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The pulmonary and systemic circulatory response to dopamine infusion

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1. The pulmonary and systemic circulatory responses to dopamine infused at 8, 15, 25 and 30 μg/kg per min were studied in eight mongrel dogs.

2. Mean pulmonary artery pressure, mean left atrial pressure, mean aortic pressure, mean aortic flow and the electrocardiogram were monitored in open-chest preparations. Pulmonary vascular resistance, systemic vascular resistance and stroke volume were calculated.

3. Significant increases in mean pulmonary and aortic pressures were noted at dopamine infusions of 25 and 30 μg/kg per min. The left atrial pressure fell significantly at 15 μg/kg per min and rose significantly at 30 μg/kg per min. Mean aortic flow increased at all four doses, while heart rate showed no change. Pulmonary vascular resistance did not change significantly at any dose level, but systemic vascular resistance fell slightly at 8 and 15 μg/kg per min and rose significantly at 30 μg/kg per min. Stroke volume was significantly elevated at infusions of 25 and 30 μg/kg per min.

4. The systemic circulatory response to dopamine is similar to that described by previous investigators.

5. The increased pulmonary pressures without change in resistance suggest a dopamine-induced increase in smooth muscle tension in the pulmonary vasculature.

Dopamine (3,4 dihydroxyphenylethylamine) is a naturally occurring catecholamine and is the direct biochemical precursor to norepinephrine (Blaschko, 1957). Investigators have recently described the cardiovascular response to this agent in animals and in man (McDonald & Goldberg, 1963 ; Black & Rolett, 1966, 1968). Vasoconstriction has been noted in the femoral vascular bed (McDonald & Goldberg, 1963). At low doses, however, a slight but significant drop in systemic vascular resistance has been reported without significant change in heart rate or arterial pressure (McDonald & Goldberg, 1963 ; Black & Rolett, 1966, 1968). In addition, animal studies demonstrate direct cardiac stimulation through a beta-adrenoceptor mechanism (Black & Rolett, 1966). Studies in both dogs and man offer evidence that dopamine is a selective renal and mesenteric vasodilator (McNay, McDonald & Goldberg, 1965 ; McDonald, Goldberg, McNay & Tuttle, 1964 ; Goldberg, McDonald & Zimmerman, 1963). These properties make dopamine an attractive agent for the

treatment of patients with acute cardiovascular failure and shock. Two reports describing the response to dopamine treatment of patients in congestive heart failure (Goldberg *et al.*, 1963) and shock (MacConnell, McNay, Meyer & Goldberg, 1966) have been published. Although dopamine has been considered for clinical use in patients with circulatory failure, no studies have reported the effect of dopamine on the altered pulmonary vascular responsiveness and hypoxia which often accompany this failure. It is the purpose of this report to describe the haemodynamic response of the pulmonary circulation to dopamine infusion at four different doses and, at the same time, to compare the pulmonary vascular response to changes induced in the systemic circulation.

Methods

Eight mongrel dogs (15–22 kg) were anaesthetized with a mixture of alpha-chloralose and urethane, 65 mg/kg, and 400 mg/kg, respectively. Supplemental anaesthetic was administered when corneal reflexes were noted. The chest was opened in the mid-line and the animals were prepared to record changes in the circulatory system. Pulmonary artery pressure was monitored through a No. 7 Birdseye catheter positioned in the main pulmonary artery via the right external jugular vein. Left atrial pressures were measured by a flange-tipped PE 260 catheter positioned through a stab wound in the left atrial appendage and secured with a purse-string suture. Central aortic pressure was monitored through a PE 260 fluid-filled catheter placed in the ascending aorta via the right femoral artery. The right femoral vein was cannulated with a PE 260 catheter for drug infusion. All fluid-filled catheters were flushed frequently, and/or kept patent by means of a heparinized (4 U.S.P. units/ml.) saline drip. All pressures were measured with Statham P23Db pressure transducers. Mean pressures were electrically determined by integration of the phasic pressure tracings.

Mean aortic blood flow was measured with a gated sine wave electromagnetic flow meter (Biotronex, Silver Spring, Md.) placed around the ascending aorta distal to the coronary arteries. Each aortic flow probe was calibrated by comparison with multiple cardiac outputs determined by standard indicator dilution techniques. Aortic flow was used as cardiac output for all of these studies, and aortic flow was assumed to equal pulmonary blood flow. The electrocardiogram was followed by means of subcutaneous electrodes placed in the appropriate extremity. All recordings were made on a multi-channel Beckman Model R direct-writing oscillograph.

The animals were intubated with a cuffed endotracheal tube and ventilated with a Harvard respirator. Arterial blood samples were analysed frequently utilizing a Model AME-1 Astrup micro-apparatus. The pH and pO_2 were measured 5 min before any intervention and before killing each animal.

In order to determine pulmonary and systemic responses to dopamine, the drug was infused for 10 min periods at doses of 8, 15, 25 and 30 μg/kg per min. These doses were administered in randomized fashion from animal to animal, and all infusions were delivered with a variable-speed Harvard apparatus infusion pump. After control measurements, each infusion was begun and data recorded throughout the 10 min infusion period. Because the animals reached steady state within 5 min, 5 min data were chosen as peak response data. At least 15 min were allowed between infusions for each animal to return to control.

Pulmonary vascular resistance was determined by subtracting the mean left atrial pressure from the mean pulmonary artery pressure and dividing the result by the mean cardiac output (aortic flow). This calculation is based on the assumption that pulmonary flow is equal to aortic flow at all times. An index of systemic resistance was determined by dividing the mean aortic pressure by the mean cardiac output. Stroke volume was calculated by dividing the mean cardiac output by the heart rate and is expressed as ml./beat. The data were evaluated for statistical significance by using an IBM 360/50 digital computer which had been programmed to calculate means and standard errors and to perform a paired t test analysis. Results are accepted as significant at the $P<0{\cdot}05$ level.

Results

Pulmonary artery pressure

At low doses of dopamine (8 and 15 μg/kg per min) there was no significant change in pulmonary artery pressure. At high doses (25 and 30 μg/kg per min), however, a significant elevation of the mean pulmonary artery pressure was demonstrated (Table 1). The response to the two higher doses was significantly greater than the response to the lower doses ($P<0{\cdot}05$) but no difference between 8 and 15 μg/kg per min or between 25 and 30 μg/kg per min was apparent statistically. These results, expressed as percentage change, are shown in Fig. 1.

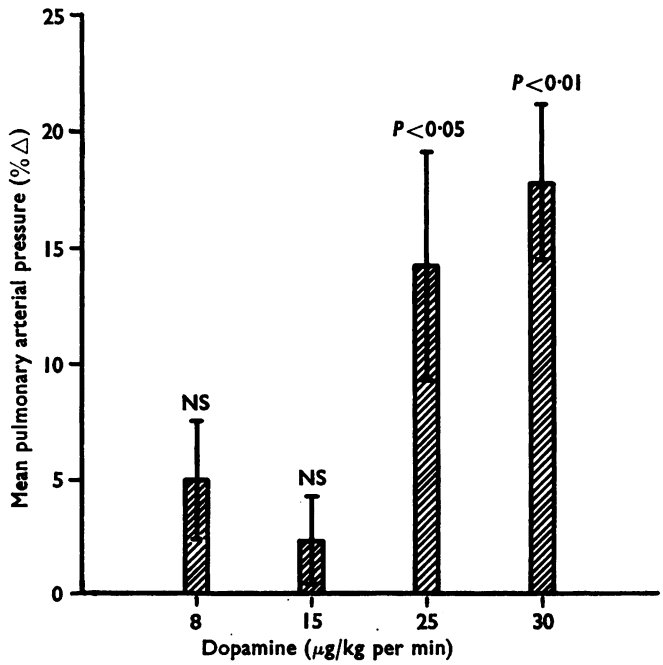

FIG. 1. Mean change (%Δ) and standard errors of the change in pulmonary arterial pressure produced by infusions of various doses of dopamine in μg/kg per min are shown. No significant (NS) changes were noted at 8 and 15 μg/kg per min. Significant changes were produced by 25 and 30 μg/kg per min dopamine. There was no difference between the increases noted at these two doses, however, but both elevations were significantly different from the response produced by the two lowest doses ($P<0{\cdot}05$).

Left atrial pressure

Mean left atrial pressure fell slightly but significantly in response to dopamine infused at 15 μg/kg per min and rose significantly when infused at 30 μg/kg per min, but no significant change occurred at 8 or 25 μg/kg per min (Table 1). The 15 μg/kg per min response differed significantly from the 30 μg/kg per min response ($P<0.05$).

TABLE 1. *Haemodynamic response to dopamine*

	Control	Absolute change	Significance	% change	Significance
Dose: 8 μg/kg per min					
PA mean pressure mmHg	17·2±1·0	0·7±0·4	NS	5·0±2·7	NS
LA mean pressure mmHg	7·5±0·9	−0·4±0·4	NS	−3·4±6·6	NS
Ao mean pressure mmHg	109·6±7·1	−5·5±3·1	NS	−4·2±2·9	NS
PVR mmHg/l. per min	6·7±0·8	−0·4±0·2	NS	−5·6±3·0	NS
SVR mmHg/l. per min	70·7±6·6	−9·1±3·1	<0·05	−12·6±4·0	<0·05
Flow l./min	1·6±0·2	0·23±0·07	<0·05	15·8±6·1	<0·05
SV ml./beat	9·3±1·1	0·4±0·5	NS	6·6±6·2	NS
Heart rate	172·4±6·7	13·8±7·2	NS	9·2±5·6	NS
Dose: 15 μg/kg per min					
PA mean pressure mmHg	17·6±0·4	0·5±0·4	NS	2·3±2·1	NS
LA mean pressure mmHg	7·1±1·0	−1·0±0·3	<0·01	−14·7±4·2	<0·01
Ao mean pressure mmHg	108·5±4·9	2·7±7·3	NS	3·1±6·7	NS
PVR mmHg/l. per min	6·5±0·8	−0·3±0·3	NS	−4·0±4·6	NS
SVR mmHg/l. per min	66·9±7·0	−6·9±3·1	NS	−12·0±4·8	<0·05
Flow l./min	1·8±0·2	0·28±0·07	<0·01	17·8±4·4	<0·01
SV ml./beat	9·6±1·1	0·8±0·5	NS	11·2±6·1	NS
Heart rate	180·9±5·6	12·8±6·0	NS	7·4±3·5	NS
Dose: 25 μg/kg per min					
PA mean pressure mmHg	17·3±0·7	2·6±1·0	<0·05	14·3±5·1	<0·05
LA mean pressure mmHg	7·4±1·0	−0·0±0·7	NS	−2·0±10·4	NS
Ao mean pressure mmHg	105·4±5·5	22·6±8·1	<0·05	21·8±8·3	<0·05
PVR mmHg/l. per min	6·5±0·7	−0·5±0·3	NS	−9·4±5·0	NS
SVR mmHg/l. per min	70·0±8·1	−3·3±10·0	NS	−2·0±11·5	NS
Flow l./min	1·7±0·3	0·51±0·12	<0·01	36·7±11·7	<0·05
SV ml./beat	9·5±1·2	2·4±0·7	<0·05	28·1±9·5	<0·05
Heart rate	174·3±7·0	9·5±8·9	NS	6·3±5·0	NS
Dose: 30 μg/kg per min					
PA mean pressure mmHg	16·9±0·6	3·1±0·7	<0·01	17·8±3·4	<0·01
LA mean pressure mmHg	8·2±0·8	1·8±0·8	<0·05	21·5±9·8	NS
Ao mean pressure mmHg	98·6±6·4	47·0±9·8	<0·01	48·7±12·4	<0·01
PVR mmHg/l. per min	5·8±0·7	−0·2±0·2	NS	−4·5±4·5	NS
SVR mmHg/l. per min	63·4±5·4	27·3±11·2	<0·05	41·4±16·2	<0·05
Flow l./min	1·6±0·2	0·23±0·10	<0·05	12·0±5·0	<0·05
SV ml./beat	9·5±0·9	3·7±1·4	<0·05	42·4±18·4	NS
Heart rate	165·8±9·6	−5·8±6·5	NS	−2·9±3·7	NS

Responses to dopamine at 5 min for all infusions.
PA mean, Mean pulmonary artery pressure: LA mean, mean left atrial pressure; Ao mean, mean aortic pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; AoF, mean aortic flow; SV, stroke volume; HR, heart rate.

Aortic pressure

Aortic pressure did not change significantly with infusion of the two low doses; however, a significant pressor response was induced with infusion of 25 and 30 μg/kg per min (Fig. 2, Table 1). It was impossible to separate the responses to 8 and 15 μg/kg per min. Pressor responses induced by the high doses (25 and 30 μg/kg per min) were significantly greater than the low dose response. In addition, the increase in pressure at 30 μg/kg per min was significantly greater than the increase at 25 μg/kg per min ($P<0.01$).

Mean aortic flow

Significant increases in cardiac output were demonstrated at all doses (Table 1). No significant difference was demonstrated between the four doses of dopamine administered.

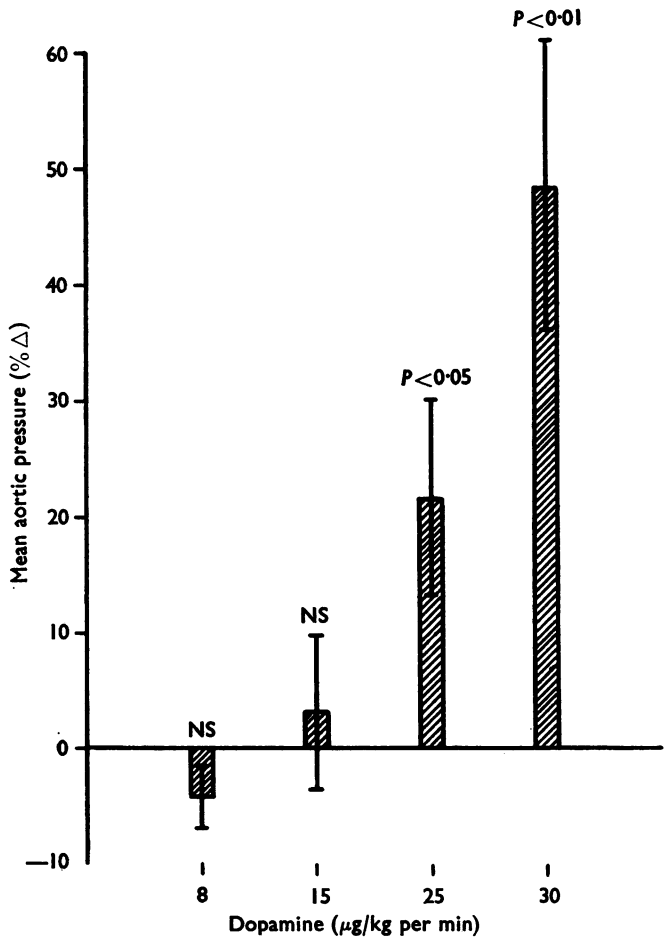

FIG. 2. Mean change (%Δ) and standard errors of the change in aortic pressure produced by various concentrations of dopamine are shown. No significant changes were noted at 8 and 15 μg/kg per min, whereas significant increases were noted at 25 and 30 μg/kg per min dopamine infusion. The increase at 30 μg/kg per min was significantly greater than that at 25 μg/kg per min.

Heart rate

No significant change in heart rate was demonstrable as a result of the four dopamine infusions, yet the slight slowing at 30 μg/kg per min differed significantly ($P<0{\cdot}05$) from the mild tachycardia induced at 8 and 15 μg/kg per min (Table 1).

Pulmonary vascular resistance

No significant change in pulmonary vascular resistance at any level of dopamine infusion was observed (Table 1). In addition, no differences were detected between the four dopamine doses.

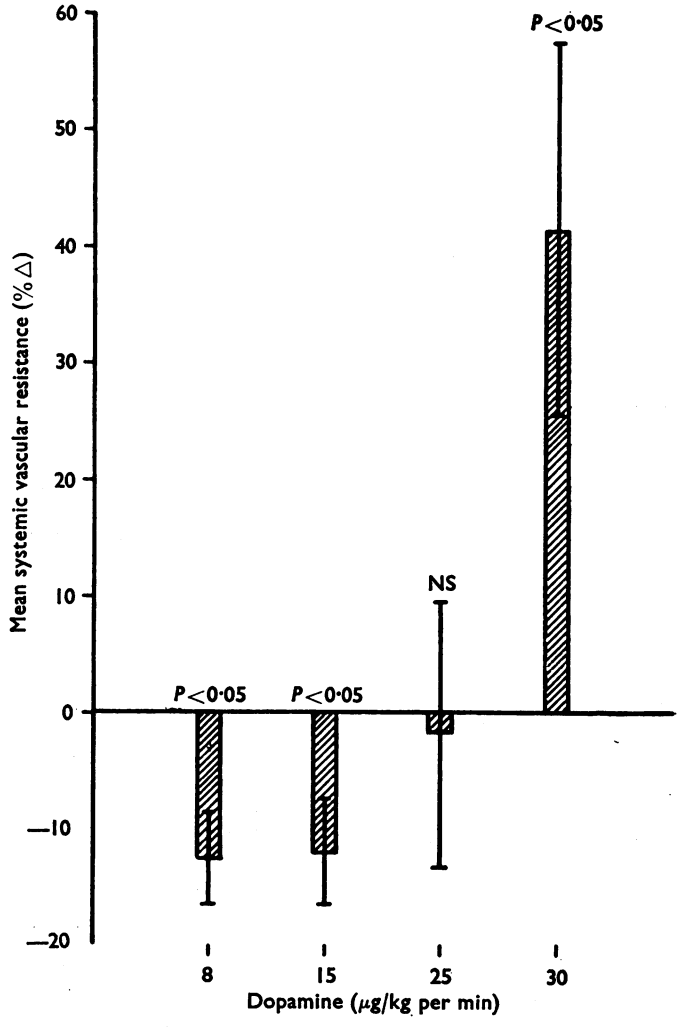

FIG. 3. Mean change (%Δ) and standard errors for the systemic vascular resistance produced by various infusions of dopamine are shown. At 8 and 15 μg/kg per min, significant decreases in systemic vascular resistance were noted. At 25 μg/kg per min dopamine, no significant change was observed, while at 30 μg/kg per min dopamine, significant and marked increases in peripheral vascular resistance occurred.

Systemic vascular resistance

A significant fall in systemic vascular resistance at the two low doses was noted (Fig. 3). There was no significant change at 25 μg/kg per min, but peripheral resistance rose significantly by $41{\cdot}4 \pm 16{\cdot}2\%$ at 30 μg/kg per min (Table 1). The responses at 8, 15 and 25 μg/kg per min could not be separated statistically; however, the increase in resistance demonstrated at 30 μg/kg per min was significantly greater than the response observed during the first three doses ($P<0{\cdot}01$).

Stroke volume

Low dose infusion of dopamine (8 and 15 μg/kg per min) failed to increase the stroke volume significantly; however, infusions at 25 and 30 μg/kg per min produced statistically significant increases (Table 1). The response at higher doses was significantly greater than the response at low doses ($P<0{\cdot}05$), but again it was impossible to separate the changes at 8 μg/kg per min from 15 μg/kg per min or 25 μg/kg per min from 30 μg/kg per min.

Blood gases

Average blood gases before dopamine infusion were pH=7·42 and pO_2=98. At the end of the experiments, average blood gases were pH=7·39 and pO_2=95. These values did not differ significantly.

Discussion

The pulmonary and systemic circulatory responses to dopamine infusion were studied in this investigation. The pulmonary artery pressure rose with all four of the dopamine doses administered. Only at the higher doses (25 and 30 μg/kg per min), however, was evidence of a statistically significant pressor response noted; the pressor responses at 25 and 30 μg/kg per min were of comparable magnitudes. At no time were the increased pulmonary pressures accompanied by significant changes in pulmonary vascular resistance (Table 1). Therefore, since vessel calibre remained unchanged while pressure rose, dopamine must act by increasing the level of smooth muscle tension in the blood vessels of the lung. The very slight tendency toward decreased pulmonary vascular resistance which occurred suggests that the action of dopamine on vessel calibre in the pulmonary vascular beds during increased cardiac output is that of slight dilatation only. This would be comparable with its effect on the peripheral circulation, where a small reduction in systemic resistance generally occurs.

Increase in aortic pressure in response to larger doses of dopamine—25 and 30 μg/kg per min (Table 1 and Fig. 2)—are in accord with findings of other investigators (McDonald & Goldberg, 1963).

Heart rate did not change significantly at any level of dopamine infusion. However, the tendency toward an increase at the three low doses and a decrease at 30 μg/kg per min was noted. This decrease in heart rate at the highest administered dose was probably due to the activation of baroreceptors and other pressor receptor mechanisms by the increase in peripheral pressure.

The systemic vascular response to dopamine was dose-dependent; a slight but significant decrease in resistance occurred at the two low doses (8 and 15 μg/kg

per min) and a very large, significant vasoconstriction at the high, 30 μg/kg per min. Similar dose-related responses of the systemic circulation have been reported (McDonald & Goldberg, 1963; Black & Rolett, 1968). The 25 μg/kg per min response, an intermediate response, may represent a balanced stimulation of peripheral alpha and beta-adrenoceptors. Thus, low doses of dopamine would appear to stimulate the beta-adrenoceptor, thereby causing a fall in resistance. It is also possible, however, that dopamine has a slight direct vasodilatory effect, independent of beta-adrenoceptor stimulation.

Although mean aortic flow rose significantly with all levels of infusion, statistically significant incremental increases in output with increasing doses of dopamine could not be demonstrated. It appears that the output increases as the dose is raised from 8 to 25 μg/kg per min and then increases to a lesser degree at the 30 μg/kg per min level. The smaller increase in output at 30 μg/kg per min is correlated with a large increase in peripheral pressure and resistance; it may represent inadequate response to increasing afterload secondary to direct peripheral vasoconstriction caused by high doses of dopamine. However, it may also be due to the reflex slowing of the heart rate, since the stroke volume did change significantly. The latter explanation seems more likely.

The significant decrease in left atrial pressure when dopamine was infused at 15 μg/kg per min and slight increase in response to the 30 μg/kg per min dose did not produce atrial pressures outside the normal physiological range. The fall at 15 μg/kg per min is explained by an increase in cardiac output without a significant change in afterload. These findings would imply an increase in cardiac contractility, which has been observed by others (Black & Rolett, 1966). A similar increase in cardiac output, accompanied by increases in peripheral pressure and systemic resistance, accounted for the rise at 30 μg/kg per min.

The increase in stroke volume was significant at only 25 and 30 μg/kg per min, but at all doses the trend was toward increased stroke volume, the increases appearing to be dose-related (Table 1). Since the cardiac output produced by 30 μg/kg per min was less than that produced by 25 μg/kg per min, the maintenance of stroke volume may be explained by the decreased heart rate which occurred as a result of the large pressor response.

The results of this study confirm previous reports on systemic response to dopamine (McDonald & Goldberg, 1963; Black & Rolett, 1966, 1968), as well as demonstrate that dopamine causes a pressor response in the pulmonary artery at high doses but creates no significant change in pulmonary resistance. However, these results do suggest that dopamine increases smooth muscle tension in the pulmonary vasculature. Dopamine-induced increases in pulmonary pressures would then be secondary to increased cardiac output and increased wall tension.

Despite the difficulties inherent in applying an open-chested, anaesthetized animal model to the clinical situation, it seems that these findings may have clinical relevance. The dopamine-induced elevation of pulmonary pressures in the clinical setting of pulmonary hypertension may be detrimental to the patient with a compromised right heart. It is even possible that an increase in smooth muscle tension without accompanying increase in cardiac output might result in undesirable vasoconstriction in the patient with pulmonary hypertension or congestive heart failure.

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