

CARDIOVASCULAR RESPONSES TO PHENYLEPHRINE DURING ACUTE EXPERIMENTAL ANAEMIA IN ANAESTHETIZED CATS

A. TALWAR, M. E. HUSSAIN, C. K. GUPTA AND M. FAHIM*

*Department of Physiology,
Vallabhbhai Patel Chest Institute,
University of Delhi, Delhi - 110 007*

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Abstract: Experiments were performed on anaesthetized artificially ventilated cats to study the effects of phenylephrine (PE) on cardiovascular responsiveness, before and after induction of experimental anaemia. Acute anaemia was induced by replacement of blood by dextran in three steps of 20% each of total estimated blood volume. The effect of PE (20 µg/kg) was investigated at four stages: control and after 1st, 2nd and 3rd exchanges of blood. Induction of anaemia produced a significant increase in heart rate (HR) and cardiac output (CO) and a decrease in right atrial pressure (RAP). No significant change in mean arterial pressure (MAP), LV dP/dt max and blood gas tension was observed. Administration of bolus dose of PE produced a rapid rise in MAP, LVdP/dt max, and a decrease in HR without a change in the RAP. The pattern of response to PE was similar after induction of acute anaemia, however the magnitude of the response was significantly reduced. The attenuation in the response to PE was related to the fall in the haematocrit (HCT) level. This shows that induction of experimental anaemia, produced an increase in CO due to an increase in HR and SV and the effect of PE on cardiovascular responsiveness was significantly attenuated. The reduced sensitivity to PE during acute anaemia could be due to many factors such as inadequate O₂ supply, effect of local vasodilating agents or some other cardiotoxic agents which are known to contribute to vascular responsiveness.

Key words: phenylephrine cardiovascular anaemia cats

INTRODUCTION

Anaemia is accompanied by reduction in the concentration of circulating erythrocytes (haematocrit ratio) and a fall in whole blood viscosity. The partial pressure of oxygen (PO₂) of arterial blood may be normal but oxygen content of blood is reduced in proportion to the reduction in haematocrit (1). The performance of left ventricle may also be disturbed due to inadequate myocardial O₂ supply (2). Studies in anaesthetised dogs have demonstrated that after induction of experimental anaemia by dextran for blood exchange transfusion, the cardiovascular responses to some alpha and beta adrenergic stimulants, certain drugs and neurotransmitters are significantly

changed (3-6). However, variable and inconsistent vascular responsiveness to these agents has been observed in earlier studies.

Phenylephrine is an important vasoactive alpha adrenergic stimulant and is widely used in various cardiovascular studies in animals as well as in humans (7, 8). However, limited information is available regarding the responsiveness of this vasoactive agent during experimental anaemia induced by graded haemodilution. Some workers (5) have reported that the mean arterial pressure change due to PE infusion is attenuated following haemodilution but they did not study its effect during graded haemodilution or its effect on cardiac functions.

*Corresponding Author

Therefore, the purpose of this study was to investigate the effect of PE on the responsiveness of various cardiovascular parameters before and after induction of experimental graded anaemia.

METHODS

Experiments were performed on 20 adult cats of either sex weighing 3-6 kg. They were anaesthetized with a mixture of 70 mg/kg chloralose (BDH) and 350 mg/kg urethane (E. Merck). Trachea was cannulated and the cats were ventilated with a respiratory pump (Inco, India). A polyethylene catheter was placed in the descending aorta through a femoral artery for recording arterial blood pressure (ABP) with a pressure transducer (Statham P23 Db). Blood samples were withdrawn in heparinized syringes anaerobically through this catheter for the measurement of arterial blood PO₂, PCO₂ and pH with the help of a blood gas monitor (Radiometer BMS-3-MK-2 microsystem and PMH-73 pH electrode). The arterial blood samples were also used for the measurement of haematocrit (HCT) with the help of a microcentrifuge (Jenetzki TH 12) and haemoglobin (Hb) with the help of haemometer (Shandilya, India). The right femoral vein was cannulated for intravenous injections and infusion of dextran. A polyethylene catheter was placed in the right atrium through external jugular vein for recording right atrial pressure (RAP) with a pressure transducer (Statham P23 Db). Another polyethylene catheter was placed into the left ventricle through left carotid artery for recording left ventricular pressure (LVP) with a pressure transducer (Statham P23 Db). The left ventricular pulse was differentiated electronically with a differentiator (Lectromed Model 5270) to record LV dp/dt and was also used to drive a cardiometer (Lectromed model 5260) for recording heart rate (HR). All these parameters were recorded on a polygraph (Lectromed, U.K.). Cardiac output (CO) was measured by thermodilution technique using a swan-Ganz flow directed thermodilution Catheter (Model 93-A-131-7F) and cardiac output computer (COM 1 Edward Co., USA).

Cardiovascular measurements were made 30 min after completion of surgical procedures. Normovolaemic haemodilution was induced by dextran (mol. wt. 150,000) for blood exchange. The dextran (Rallis India), a 6% solution of dextran in 5% w/v

dextrose was warmed to 37°C before infusion through the femoral vein catheter. The viscosity of 6% dextran solution is approximately equal to that of plasma. Blood was replaced by dextran in steps of 20% each of total estimated blood volume (9% of body weight). Hb and HCT were estimated after each exchange. Cardiovascular variables were recorded after a stabilizing period of 30 min following each exchange. The rectal temperature of the animal was maintained between 37-38°C.

Statistical analysis:

The statistical analysis was done for each drug separately. All the variables were subjected to log transformation in order to achieve variance stability and normality before the data was subjected to statistical analysis. The data on initial findings ((control level) was subjected to analysis of variance ANOVA (a two way classification) after ascertaining homogeneity of variance and normality. On evidence of significant variation amongst various anaemic stages and other appropriate comparisons were done through linear contrasts (9).

RESULTS

Effect of Haemodilution: The results of the present study are presented in Fig. 1 and 2. Normovolaemic haemodilution was done in three steps of 20%.

Normovolaemic haemodilution was done in three steps of 20% estimated blood volume each. After the last blood for dextran exchange (total 60% of estimated blood volume) the actual volume of blood replaced by dextran would be approximately 50% or less and not 60% because after the 1st exchange in the subsequent withdrawal of blood, the 20% of volume contained blood mixed with previously infused dextran. On induction of acute normovolaemic haemodilution by this process, the HCT dropped from baseline level of $41 \pm 3\%$ to $28 \pm 2\%$, $20 \pm 2\%$ and $14 \pm 2\%$ and Hb dropped from control value of 13 ± 0.5 g/dl to 4.6 ± 0.5 , 7.0 ± 0.2 , 3.9 ± 0.2 g/dl after 1st, 2nd and 3rd exchanges of blood respectively. MAP did not show any significant change ($P > 0.05$) following exchange of blood. With the fall in HCT, there was a corresponding significant increase in HR and CO and fall in RAP. Haemodilution did not produce any significant ($P > 0.05$) effect in LV dp/dt max or left ventricular end diastolic pressure (LVEDP).

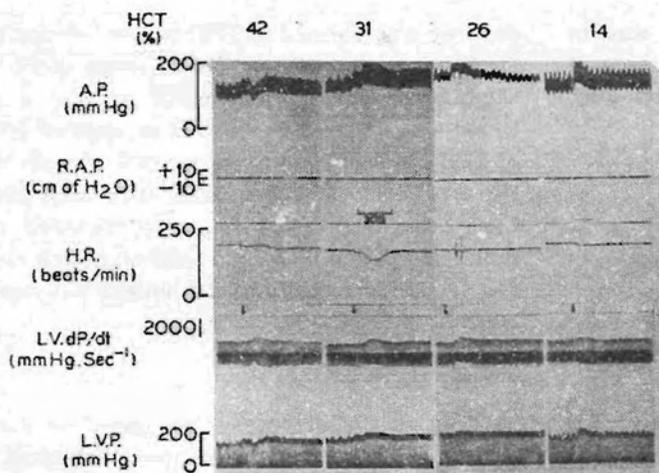


Fig. 1: Representative tracings demonstrating change in arterial blood pressure (ABP), Right atrial pressure (RAP), Heart rate (HR), LV dp/dt max and left ventricular pressure (LVP), to bolus injection of PE (20 µg/kg) at different HCT levels following induction of graded experimental anaemia.

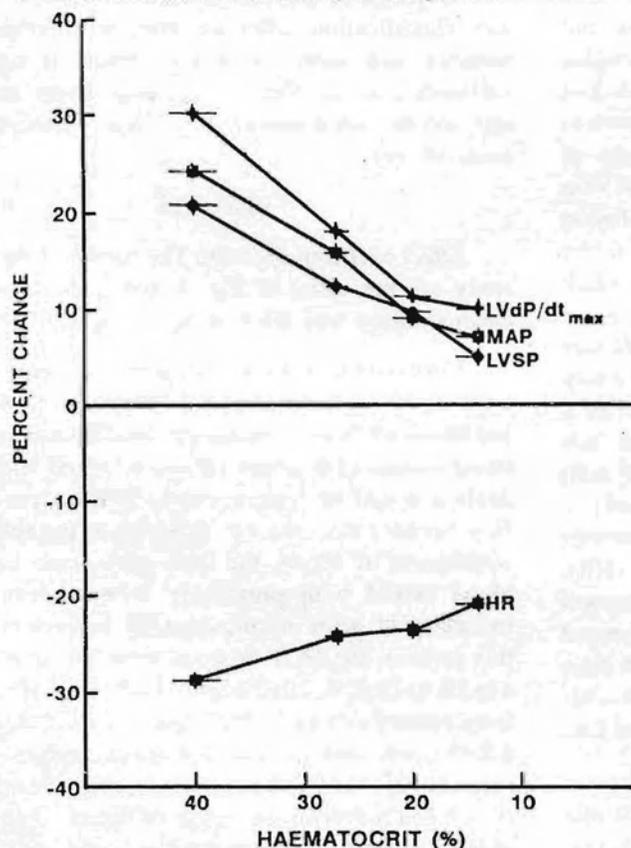


Fig. 2.: Percent change in heart rate (HR), LV dp/dt max, LVSP, MAP following intravenous administration of Phenylephrine (20 µg/kg) at control. (HCT 41.0±3.0%) and after 1st (HCT 28±2), 2nd (HCT 20±2) and 3rd (HCT 14±2) exchange of blood with dextran.

Blood gas tension and pH did not show any significant ($P>0.05$) change with the fall in HCT level.

Effect of Phenylephrine: Intravenous administration of 20 µg/kg PE at control HCT produced a rapid rise in BP and simultaneous increase in LV dp/dt max (Fig. 1 and 2). However, there was no change in RAP. Haemodynamic parameters recovered 20 min after intravenous injection of PE. The pressor response was accompanied by a marked reflex bradycardia (Fig. 2). Systolic arterial pressure (SAP) increased from 144 ± 2 to 174 ± 3 mmHg, diastolic arterial pressure (DAP) increased from 89 ± 3 to 115 ± 1 mmHg, LV dp/dt max increased from 3486 ± 50 to 4544 ± 50 mmHg/sec, HR decreased from 178 ± 1 to 141 ± 4 beats/min. There was no change in LVEDP and RAP.

Following induction of acute normovolaemic anaemia, the pattern of response to PE was similar, however, the magnitude of response was significantly ($P<0.05$) reduced with progressive haemodilution (Fig. 2).

Before replacement of blood with dextran, PE produced $24.3\pm 0.4\%$ rise in MAP over control, which was reduced to $15.9\pm 0.3\%$, $9.2\pm 0.2\%$, 7.2 ± 0.4 after 1st, 2nd and 3rd exchanges respectively (Fig. 2). LVSP increased by $20.8\pm 0.5\%$ at control HCT and 12.5 ± 0.3 , 9.7 ± 0.2 , $5.0\pm 0.4\%$ after 1st, 2nd and 3rd exchanges respectively (Fig. 2). LV dp/dt max increased by $30.3\pm 0.4\%$ at control HCT and $18.1\pm 0.3\%$, $11.3\pm 0.2\%$, $10.1\pm 0.2\%$ after 1st, 2nd and 3rd exchanges respectively (Fig. 2). HR decreased by $28.8\pm 0.4\%$ before blood replacement and 24.1 ± 0.3 , 23.5 ± 0.2 , $20.7\pm 0.2\%$ after 1st, 2nd and 3rd exchanges respectively.

DISCUSSION

In the present study, we observed that acute normovolemic anaemia produced an increase in cardiac output supporting earlier finding in anaesthetized (10) and conscious animals (11). This increased CO could be due to change in TPR, fall in viscosity of blood, increase in central venous pressure and stimulation of chemoreceptors (12). In our study the influence of chemoreceptors was eliminated or minimized since we kept arterial PO₂, PCO₂ and pH under normal range. However, stimulation of chemoreceptors due to reduced O₂ content of blood cannot be ruled out. Although we selected a high Mol. wt. (150,000) dextran for blood replacement, a change in blood viscosity probably occurs and may contribute to the fall in TPR as suggested by Fan et al (13). A significant role of parasympathetic efferents in reflex tachycardia response during experimental anaemia has been emphasized (10). Increase in SV and HR may be the contributing factors to the increase in CO as observed by others (10, 14). Another important factor for the discrepancies in the result of various workers could be due to the anaesthetic agent used by them in their studies. Since anaesthetics are known to inhibit and even abolish vagal tone (14), we preferred the anaesthetic mixture of chloralose and urethane, which provided an anaesthetized preparation with normal ABP and HR in a small range. HR of our anaesthetized cat was slightly higher as compared to conscious animals. This could partly be a reason for a small increase in HR in response to haemodilution. The increase in CO was largely due to an increase in SV. Whereas, in our earlier study in anaesthetized dogs (16) increase in CO in response to haemodilution was largely due to increase in HR.

In our study, PE produced a significant increase in HR, LV dP/dt, LVSP and BP in control as well as under acute anaemic conditions. However, the degrees of responsiveness to the same dose of PE (20 µg/kg) was significantly reduced after graded induction of anaemia (Fig. 2). The percent change (increase) in LV dP/dt max, MAP, LVSP were significantly ($P < 0.05$) attenuated as the haemodilution (%) level was increased from control to acute level of haemodilution. Similarly,

the bradycardia response to PE was also attenuated following fall in haematocrit due to haemodilution. The attenuation in responsiveness was seen at all the three levels of experimental anaemia i.e. mild, moderate and acute. The attenuation in responsiveness in all the parameters was observed on induction of even mild anaemia (27% HCT).

The use of PE as hypertensive agent is well known and is a powerful alpha receptor stimulant with little or no effect on beta receptors of heart. It directly acts on receptors and a small part of its effect is mediated through the release of norepinephrine (15). The mechanism for the reduced responsiveness to PE during experimental anaemia is not yet very clear. However, some workers have suggested that the attenuation in cardiac responsiveness to certain vasoactive agents could be due to inadequate myocardial oxygen delivery associated with catecholamines or to antagonism by local vasodilating effect on anaemic hypoxia (4, 5). In our study on some other vasodepressor agents (16), a reduced responsiveness during haemodilution was observed indicating that either of the two mechanism alone discussed earlier, is not responsible for this attenuation in responsiveness. Involvement of other unknown factors e.g. nitric oxide (NO) and prostacyclin (17-18) in the reduced responsiveness of the cardiovascular system to vasoactive agents under acute anaemic condition is also possible. Out of these factors neurohormonal and endothelium derived factors e.g. nitric oxide (NO), prostacyclin, are increasingly being suspected to be the effective regulators of vascular tone, BP and tissue perfusion (17-18). The involvement of these factors cannot be ruled out. In conclusion our study indicates that during acute experimental anaemia, there is an increase in CO due to an increase in HR and SV. Fall in TPR during haemodilution could partly be due to decrease in viscosity of blood. The effect of PE on various cardiovascular parameters is significantly attenuated following graded induction of acute anaemia. The reduced sensitivity of the drug under such condition could be related to reduced myocardial O₂ supply, antagonism by local vasodilating agents and many other factors which are known to contribute in vascular responsiveness to cardiostimulant agents.

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REFERENCES

- Bartlett D Jr, Tenny SM. Tissue gas tension in experimental anaemia. *J Appl Physiol* 1963; 52: 16-20.
- Chapler CK, Cain SM, Stainby WN. Blood flow and oxygen uptake in isolated canine skeletal muscle during acute anaemia. *J Appl Physiol* 1979; 46: 1035-1038.
- Crystal GJ, Salem MR. Myocardial and systemic hemodynamics during isovolemic haemodilution alone and combined with nitroprusside induced controlled hypotension. *Anesth Analg* 1991; 72: 227-237.
- Biro GP, Clarke TNS, Pray Roberts C. Cardiac responsiveness to beta adrenergic stimulation in experimental anemia. *Can J Physiol Pharmacol* 1975; 54: 675-685.
- Mahdi M, Crystal GJ, Salem MR, Paulissian R. Haemodilution attenuates pressor response during phenylephrine infusions in dogs (Abstract). *Anesth Analg* 1990; 70: 9254.
- Chiong MA, Hatcher JD. Cardiovascular reactivity in anaemic dogs. *Can J Physiol Pharmacol* 1965; 43: 327-337.
- Hussain ME, Balakrishna, Singh M, Fahim M. Inhibition of arterial baroreceptor reflex during coronary artery occlusion. *Jap J Physiol* 1992; 42 (5): 741-752.
- Oren RM, Schobet HP, Weiss RM, Stanford W, Ferguson DW. Importance of left atrial baroreceptors in cardiopulmonary baroreflex of normal human. *J Appl Physiol* 1993;74 (6): 2672-2680.
- Armitage, P. Statistical methods in medical research. 1987; London, Blackwell Scientific.
- Fahim M, Singh M. Haemodynamic responses during acute normovolemic haemodilution in anaesthetized dogs. *Jap J Physiol* 1992; 42: 753-763.
- Glick GH, Plauth HW Jr, Braunwald E. Role of autonomic nervous system in the circulatory response to acutely induced anemia in unanaesthetized dogs. *J Clin Invest* 1964; 43: 2113-2124.
- Cropp GJA. Ventilation in anemia and polycythemia. *Can J Physiol Pharmacol* 1970; 48:382-393.
- Fan FC, Chen RYZ, Schuessler GB, Chien S. Effect of hematocrit variations on regional haemodynamic and oxygen transport in the dog. *Am J Physiol* 1980; 238 (1): 4545-4552.
- Kirchheim HR. Systemic arterial baroreceptor reflexes. *Physiol Rev* 1976;56: 100-176.
- Bhatia SK, Frohlich ED. Hemodynamic comparison of agents useful in hypertensive emergencies. *Am Heart J* 1973;85:367.
- Khurana A, Hussain ME, Fahim M. Cardiac responsiveness to neurotransmitters during acute normovolaemic haemodilution in anaesthetized cats (Abst). *Indian J Physiol Pharmacol* 1992; 36 (5): 39.
- Bassenge E. Clinical relevance of endothelium-derived relaxing factor (EDRF). *Br J Clin Pharmacol* 1972;34:375-425.
- Nagao T, Vahoutts PM. Endothelium-derived hyperpolarizing factor and endothelium dependent relaxation. *Am J Respir Cell Mol Biol* 1993; B: 1-6.