UNIVERSITY OF OKLAHOMA MEDICAL CENTER

MECHANISM OF ACTION OF DOPAMINE IN ENDOXIN SHOCK

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Technical Report No. 9
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MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE
OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.
800 Northeast Thirteenth Street
Oklahoma City, Oklahoma 73104
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The type of circulatory failure that is better known as septic shock is a frequently fatal condition which can occur in many infectious processes. Ebert and Abernathy have pointed out the increasing importance of endotoxin shock in clinical medicine (9). A uniform explanation for the underlying mechanism involved in endotoxin shock is not yet available. Therefore, it is not surprising that there is no generally accepted effective therapy for this form of shock and that the mortality rate in such cases is extremely high. Hinshaw and colleagues have been concerned with the adverse biological effects of lethal injections of endotoxin in the dog and monkey and have helped to clarify many points of question concerning the action of endotoxin in these different species (11, 18-37).

Since most studies concerned with the mechanism of endotoxin shock have been conducted on the canine species, the results of experiments done in this animal will be discussed here, although shock in primates can be different. The development of systemic hypotension following endotoxin injection in the dog may be accounted for by decreases in total peripheral resistance (12, 20, 24) and cardiac output (20, 24, 59). Histamine and related agents appear to influence peripheral resistance and pooling by their detrimental effects on both pre-capillary and post-capillary segments (5, 7, 25). Numerous studies have been conducted to determine the effects of endotoxin on the heart during hemorrhagic and endotoxin shock (1, 8, 9, 12, 17, 44, 51). Only indirect effects resulting from low blood flow and diminished tissue perfusion appear to damage cardiac tissue. In general, there is net dilatation in pre-capillary vascular segments and net constriction in post-capillary segments. The result is a decrease in total peripheral resistance and a progressive decrease in cardiac output, leading to the progressive development of systemic hypotension. In other words, the primary drop in arterial pressure, following an intravenous injection of endotoxin
in dogs, can be attributed to a decrease in venous return (44, 59). It has been further shown that the principal cause of the drop in venous return is hepatosplanchnic pooling, resulting primarily from hepatic venous constriction (32). Because of the obvious precipitation of severe shock (hypotension) by such a pooling mechanism, any pharmacological agent capable of blocking this action of endotoxin could be considered of major interest in the treatment of shock.

Dopamine (34 dihydroxyphenylethylamine) has many interesting properties. Its effect on the peripheral vasculature is apparently highly variable and species dependent. Investigators have reported that it is depressor in the guinea pig and rabbit but pressor in the cat and dog (40, 41). Burn and Rand have shown that dopamine is pressor in the spinal cat but depressor in the cat anesthetized with urethane (4). Large doses appear to elicit a pressor response in the dog (45), while small doses exert a depressor action (14). Ross and Brown studied the effects of dopamine on various vascular beds in the anesthetized cat (52). They reported vasodilatation in the gastric, superior mesenteric and inferior mesenteric arteries, while vasoconstriction was observed in the hepatic and splenic arteries. In the dog, the effect of dopamine on systemic blood pressure appears to be the result of a balance between vasoconstriction in peripheral vascular beds and vasodilatation in the superior mesenteric, renal and celiac vascular beds (10). Dopamine, at doses not affecting mean blood pressure, decreases renal vascular resistance and increases renal blood flow both in man and in dog (47-50). Since dichloroisoproterenol, a beta adrenergic blocking agent, does not block the renal effects of dopamine, there is the possibility of a unique mode of action of dopamine on the renal bed (48). Dopamine infusion in water-loaded dogs increases Na+, K+ and osmolal excretion and p-aminobenzoate and inulin clearances (50). Dopamine
is reported to have direct actions on the heart (39,2,46). It increases mainly the cardiac output and stroke volume via a positive inotropic effect. Small doses (2-4 μg/kg) of dopamine in the dog have little or no cardiac effect and produce a slight pressor-depressor effect. Intermediate doses (8-16 μg/kg) produce an increase in heart contractile force and heart rate, and blood pressure effects are more pronounced. Higher doses (32-64 μg/kg) produce marked increments in heart contractile force, heart rate and arterial pressure (46).

Preliminary clinical studies have indicated that dopamine is beneficial in patients in various shock states (13,15,16,42,43,47,58). MacCannell et al. administered dopamine to 11 hypotensive patients, 6 of whom had signs of shock (post-infection, cardiogenic and neurologic). Although most of the patients had received prior medication, dopamine improved peripheral circulation and urine output in 5, and an additional 5 showed improvement in one of these functions. Six patients, while receiving norepinephrine, epinephrine, or metaraminol, when administered dopamine, increased their urine output to greater than 80 ml per hour. Dopamine increases sodium excretion in patients with severe congestive heart failure (15). Dopamine differs from other sympathomimetic amines in increasing the glomerular filtration rate and renal plasma flow (47) and by not increasing the circulating free fatty acids (3). There have been no reports of dopamine producing bradycardia in man. Use of alpha and beta adrenergic receptor blocking agents suggests that the pressor effect of dopamine is due to both slight alpha adrenergic receptor stimulation and beta inotropic action, and its vasocilating action is due to stimulation of beta adrenergic receptors (6).

Our laboratory has been primarily concerned with exploring the actions of dopamine on the peripheral circulation of Escherichia coli endotoxin-shocked dogs, with special emphasis
on its possible effects in altering venous return by obliterating intra- or extravascular pooling (38,53-57).

In order to study the effects of dopamine specifically on the peripheral circulation, one series of studies was carried out on thirty-one adult mongrel dogs using the venous return preparation (59,24). Dopamine infusion at low rates (7 μg/kg/min) tended to decrease the mean systemic arterial pressure, reservoir volume, heart rate, and total peripheral resistance, with very little effect on the magnitude of the pulse pressure. At higher doses (17 and 34 μg/kg/min) there were increases in all of the above parameters. Dopamine prevented the pooling of blood in the animal which typically follows endotoxin injection in the dog. There was no significant difference in mean systemic arterial pressure between the untreated (received endotoxin only) and the treated (received endotoxin and dopamine infusion) groups. Dopamine abviated the post-endotoxin bradycardia. Results were similar when dopamine was given as pre-treatment or as post-treatment.

Since one of the major factors responsible for the decrease in venous return in endotoxin shock in the dog is pooling of blood in the liver, a series of experiments (ten animal's) was conducted to determine the effects of dopamine on the isolated, perfused liver preparation. Results showed that the large increase in liver volume usually seen after endotoxin administration is entirely prevented with dopamine infusion; liver volume decreased markedly during the dopamine infusion prior to endotoxin administration and continued to decrease, but at a slower rate, following endotoxin. The changes were so marked that they could be observed visually. In addition, the dopamine produced hepatic artery constriction. Although these findings are of a preliminary nature, they mark the first experimental demonstration of a beneficial action of dopamine in shock by prevention of peripheral pooling and subsequent
maintenence of cardiac output.

Survival studies, consisting of twelve intact non-perfused dogs pre-treated and infused with dopamine, suggest a survival benefit from dopamine since a greater percentage of treated animals survived (50% vs 17%). Mean arterial pressure, central venous pressure, heart rate, and venous pH were relatively well maintained in the dopamine-infused animals.

In summary, dopamine infusion is very effective in preventing the peripheral pooling that occurs after endotoxin injection; however, its effectiveness is much more striking when administered as pre-treatment and continued during the post-endotoxin period. The hepatosplanchnic region appears to be the site of action of dopamine in preventing pooling, since the weight of the isolated perfused liver and portal vein pressure are markedly reduced in endotoxin shock when dopamine is infused. In addition, pooling in the eviscerated dog given endotoxin is not altered by dopamine infusion in experiments utilizing a venous return preparation with constant cardiac inflow (unpublished results from this laboratory).

Figure 1 illustrates a suggested mechanism of action of dopamine in endotoxin shock. The chronotropic and inotropic effects on the heart would increase the cardiac output. Actions on the hepatic bed would include hepatic artery constriction which would result in shunting of blood through extrahepatic regions, decreasing the amount of blood pooled in the liver. In order to account for the massive release of blood from the liver with dopamine, active contraction of the sinusoidal linings of the liver should be taken into consideration. The decreased pooling in the liver and active contraction of the sinusoidal linings would increase venous return. In extrahepatic beds, there is possibly a decreased venous constriction, also producing an increase in venous return, that in turn can enhance cardiac output.

It should be pointed out that, although dopamine appears to have potential therapeutic value in various shock states, it is still under experimental investigation.
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Figure 1. Suggested mechanism of action of dopamine in endotoxin shock.
Mechanism of action of dopamine in endotoxin shock

Dopamine infusion is very effective in preventing the peripheral pooling that occurs after endotoxin injection; however, its effectiveness is much more striking when administered as pre-treatment and continued during the post-endotoxin period. The hepatosplanchnic region appears to be the site of action of dopamine in preventing pooling, since the weight of the isolated perfused liver and portal vein pressure are markedly reduced in endotoxin shock when dopamine is infused. In addition, pooling in the eviscerated dog given endotoxin is not altered by dopamine infusion in experiments utilizing a venous return preparation with constant cardiac inflow (unpublished results from this laboratory). Although dopamine appears to have potential therapeutic value in various shock states, it is still under experimental investigation.