control value.

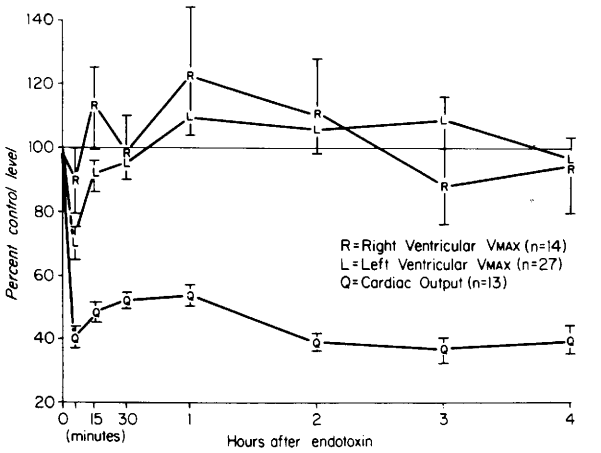

FIG. 3 Graphic comparison of an index of contractility, V_{max}, for the right (R) and left (L) ventricles, normalized with reference to the control value (100%) during endotoxin shock. For contrast, the cardiac output (Q) is presented. See text for significant differences.

tricle is initially more affected, but both ventricles recover to higher than control value by 1 hr. (The only statistically significant difference bewteen R and L V_{max} is at 15 min; $P < 0.01$). The left ventricular V_{max} remains greater than control for the first 3 hr, and falls slightly at the fourth hour; the index for the right ventricle has a greater variance for any single period, and the mean varies more from time to time, but there is no evidence in this data for failure of either the right or left ventricle to account for the very poor cardiac output during the first 4 hr.

The administration of 25 ml/kg of low molecular weight Dextran restored cardiac output to preendotoxin levels, but aortic mean pressure was restored only to 90% of control. The difference between output and pressure was also seen in the subsequent course. There was a significant difference ($P < 0.01$) in cardiac output between the fluid-treated group and the control group for the entire 4 hr, but the difference for the aortic mean pressures was significant ($P < 0.05$) at 30 min, one and 2 hr after endotoxin, but not by 3 or 4 hr. The arterial PO_2 for the untreated group fell briefly, but recovered to control level by 15 min, and remained above control thereafter. The difference in PO_2 between the two groups became significant by 2 hr, and was highly significant by 4 hr ($P < 0.01$), with the fluid-treated group showing deterioration. In addition, survival time was actually less in the animals treated with Dextran, although the differences were not significant. The dogs receiving dextran survived 8.5 hr, compared to 10.5 hr for the untreated.

Discussion. The course of the dog's pulmonary vascular resistance (PVR) after endotoxin is quite similar to the other species that have been reported, including the cat (4), sheep (6), calf (14), and primate (15). The marked changes in PVR have been neglected in the dog in favor of hepatosplanchnic trapping of blood (1). The duration of hepatosplanchnic trapping of blood, however, is less than 30 min (2), and relief by portocaval shunting fails to improve the hemodynamic course or survival (3). It is also of interest that endotoxin shock has a lethal course similar to the dog in animals that have no throttlelike mechanism in their hepatic veins (6, 15, 16). Detailed time course of pulmonary vascular changes in these other species have not been supplied in previous reports, but most publications suggest that the increases last only 30 min or less. We found that the marked elevation of resistance in the canine pulmonary vasculature was brief, and the resistance returned to moderate levels by 30 min after endotoxin (Fig. 2). This time course is strikingly similar to that of the portal vein pressure (3). These two vascular beds, pulmonary and splanchnic, also accumulate most of the endotoxin, judging from radioactive tagging, with the largest concentration in the lung, liver, and spleen (17). In short, the dog's pulmonary vasculature appears to be no less a target organ for endotoxin shock than in other species, and the brief hepatosplanchnic pooling is merely another vascular manifestation of this toxin, unique to the carnivores, but not uniquely lethal.

Halmagyi's inference of cor pulmonale in the sheep was based on an increase in right ventricular afterload that was relatively modest, a doubling of the mean pressure in the pulmonary artery (6). Although Halmagyi did not postulate a primary myocardial depression, this has been suggested recently for the canine left ventricle (10, 11) which has a substantially reduced afterload or aortic pressure. If the right ventricle were equally depressed, the effect should be more important, and more easily demonstrated, since the right ventricular afterload is roughly doubled. However, we do not find a significant reduction of myocardial contractility, using the index V_{max}, for either left or right ventricle during the first 4 hr, at which time the cardiac output was reduced drastically. Since our studies did not extend beyond 4 hr, we cannot speak to the late depression of myocardial contractility, described by Lefer's and Hinshaw's groups, after 4–8 hr. It is also possible that compensatory mechanisms in our intact animal preparation masked a direct myocardial depression. Two such compensatory mechanisms are catecholamine release and the positive inotropic effect of tachycardia, both of which are present in endotoxin shock due to baroreceptor activity. Regardless of how the contractility is maintained, the early vascular collapse cannot reasonably be attributed to cor pulmonale.

Although the dog's response to fluid ther-

apy has been used as evidence that vascular collapse in the dog is due to intravascular pooling (7), the transient nature of the improvement suggests that extravasation of the circulating volume is more important. Vascular leakage due to endothelial injury (18), enhanced by venoconstriction (2), continues throughout endotoxin shock, in the lung (19) as well as in the systemic circulation (20). This leakage accounts for the declining course of the arterial PO_2 after Dextran, compared to the PaO_2 in the control animals, and causes a therapeutic dilemma in the treatment of endotoxin shock. The administration of plasma or Dextran, not to mention saline or lactated Ringer's solution, restores flow and improves pressure, but the intravascular volume continues to be lost at the expense of the arterial PO_2.

Summary. The pulmonary vascular resistance in herbivores has been reported to increase threefold in endotoxin shock; poor cardiac output has been attributed to cor pulmonale. The poor cardiac output in dogs has been attributed to splanchnic pooling. However, we previously reported that splanchnic pooling was brief, and had resolved, while cardiac output remained low. In the present study of 27 anesthetized dogs we found a marked reduction in cardiac output and aortic pressure following endotoxin, and an increase in systemic resistance to only 125%. Pulmonary arterial resistance rose to a peak of 450% of normal at 5 min, but by 30 min had fallen to 200% of control. The relative contractility of the two ventricles, based on V_{max} was equal to or greater than control for most of the 4 hr. Although the afterload for the right ventricle is actually increased, in contrast to a reduction for the left ventricle, contractility for both ventricles was maintained. Treatment with Dextran transiently restored cardiac output, but caused a significant gradual reduction in arterial PO_2 as a result of extravasation.

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