



## INTRODUCTION

It has been shown that rapid blood loss evokes a biphasic haemodynamic response (1, 2, 3). The first phase (moderate haemorrhage) is associated with increase in sympathetic nerve activity, plasma catecholamine levels, peripheral vascular resistance and heart rate. When blood volume has been critically depleted during severe haemorrhage, the sympathetic drive to the periphery falls steeply, and vascular resistance, arterial pressure and heart rate decrease until syncope occurs (3, 4, 5). The sudden decrease in arterial pressure during severe haemorrhage has been attributed to sympathetic withdrawal and subsequent bradycardia and systemic arterial vasodilatation (6, 7, 8). Scant information is available regarding the compensatory mechanisms other than the baroreflex, which will try to restore the mean arterial pressure before there is complete failure of compensatory mechanisms in progressive shock states.

Therefore it was planned to produce haemorrhage of increasing severity and time the sequence of events happening after the induction of haemorrhage to understand the complex interplay of the various compensatory mechanisms which try to restore the blood pressure.

## MATERIALS AND METHODS

The experiments were performed on 20 healthy mongrel dogs of either sex. The ethical clearance was obtained from the ethics committee and all experiments were

approved by the Institutional Animal Care and Use Association, and were carried out under the guidelines of Care and Use of Experimental Animals.

### Animal preparation

Twenty healthy mongrel dogs of either sex were randomly assigned to two groups. In one group (n = 10) 20% of the total blood volume loss was induced and in the other group (n = 10) 35% of the total blood volume loss was induced. The animals were anaesthetized with alpha chloralose 80 mg/kg i.v. and when required supplemented by 20 mg/kg. The animal was placed in supine position, intubated through a tracheal incision and ventilated with room air. Polyethylene catheters were placed in the femoral artery for recording arterial blood pressure with a pressure transducer (Statham P32 Db) on a polygraph (Lectromed, U.K.) through a strain gauge coupler amplifier (Lectromed Model 5220). The arterial pressure pulse was used to drive a cardiometer (Lectromed Model 5260) for recording the heart rate. A polyethylene catheter was placed into the right atrium through right external jugular vein for recording right atrial pressure using a transducer (Statham P32 Db) and injecting cold saline for cardiac output measurement. Arterial blood pH,  $P_{O_2}$ ,  $P_{CO_2}$  and base deficit were measured with an automatic pH/Blood gas system (COMBISYS-ESCHWEILER, Germany). Cardiac output was measured by thermodilution technique (9, 10) using a cardiac output computer (COM 1 Edward Company, USA).

Total peripheral resistance was calculated by the formula:

$$\frac{\text{(Mean arterial pressure/cardiac output)}}{\text{X } 80 \text{ dynes. sec. cm}^{-5}}$$

#### Induction of haemorrhage

In the first group basal cardiovascular parameters, arterial blood pH,  $P_{O_2}$ ,  $P_{CO_2}$  and base deficit were recorded and haemorrhage was induced by withdrawing 20% of estimated blood volume from arterial catheter. Total blood volume was estimated as 70 ml/kg. In the second group basal cardiovascular parameters, arterial blood pH,  $P_{O_2}$ ,  $P_{CO_2}$  and base deficit were recorded and haemorrhage was induced by withdrawing 35% of estimated blood volume from arterial catheter. Induction of haemorrhage was completed in 5 minutes in both groups. The animals were monitored for 60 min after the induction of haemorrhage for the recovery due to natural compensatory mechanisms.

#### Recordings

Arterial blood samples were withdrawn anaerobically for blood gas and pH analysis and cardiovascular variables were recorded before haemorrhage, 1 min after the induction of haemorrhage, 5 min after the induction of haemorrhage, 30 min after haemorrhage and 60 minutes after the induction of haemorrhage.

No animal received fluid resuscitation.

#### Statistical analysis:

All data are expressed as mean  $\pm$

standard error of mean from twenty animals (ten animals in each group). Statistical significance of the difference between control and post haemorrhagic values was determined by analysis of variance. Analysis of individual mean was done by using paired t Test. The significance level was set at  $P < 0.05$ .

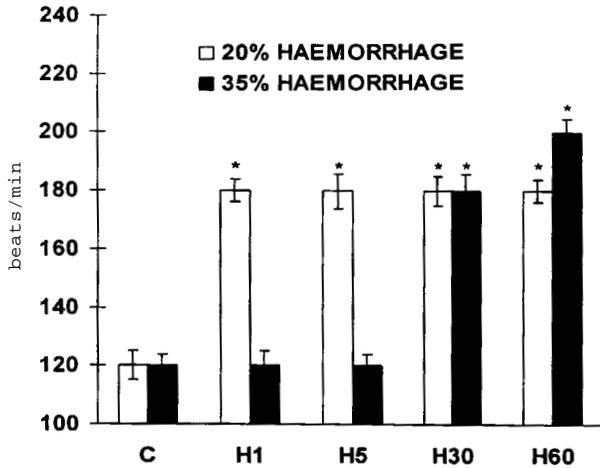
## RESULTS

There was a significant rise in heart rate after 1 min of haemorrhage from control value of  $120 \pm 3.48$  to  $180 \pm 1.24$  beats/min in 20% blood loss while no rise in heart rate was observed in 35% blood loss. Heart rate remained significantly elevated in 20% blood loss while significant rise in heart rate was produced 30 min after the induction of haemorrhage in 35% blood loss (Fig. 1).

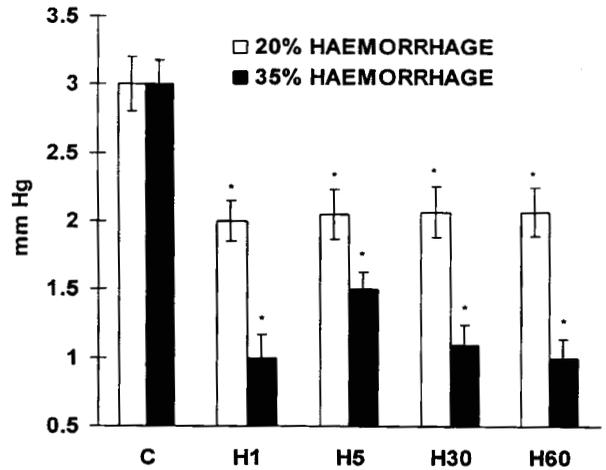
There was a significant fall in stroke volume after 1 min of haemorrhage from control value of  $14.75 \pm 1.04$  to  $7.27 \pm 0.657$  ml/stroke in 20% blood loss while more significant fall to  $5.51 \pm 0.077$  ml/stroke was observed in 35% blood loss. With time the stroke volume was maintained at a lower level compared to control value in 20% blood loss while an initial significant rise in stroke volume at 5 min followed by the second decrease in stroke volume at H30 and H60 was produced in 35% blood loss. (Fig. 1).

There was a significant fall in right atrial pressure after 1 min of haemorrhage from control value of  $3 \pm 0.32$  to  $2 \pm 0.211$  mm Hg in 20% blood loss while more significant fall to  $1 \pm 0.21$  mm Hg was observed in 35% blood loss. With time the right atrial pressure was maintained at a lower level compared to control value in 20%

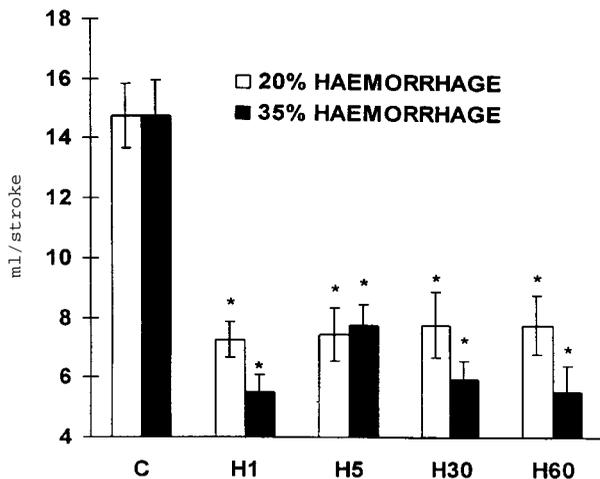
## HEART RATE



## RIGHT ATRIAL PRESSURE



## STROKE VOLUME



## CARDIAC OUTPUT

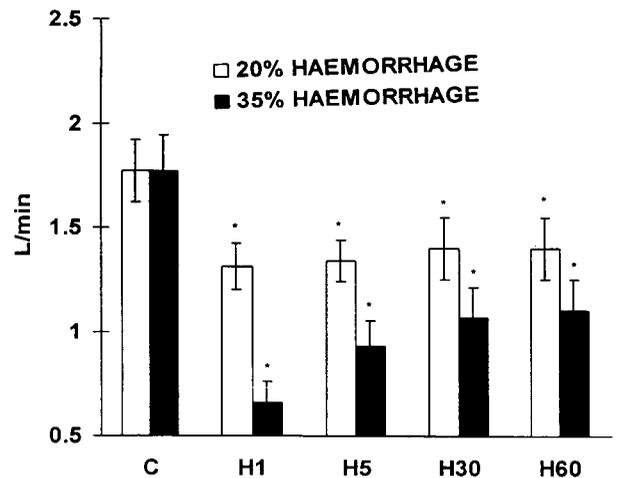


Fig. 1: Effects of 20% and 35% haemorrhage on heart rate and stroke volume. Values are mean  $\pm$  standard error of mean of observations from 10 dogs for 20% haemorrhage and 10 dogs for 35% haemorrhage. C - control value before haemorrhage; H1 - 1 min after haemorrhage; H5 - 5 min after haemorrhage; H30 - 30 min after haemorrhage; H60 - 60 min after haemorrhage.

\* - significantly different ( $P < 0.05$ ) from control value before haemorrhage (C).

Fig. 2: Effects of 20% and 35% haemorrhage on right atrial pressure and cardiac output. Values are mean  $\pm$  standard error of mean of observations from 10 dogs for 20% haemorrhage and 10 dogs for 35% haemorrhage. C - control value before haemorrhage; H1 - 1 min after haemorrhage; H5 - 5 min after haemorrhage; H30 - 30 min after haemorrhage; H60 - 60 min after haemorrhage.

\* - significantly different ( $P < 0.05$ ) from control value before haemorrhage (C).

blood loss while an initial significant rise in right atrial pressure at 5 min followed by the second decrease in right atrial pressure at H30 and H60 was produced in 35% blood loss. (Fig. 2)

There was a significant fall in cardiac output after 1 min of haemorrhage from control value of  $1.77 \pm 0.222$  to  $1.31 \pm 0.148$  L/min in 20% blood loss while more significant fall to  $0.66 \pm 0.021$  L/min was observed in 35% blood loss. With time the cardiac output was maintained at a lower level compared to control value in 20% blood loss while a progressive recovery in cardiac output was produced in 35% blood loss. (Fig. 2).

There was a significant fall in mean arterial blood pressure from control value of  $106.6 \pm 3$  to  $85.33 \pm 3.1$  mm Hg in 20% blood loss while a more significant fall from  $112 \pm 3.2$  to  $40 \pm 2$  mm Hg was produced by 35% blood loss. Both the groups showed recovery with time in mean arterial blood pressure after 5 min, 30 min, and 60 min compared to H1. (Fig. 3).

There was a significant rise in total peripheral resistance after 1 min of haemorrhage from control value of  $4820.7 \pm 150$  to  $5210.9 \pm 175$  dyne sec  $\text{cm}^{-5}$  in 20% blood loss. There was a fall in total peripheral resistance after 1 min of haemorrhage from control value of  $5062.1 \pm 169.9$  to  $4848 \pm 165$  dyne sec  $\text{cm}^{-5}$  in 35% blood loss. There was a rise with time in total peripheral resistance in 20% blood loss while an initial immediate fall followed by a rise in total peripheral resistance was produced in 35% blood loss. (Fig. 3).

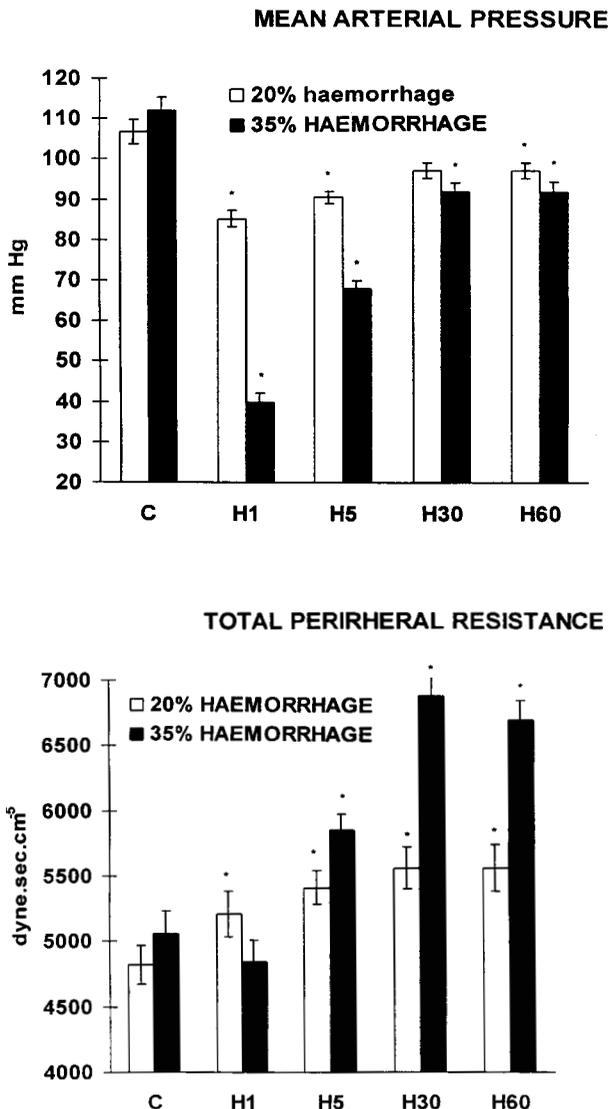


Fig. 3: Effects of 20% and 35% haemorrhage on mean arterial pressure and total peripheral resistance. Values are mean  $\pm$  standard error of mean of observations from 10 dogs for 20% haemorrhage and 10 dogs for 35% haemorrhage. C - control value before haemorrhage; H1 - 1 min after haemorrhage; H5 - 5 min after haemorrhage; H30 - 30 min after haemorrhage; H60 - 60 min after haemorrhage.

\* - significantly different ( $P < 0.05$ ) from control value before haemorrhage (C).

There was a significant rise in base deficit after 1 min of haemorrhage from control value of  $-1.5 \pm 0.02$  mmol/L to  $-5 \pm 0.09$  mmol/L in 20% blood loss while a more significant rise in base deficit from  $-1.5 \pm 0.02$  to  $-10.5 \pm 0.02$  mmol/L was produced in 35% blood loss. With time the base deficit was maintained at a higher level compared to control value in both 20% and 35% blood loss.

TABLE I: Base deficit (mmol/L) after 20% and 35% haemorrhage.

	20% haemorrhage	35% haemorrhage
C	$-1.5 \pm 0.02$	$-1.5 \pm 0.02$
H1	$-5 \pm 0.09^*$	$-10.5 \pm 0.02^*$
H5	$-4.5 \pm 0.03^*$	$-8 \pm 0.03^*$
H30	$-4.3 \pm 0.04^*$	$-6 \pm 0.03^*$
H60	$-4.1 \pm 0.03^*$	$-5.5 \pm 0.04^*$

Values are mean  $\pm$  standard error of mean of observations on 10 dogs.

C - before haemorrhage; H1 - 1 min after haemorrhage; H5 - 5 min after haemorrhage; H30 - 30 min after haemorrhage; H60 - 60 min after haemorrhage.

\* - significantly different ( $P < 0.05$ ) from (C).

## DISCUSSION

Immediately after the induction of 20% blood loss there was a fall in the mean arterial pressure, cardiac output, stroke volume and right atrial pressure, which could be attributed to a fall in circulating blood volume due to blood loss. A significant rise in heart rate and total peripheral resistance was produced which could be attributed to the baroreceptor-mediated response to fall in mean arterial pressure (11). The cardiac output was maintained at a lower level compared to control value by baroreflex mediated rise in sympathetic discharge. Thus the progressive improvement in arterial pressure was due to maintained

cardiac output and progressive rise in total peripheral resistance.

The initial fall in total peripheral resistance and no change in heart rate in 35% blood loss could be due to stimulation of vagal afferent C fibers from the left ventricle of the heart (6, 12). The mechanism of activation of the ventricular receptors is probably a combined effect of an increased sympathetic outflow and a low ventricular filling. These two stimuli together induce a powerful contraction around an almost empty chamber, giving rise to deformation and squeezing of the myocardium, which activates the receptor (6). This reflex mechanism, of which efferent part seems similar to so called vasovagal syncope, may serve as a protective mechanism allowing for improved diastolic filling when venous return is critically reduced. This explains the significant rise in right atrial pressure, stroke volume and cardiac output due to improved diastolic filling mediated by vagal efferents at H5 in 35% blood loss.

The vagus mediated improved diastolic filling results in decrease in activation of vagal afferent C fibers from the left ventricle of the heart. This causes an increase in the sympathetic outflow from medulla resulting in rise in total peripheral resistance at H5. This accounts for a second decrease in stroke volume and right atrial pressure at H30 and H60 due to a fall in venous return.

There was no increase in heart rate at H1 and H5 due to vagal stimulation and also at lower mean arterial pressure there is hypoperfusion at tissue level so body tries

to conserve oxygen by decreasing myocardial oxygen consumption. Therefore the initial rise in cardiac output was in accordance to frank - starling law but later on the cardiac output was maintained at a significant high level compared to H1 by increased sympathetic drive.

When the mean arterial pressure reached the threshold of baroreceptor, the baroreceptor-mediated increase in heart rate and total peripheral resistance was produced. Thus the arterial pressure was maintained by baroreceptor mediated compensatory mechanism till 60 min after induction of haemorrhage.

We conclude that baroreceptor mediated compensatory mechanism fail to restore blood pressure in severe blood loss. In such

condition increased vagal tone serve as a protective mechanism by allowing improved diastolic filling when venous return is critically reduced. Vagal stimulation cause decrease in myocardial oxygen consumption by preventing any rise in heart rate thus breaking the positive feedback loop of producing myocardial depression in severe shock. Thus the initial rise in mean arterial pressure was produced by vagal stimulation followed by maintenance by baroreflex in 35% blood loss.

#### ACKNOWLEDGEMENTS

The authors wish to thank to Dr. P.K. Reddy, Dr. Anita Pawar and Mr. Maman Singh for their help in experiments and to Mr. Mazumdar for his help in the preparation of figures.

#### REFERENCES

- Schadt JC, Mckown MD, Mckown DP, Franklin D. Hemodynamic effect of hemorrhage and subsequent naloxone treatment in conscious rabbits. *Am J Physiol* 1984; 247 *Heart Circ Physiol* 20: R497-R505.
- Ludbrook J, Graham WF. The role of cardiac receptor and arterial baroreceptor reflexes in control of the circulation during acute change in blood volume in the conscious rabbit. *Cir Res* 1984; 54: 424-435.
- Barcroft L, McMichael J, Edholm OG, Sharpetschafer EP. Posthaemorrhagic fainting. Study by cardiac output and forearm flow. *Lancet* 1944; 1: 489-491.
- Bruke SL, Dorward PK. Influence of endogenous opiates and cardiac afferents on renal nerve activity during haemorrhage in conscious rabbits. *J Physiol* 1988; 402: 9-27.
- Morita M, Nashida Y, Motochigawa H, Uemura N, Hosomi H, Vatner SF. Opiate receptor mediated decrease in renal nerve activity during hypotensive haemorrhage in conscious rabbits. *Circ Res* 1988; 63: 165-172.
- Oberg B, White S. The role of vagal cardiac nerves and arterial baroreceptors in the circulatory adjustments to the haemorrhage in the cats. *Acta Physiol Scand* 1970; 80: 395-403.
- Morita H, Vatner SF. Effect of haemorrhage of renal nerve activity in conscious dogs. *Circ Res* 1985; 57: 788-793.
- Victor RG, Thoren P, Morgan DA, Mark AL. Differential control of adrenal and renal sympathetic nerve activity during haemorrhagic hypotension in rats. *Circ Res* 1989; 64: 686-694.
- Fahim M, Pressman BC. Improvement of cardiac performance by carboxylic ionophore monensin in greyhound and mongrel dogs. *Naunyn - Schmiedeberg's Arch Pharmacol* 1986; 333: 412-420.
- Fahim M, Gina Del Valle, Pressman BC. Comparison of the effects of the ionophore Salinomycin and adrenaline on the haemodynamics and work efficiency of the dog heart. *Cardiovascular Research* 1986; 20: 145-152.
- Secher NH, Bie P. Bradycardia during reversible haemorrhagic shock - a forgotten observation? *Clinical Physiology* 1985; 5: 315-323.
- Thoren P. Role of cardiac vagal C fibers in cardiovascular control. *Rev Physiol Biochem Pharmacol* 1979; 86: 1-94.