# THE TREATMENT OF SHOCK BASED UPON PHYSIOLOGICAL PRINCIPLES AND IMPEDENCE METHOD FOR MEASURING CARDIAC OUTPUT IN SHOCK

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Preliminary clinical studies in 50 patients are consistent with the experimental findings in dogs. Likewise, similar therapeutic techniques in man have provided additional evidence that reduction of the peripheral vasoconstrictive response is associated with improvement in survival. Experimentally, tolerance has been produced to both epinephrine and endotoxin. Tolerant dogs do not exhibit the same magnitude of vasoconstrictive response to usually lethal septic or cardiogenic shock. Survival rate in shock appears to be correlated with the reduction of the peripheral vasoconstrictive response in the face of an effective circulating blood volume.

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Investigations of the treatment and prevention of shock have been subdivided into three categories :

1. Gram-negative bacterial endotoxin shock.
2. Cardiogenic Shock
3. Tolerance in Shock

Models of each have been developed and standardized in the dog and have been evaluated from the hemodynamic, biochemical and survival aspects.

Endotoxin Shock

A total of 159 dogs were used in this study. The first 50 dogs were used to establish the $LD_{50}$ and $LD_{100}$ of a single batch of Difco E-coli endotoxin. The $LD_{50}$ in this group of dogs was 0.69 mg/kg and the $LD_{100}$ dose was 2.0 mg/kg. The remaining 109 dogs were subdivided as follows: At the $LD_{50}$ level, controls, 9 dogs; treatment with 5% dextrose in water, 28 dogs; treatment with Ringer's solution buffered to a pH of 7.4, 9 dogs; and the $LD_{100}$ dosage, control dogs, 27, Ringer's solution, pH to 7.4, 24 dogs, and phenoxybenzamine, 12 dogs (Table 1). The following hemodynamic and biochemical determinations were made in each group. Heart rate, blood pressure, right atrial pressure, stroke volume, total peripheral resistance, left ventricular minute work, blood volume, plasma volume, hematocrit, hemoglobin, lactic acid, pH, $pCO_2$, $pO_2$, temperature, urinary output and the following weights were determined: heart, right and left lung, liver, right and left kidney and spleen. All data has been programmed into a digital computer. The following significant details have been noted: Survival rate in the $LD_{50}$ group was controls, 55 per cent; 5 per cent dextrose in water, 25 per cent; Ringer's solution, 78 per cent and Decadron, 10 mg/kg I.V., 47 per cent. Survival rate was determined at the 72-hour level. From previous experience, we have learned that dogs living beyond this period of time will survive indefinitely, or if death occurs, it is usually due to causes unrelated to the administration of the endotoxin. Both the 5 per cent dextrose in water and the Ringer's solution were given in the volume of 25 ml/kg/hr. with therapy beginning 30 minutes after the administration of the endotoxin and continuing for 60 hours. The survival rate in dogs given a $LD_{100}$ dose of endotoxin was: controls, 15 per cent; Ringer's solution with pH adjusted to 7.4, 50 per cent; and treatment with Ringer's solution plus phenoxybenzamine, 1 mg/kg intravenously given 30 minutes after the injection of the endotoxin, 67 per cent.

The following hemodynamic events were noted in control dogs, both those given an $LD_{50}$ or $LD_{100}$ dose of endotoxin. Initially, there was a marked fall in blood pressure which remained at a significantly lower level than pre-endotoxin blood pressure throughout the acute phase of the experiment. Similarly, the cardiac output, right atrial pressure, stroke volume, blood volume, and plasma volume, remained at significantly lower levels than during the pre-shock period. During this same time total peripheral resistance was significantly elevated. There was also a significant fall in the urinary output, reflecting a decrease in renal blood flow. A significant fall in blood pH and rise

in lactic acid levels also occurred, indicating inadequate cellular perfusion. The magnitude of these changes were more marked in the $LD_{100}$ group when compared to the $LD_{50}$ group.

In the $LD_{50}$ group treated with dextrose and water, there was no significant improvement in survival rate and no significant improvement in hemodynamic or biochemical changes compared with untreated controls. In contrast, the dogs treated with Ringer's solution had a significantly greater survival rate, reflected by a return of the hemodynamic and biochemical changes toward pre-shock levels. Moreover, during the final 2 hours of the acute phase of the experiment, these hemodynamic and biochemical measurements were not significantly differet from the pre-shock levels. In the dogs treated with decadron, the survival rate was modestly improved, as were the hemodynamic and biochemical changes. However, the venous pressure remained significantly low, accounting for the reduced cardiac output. This simply indicated the need for additional volume replacement. Similarly, in the $LD_{100}$ group, the hemodynamic and biochemical changes were more marked than in the $LD_{50}$ group. These changes were consistent with a reduction in tissue perfusion and increased peripheral vasoconstriction in untreated dogs. Correction of these abnormalities by the administration of Ringer's solution or phenoxybenzamine resulted in an improvement in survival. In both instances, the hemodynamic and biochemical changes returned toward the pre-shock levels. However, they did remain significantly lower in the final 2 hours of the acute phase of the experiment. These changes reflect the severity of the damage due to the $LD_{100}$ dosage of endotoxin compared with an $LD_{50}$ dosage.

In summary, the administration of endotoxin has been previously correlated with a significant degree of pooling of plasma within the splanchnic bed of the dog. This results in an absolute reduction in the effective circulating blood and plasma volumes of the dog. This reduction in volume is reflected by the reduction in venous return, as measured by the central venous pressure and the concomitant reduction in the cardiac output blood pressure. This fall in blood pressure stimulates the baroreceptors, resulting in the outpouring of the catecholamines, epinephrine and norepinephrine as has been shown previously in this laboratory, resulting in peripheral vasoconstriction in the visceral microcirculation. Therapy directed toward restoration of the blood volume and reduction of peripheral vasoconstrictive results in a statistical significant improvement in survival in dogs after the administration of endotoxin.

Cardiogenic Shock

The cardiogenic shock model in the dog has been described in previous reports. Briefly, it is a closed chest technique of inducing primary pump failure and cardiogenic shock following intracoronary artery microsphere embolization. The syndrome has been previously characterized by a fall in cardiac output and a rise in peripheral resistance. A total of 205 dogs using this model, were evaluated over the past year. These dogs were subdivided into three general groups; controls, controls with regional blood flow determinations and a treatment group, (Table 2). The following hemodynamic and biochemical determinations were carried out: heart rate, blood pressure, right atrial pressure, cardiac output, stroke

volume, total peripheral resistance, left ventricular minute work, blood volume, plasma volume, hemoglobin, hematocrit, pH, $pCO_2$, $pO_2$, oxygen saturation, LDH, total and heat stable fraction, creatinine, phosphokinase, BUN, lactic acid, urinary output, dog weight, heart and lung weight and temperature and, recently, determination of plasma epinephrine and norepinephrine. Blood flow studies were made by the use of a square wave electromagnetic flow meter placed on the superior mesenteric artery, portal vein and renal artery. Coronary blood flow studies were made by a new technique developed in this laboratory for the delivery of radioactive Xenon into the coronary circulation. This technique utilizes a specially constructed double lumen balloon cannula for the delivery of the Xenon into the coronary circulation. This technique circumvents the need for expensive fluoroscopic equipment used in the customary placement of a cannula into the coronary artery. This new balloon technique has been compared to the selective cannulation technique and the results in terms of coronary blood flow have not been statistically different using either technique. All data obtained from this study has been programmed into a digital computer and analyzed for statistical significance. The salient features of this study are as follows: Hemodynamically in control animals, there is a statistically significant fall in cardiac output and blood pressure, and a significant rise in total peripheral resistance. This rise in peripheral resistance is mirrored by a significant reduction in blood flow to the small bowel, liver, kidneys and coronary circulation. Of note, however, is the significant increase in percentage of the cardiac output delivered to the coronary arteries during the shock period. This percentage rises from the prembolization level of 5 per cent to 25 per cent during shock. Again, inadequate cellular perfusion was mirrored by the reduction in renal blood flow and uriniary output, a significant level of lactic acidosis and cellular enzyme rises, reflecting cellular damage. Therapy with the vasopressors, levarterenol or angiotensin increased peripheral resistance and peripheral vasoconstriction and did not improve survival. Therapy with a vasodilator, phenoxybenzamine, given in a dosage of 1 mg/kg intravenously, in three separate experimental groups, at 5, 30 and 60 minutes after the production of shock, resulted in a significant improvement in survival. In each case, there was a reduction in the peripheral vasoconstrictor response and an increase in tissue perfusion reflected by the blood flow studies, blood lactic acid and pH changes. The magnitude of reduction of the vasoconstrictor response is correlated with the improvement in the survival rate. Similarly, therapy with the steroids, Solu-Medrol in the dosage of 30 mg/kg intravenously, and 15 mg/kg intravenously significantly reduced the vasoconstrictive response associated with cardiogenic shock and, similarly, were associated with a significant improvement in survival. Therapy with 5 per cent dextrose and water used to maintain the blood pressure at 85 per cent of the preembolization level, was only modestly successful, for there was an insignificant rise in the cardiac output and fall in total peripheral resistance. Therapy with Rheomacrodex resulted in a significant improvement in survival secondary to its reduction of the vasoconstrictive response. Plasma catecholamine levels rose 50 per cent during the shock period in control dogs. This rise in catecholamines paralled the rise in total peripheral resistance.

Tolerance in Shock

The general concept of shock developed in this laboratory using the endotoxin and cardiogenic shock models and, previously the hemorrhagic shock model,

indicated that shock was defined in each case by inadequate tissue perfusion and a significant degree of peripheral vasoconstriction. Restoration of effective circulating blood volume and reduction of peripheral vasoconstriction resulted in a significant improvement in survival rate. It occurred to us that it might be possible to make dogs tolerant to shock by ablating this vasoconstrictive response. Previous studies by Rosenthal and DiPalma with acute tolerance to epinephrine had shown that the vasoconstrictive response associated with epinephrine administration could be ablated. With this background, we postulated that if dogs could be made tolerant to vasoconstrictive substances, its lethal effects might be averted. To this end, a group of 32 dogs were utilized, (Table 3). The first group of 22 dogs was made tolerant to intravenous epinephrine by gradually increasing the dosage over a 6-week period of time, until the dog could withstand 1-2 mg/kg of intravenous epinephrine without apparent adverse effects. A second group of 10 dogs were made tolerant to endotoxin. We had postulated that since endotoxin was associated with a significant vasoconstrictive response, tolerance to intravenous endotoxin might also blunt the vasoconstrictive response in shock. The endotoxin was administered in gradually increasing dosages over a 6-week period until the dogs could withstand 2 mg/kg of intravenous E. coli endotoxin, a usually lethal dose, without apparent effect.

These 20 epinephrine and endotoxin tolerant dogs were used in the cardiogenic shock experiment, as described above. The magnitude of cardiac damage in each case was the same as that seen in the control dogs, as evidenced by gross and microscopic changes and elevation of LDH and CPK levels. In the case of the epinephrine and endotoxin-tolerant dogs after the administration of the microspheres, the same hemodynamic response occurred, but the magnitude was not of the degree seen in the control dogs. Within one hour of the embolization, the peripheral resistance in each dog was not significantly higher than the precardiogenic shock level. Urinary output did not decrease significantly in tolerant dogs. Moreover, tolerant dogs did not show a lactic acidosis, indicating that tissue perfusion was adequate.

Pilot studies of epinephrine and norepinephrine levels in these animals are now under way, but there is insufficient data at this time to make a statement about the correlation of these catecholamine levels with the vasoconstrictive response. The striking fact was that in the case of the control animals used in this series, the 72-hour survival rate is 24%. In the 20 epinephrine and endotoxin tolerant animals, the 72-hour survival rate in each case was 100%. This increase in survival rate appears to be related to the insignificant vasoconstrictive response after severe myocardial damage. Of ten endotoxin-tolerant dogs, attempts at producing cardiogenic shock failed and the 72 hour survival was 100%. Again, there was an insignificant degree of peripheral vasoconstriction. Twelve epinephrine-tolerant dogs were given an $LD_{100}$ dose of endotoxin. These dogs did not develop a significant degree of vasoconstriction and 100% survived longer than 72 hours. Further studies are now under way to evaluate cellular changes and regional vascular changes. These include regional blood flow studies, biochemical studies, studies of the catecholamines including tyramine, releasable epinephrine and norepinephrine pools and electron microscopic studies of adrenergic end plates in the myocardium, in an attempt to evaluate the changes in the granulated vesicles of these

nerve endings. These granulated vesicles apparently are packets of epinephrine and norepinephrine.

From the group of epinephrine-tolerant animals that had previously been subjected to and survived usually lethal cardiogenic shock, 5 dogs were selected. One month after intracoronary embolization, an $LD_{100}$ dosage of E. coli endotoxin was administered to these dogs. This dosage of endotoxin in the control dogs results in intense peripheral vasoconstriction, pooling of blood, reduction of cardiac output and a survival rate of only 15 per cent. In contrast, in the dogs tolerant to epinephrine, the 72-hour survival rate was 100 per cent. These tolerant dogs also showed only insignificant alterations in the total peripheral resistance, cardiac output, and urine output. Blood lactic acid also changed little, indicating an adequate cellular perfusion was maintained in these tolerant dogs despite the fact they were administered a usually lethal dose of endotoxin.

In summary, we have shown in previous studies with hemorrhagic shock and in current studies with endotoxin and cardiogenic shock, that the final common pathway in all three forms of shock can be expressed as an inadequate level of tissue perfusion and the development of significant peripheral vasoconstriction. Restoration of the effective circulating blood volume and reduction of this vasoconstrictive response in all three forms of shock has resulted in a statistically significant improvement in the survival. Additionally, in the tolerance studies, we have been able to block the usual vasoconstrictive response occurring in endotoxin or cardiogenic shock. In each case, this blunting of the peripheral vasoconstrictor response has been associated with a striking improvement in survival. The clinical portent for the future of tolerance studies is exciting. It appears now possible to conceive of "immunizing" or making man tolerant toward the stress of shock whether hemorrhagic, septic or cardiac in origin. Thus susceptible groups of humans, for example, combat troops, could be prophylactically made tolerant to wound shock and be expected to have a higher survival rate. The task now is to work out a program for producing tolerance in man which would require only 3 or 4 injections and would produce tolerance for several months, or more.

Finally, we have in operation a Mobile Clinical Shock Unit which is taken to the bedside of patients in shock. Over the past 8 months, 50 patients have been studied. In each case of cardiogenic, hemorrhagic or endotoxin shock, there was a significant degree of peripheral vasoconstriction and inadequate tissue perfusion. Reduction of this vasoconstrictive response in association with restoration of the effective circulating blood volume, has been associated with a gratifying improvement in survival. Thus both experimentally and clinically, the vasoconstrictive response and the level of tissue perfusion seem to be the final common pathway in all forms of shock. Therapy directed at correcting these abnormalities appears successful. Prevention of the vasoconstrictive response in the experimental tolerance studies has produced remarkable results. The further definition of the mechanism of tolerance will be made during the forthcoming year, including clinical application. The production of tolerance may prove to be of great value in humans with high risk from one of the common causes of shock.

TABLE 1

INFLUENCE OF THERAPY UPON SURVIVAL IN ENDOTOXIN SHOCK

| Drug | No. Dogs | 72 hr. Survival |
|---|---|---|
| Endotoxin Shock (0.69 mg/kg) | | |
| Control | 9 | 5 (55%) |
| 5% Dextrose in water | 28 | 7 (25%) |
| Ringer's solution | 9 | 7 (78%) |
| Endotoxin Shock (2 mg/kg) | | |
| Control | 27 | 4 (15%) |
| Ringer's solution | 24 | 12 (50%) |
| Phenoxybenzemine (1 mg/kg I.V.) + Ringer's solution | 12 | 8 (67%) |

TABLE 2

INFLUENCE OF THERAPY UPON SURVIVAL IN CARDIOGENIC SHOCK

| Drug | No. Dogs | 72 hr. Survival |
|---|---|---|
| None | | |
| Control | 45 | 11 (24%) |
| Vasopressors | | |
| Levophed | 19 | 7 (37%) |
| Angiotensin | 15 | 0 (0%) |
| Vasodilators | | |
| Isuprel | 17 | 7 (41%) |
| Solu-Medrol-15 mg/kg | 8 | 3 (38%) |
| Solu-Medrol-30 mg/kg | 13 | 8 (62%) |
| Dibenzyline-5 min | 19 | 11 (58%) |
| " 30 min | 15 | 9 (60%) |
| " 60 min | 19 | 10 (53%) |
| Volume | | |
| 5% Dextrose in water | 12 | 4 (33%) |
| Rheomacrodex | 13 | 8 (62%) |

TABLE 3

TOLERANCE TO SHOCK

| | No. Dogs | 72 hr. Survival |
|---|---|---|
| **Epinephrine Tolerance** | | |
| Cardiogenic Shock | 10 | 10 (100%) |
| Control | 45 | 11 (24%) |
| Endotoxin Shock | 12 | 12 (100%) |
| Control | 27 | 4 (15%) |
| Both Cardiogenic and Endotoxin Shock | 5 | 5 (100%) |
| **Endotoxin Tolerance** | | |
| Cardiogenic Shock | 10 | 10 (100%) |
| Control | 45 | 11 (24%) |