Hemodynamic Effects of Dopamine in Endotoxin Shock* (33544)

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Previous studies have shown that the initial fall in blood pressure in dogs administered endotoxin is primarily due to a decrease in venous return (1). Any agent which promotes an increase in venous return would, therefore, be considered of potential therapeutic value in the treatment of endotoxin shock, or similarly related types of hypotension. MacCannell *et al.* (2) in previous studies showed through indirect methods that dopamine (3-4-dihydroxyphenylethylamine) increases cardiac output in patients through a positive inotropic action on the heart and reduces total peripheral resistance. The primary purpose of the present study was to determine the therapeutic value of dopamine in endotoxin shock by direct measurement of venous return and calculated changes in total peripheral resistance.

Materials and Methods. Fifteen adult mongrel dogs weighing between 7 and 14 kg were intravenously anesthetized with sodium pentobarbital (30 mg/kg). A tracheotomy was performed and the animals were respired by a constant pressure respirator. The systemic arterial pressure was measured via a catheter inserted into the femoral artery connected to a Statham pressure transducer and monitored on a Sanborn direct writing recorder. A reservoir system was located between the central ends of the venae cavae and the right atrium, permitting a direct measurement of venous return. The system was primed with homologous heparinized blood obtained from a donor dog. A Sigmamotor pump returned the blood from the reservoir to the right atrium. This procedure was previously reported, (1, 3). Following cannulation of the right atrium and the great veins, the atrial inflow was repeatedly adjusted until a flow of 75 ml/kg/min was obtained. The system was then allowed 20–30 min to equilibrate. The venous return was periodically measured with a graduated cylinder and a stopwatch and a control period of constant flow was established for each preparation. Experiments were divided into three groups of five animals each: The control group, which was not administered endotoxin (Difco) or dopamine (β-hydroxytyramine hydrochloride, California Biochemical Corporation); the endotoxin group, which received a predetermined LD_{80} of *E. coli* endotoxin (1.5 mg/kg); and the treated group, which received intravenous infusions of dopamine and injections of endotoxin. The dopamine was administered into the right atrial inflow cannula. Dopamine, suspended in 0.9% sodium chloride was infused via a Harvard infusion pump at a concentration of 100 μg/ml 30 min prior to an LD_{80} of *E. coli* endotoxin and continued for 1 hr after injection of endotoxin. The Sigmamotor pump speed was varied so that cardiac inflow from the reservoir was made equal to the venous return to the reservoir. Infusion rates of dopamine varied with each preparation (40 to 150 μg/min). The infusion rate was determined as follows: The suspended dopamine solution was started at 0.4 ml/min and slowly increased in rate until a slight pressor effect was noted. The system was then allowed a 20–30 min control period at this rate. Following the administration of endotoxin, changes in the infusion rates were adjusted to an average of 15 μg/kg/min, in order to maintain a minimum mean systemic arterial pressure of 75 mm Hg for each preparation for 1 hr. Following the 1-hr experimental period in the endotoxin injected group, the dopamine infusion was discontinued and the preparation was followed for an additional 10 min. The purpose of this 10-min period was to

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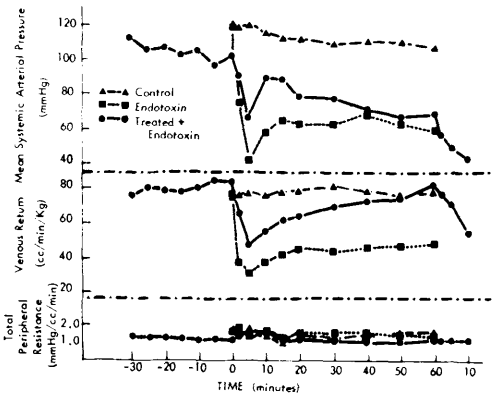

FIG. 1. Effects of dopamine on hemodynamic parameters in endotoxin shock.

determine if the dopamine exerted a continuing vascular effect on the preparation following cessation of infusion. Statistics were performed by analysis of variance and Duncan's multiple-range test for differences between means.

Results. Figure 1 illustrates the typical marked drop and sustained depression of mean systemic arterial pressure following an LD_{80} of endotoxin. In the dopamine treated group, the magnitude of the early drop in systemic arterial pressure (0–20 min) is considerably less than that of the untreated group receiving only endotoxin ($p<0.05$); however, there was no significant difference between the two groups at 40 min. The control group maintained the initial values of systemic arterial pressure throughout the 60-min period and remained elevated above the other groups at all points ($p<0.05$). Both the treated and untreated groups show precipitant decreases in venous return. However, the magnitude was less for the dopamine treated group than the untreated group ($p<0.05$). Also of importance is the fact that the venous return of the treated group returned to control values within the 1-hr period (40–60 min) ($p<0.05$) as opposed to the untreated group in which the venous return remained significantly depressed. Venous return of the dopamine treated group was markedly elevated over that of the untreated (endotoxin alone) group during the entire postendotoxin period ($p<0.05$). The control group exhibited no significant changes in venous return during the experimental period. There were no significant differences in total peripheral resistance between the three groups ($p>0.05$). A increase in heart rate was noted in all dogs receiving dopamine.

Discussion. The results of this study provide direct evidence that dopamine increases cardiac output and that this increase persists during the postendotoxin period. The systemic arterial pressure was also supported during the early postendotoxin period with dopamine. Since systemic arterial pressure did not increase but the cardiac output increased greatly, it is concluded that the increase in cardiac output is a function of an increase in venous return and reduction in total peripheral resistance. This corroborates in part the results of other investigations (2). Previous studies performed in this laboratory have shown that LD_{80} injections of endotoxin bring about hepatic pooling, and as a consequence, a reduction in the venous return which results in a decrease in cardiac output (4). Ross and Brown (5) have shown that dopamine has vasoconstrictor effects in the hepatic arterial bed in cats. Therefore, it follows that one of the salutary effects of dopamine may be due to its alpha-adrenergic action in the hepatic bed and beta-adrenergic action in extrahepatic regions, which may prevent blood from entering the liver to be pooled, but instead shunting blood into extrahepatic regions where vasodilatation favors an increase in blood flow to the inferior vena cava. Also of particular significance are the inotropic and chronotropic effects of dopamine on the heart (6), ultimately leading to increased cardiac output. MacDonald and Goldberg (6) and Ross and Brown (5) have shown that dopamine elicits systemic dilatation which again leads to reduced peripheral resistance. These may be considered the direct effects of dopamine on cardiac output and total peripheral resistance. An indirect action of dopamine on total peripheral resistance is that with increased transmural pressure, vessels may dilate passively, which becomes a further contributing factor in reducing peripheral resistance. These suggested beneficial actions of dopamine on the

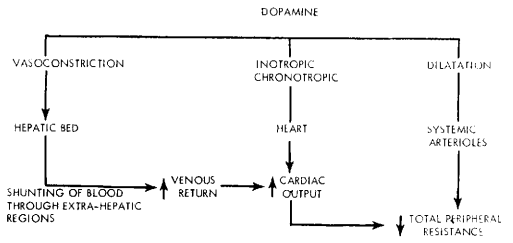

FIG. 2. Schema suggesting interactions of dopamine on cardiovascular system in endotoxin shock.

cardiovascular system after endotoxin have been schematized in Fig. 2.

Summary. Previous studies showed that the initial fall in blood pressure in dogs administered endotoxin is primarily due to a decrease in venous return. The primary purpose of the present study was to determine the therapeutic value of dopamine in endotoxin shock by direct measurement of venous return and calculated changes in total peripheral resistance. Experiments were carried out on adult mongrel dogs and the venous return preparation was utilized in this study. Results provide direct evidence that dopamine increases cardiac output and that this increase persists during the postendotoxin period. Dopamine also supports mean arterial pressure during the early phase of shock. The suggested mechanism of action of dopamine in endotoxin-shocked dogs has been largely discussed and includes both direct and indirect effects of dopamine on the heart and peripheral vasculature.

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1. Weil, M. H., MacLean, L. D., Visscher, M. B., and Spink, W. W., J. Clin. Invest. **35**, 1191 (1956).

2. MacCannell, K. L., McNay, J. L., Meyer, M. B., and Goldberg, L. I., New Engl. J. Med. **275**, 1389 (1966).

3. Hinshaw, L. B., Gilbert, R. P., Kuida, H., and Visscher, M. B., Am. J. Physiol. **195**, 631 (1958).

4. Hinshaw, L. B., Reins, D. A., and Hill, R. J., Can. J. Physiol. Parmacol. **44**, 529 (1966).

5. Ross, G. and Brown, A. W., Am. J. Physiol. **212**, 823 (1967).

6. McDonald, R. H. and Goldberg, L. I., J. Pharmacol. Exptl. Therap. **140**, 60 (1963).

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