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Cardiopulmonary Effects of Acute Blood Volume Alteration Prior to Exercise

M. K. HOPPER, R. L. PIESCHL JR, N. G. PELLETIER and H. H. ERICKSON
College of Veterinary Medicine, Kansas State University, Manhattan, Kansas 66506, USA

ABSTRACT. The effects of altering blood volume (BV) on cardiovascular adjustments to exercise were determined in six horses on a high speed treadmill. Plasma volume (PV) increased from 28.9±1.3 to 35.3±1.6 l by dextran infusion (DI). During exercise, DI increased right atrial pressure (RAP) by an average of 17% (29±3 vs 35±3 mmHg), and cardiac output ($\dot{Q}$) by 15%, entirely due to changes in stroke volume (SV) (1375±53 vs 1568±44 ml) as heart rate (HR) remained unchanged. Mean systemic arterial pressure (SAP) did not change following DI; therefore, calculated total peripheral resistance (TPR) was reduced 14.5%. PV was reduced from 28.9±1.3 to 26.5±1.5 l with furosemide (1 mg kg^{-1}) administered three hours before exercise. RAP declined during exercise by an average of 30%, and $\dot{Q}$ by 8% due to changes in SV (1375±53 vs 1275±45 ml); HR was identical to control. SAP declined (167±5 vs 158±5 mmHg; NS) but TPR remained unchanged. These studies indicate that altering BV, most likely through its effect on RAP (central venous filling pressure) has the ability to influence SV, $\dot{Q}$ and other cardiovascular adjustments to exercise which may affect performance.

Key words: Cardiac output; horses; stroke volume; oxygen consumption; atrial pressure

INTRODUCTION

Cardiovascular adjustments to exercise are critical in determining work capacity. One factor with the potential to alter these adjustments is mean right atrial pressure (RAP). Perhaps most importantly, RAP has the ability to influence exercise SV. Conditions that increase RAP, such as BV expansion,[7,11,13,17] water immersion,[21] and supine exercise,[3] have been shown to increase exercise SV, whereas conditions that decrease RAP, such as dehydration[18,20] and detraining[3,15] decrease exercise SV.

Changes in RAP may also influence reflex control of TPR via receptors located in the right atrium.[4,12] Baroreceptors exposed to pressure in this region influence peripheral vascular tone in response to changes in venous return and central venous filling pressure or RAP.[13] An increase in RAP stimulates firing of these baroreceptors, increasing inhibition of the vasomotor center, decreasing sympathetic nerve activity, and thereby reducing systemic vascular resistance.[22] This may be an ideal complement, if an increase in RAP can increase $\dot{Q}$ by increasing SV and also elicit a decline in peripheral vascular resistance to keep blood pressure constant. Although RAP may play a key role in determining the cardiovascular responses to exercise, these responses are complex, and the effect of altering RAP on the integrated response to exercise is poorly understood. The purpose of this investigation was to determine the effects of altering RAP (via blood volume manipulation) on the cardiovascular adjustments to exercise in a group of physically untrained horses. The results may be important in interpreting the cardiovascular responses to exercise associated with conditions that alter BV, such as exercise training[16] and diuretic therapy for exercise-induced pulmonary hemorrhage.

METHODS

Subjects. Six horses (two Quarter horses and four Thoroughbreds), 6–9 years old, average weight of 539 ± 8 kg were studied. They were housed in dry lots and did not train for at least 3 weeks prior to the study. They were fed a concentrate mixture and prairie hay twice daily and had free access to water.

Measurement of maximal O_2 uptake. Preliminary testing was performed on all subjects during the week prior to the experiments to determine maximal oxygen consumption ($\dot{V}O_2max$) and running speeds that elicited 50, 75, and 100% of $\dot{V}O_2max$ representing low, moderate and high intensity exercise. $\dot{V}O_2max$ was determined during 7 to 12 min of running on a high-speed treadmill (SATO, Uppsala, Sweden). Running speed was increased every 2 min until the horses were fatigued. An open flow mask was used through which expired air was collected for measuring oxygen consumption.[24]

Experimental design. One week after the preliminary studies, a repeated measures study with three treatments began: 1) control (CON); 2) intravenous dextran infusion to increase plasma volume (DI); and 3) intravenous furosemide administration (FUR), 1 mg kg^{-1} body weight, to reduce PV. Only one horse was tested per day, and 1 week of rest was allowed between trials. The order of treatments was assigned in a repeated measures Latin square. After each treatment, subjects performed a graded exercise test on a high speed treadmill. HR; mean RAP; mean SAP; arterial and venous blood oxygen content; $\dot{Q}$; SV; oxygen consumption; and venous hematocrit, hemoglobin, and viscosity were determined at rest and during the last 15 seconds of each of the three running speeds.

Animal preparation and instrumentation. Electrocardiograph (ECG) electrodes were positioned for determination of HR.[5] Two 7F introducer catheters were placed under local anesthesia in the right jugular vein. Samples of mixed venous blood were obtained with a solid-state pressure transducer catheter with an open lumen (Model SPC-761P, Millar Instruments, Houston, TX) positioned in the pulmonary artery. Mean RAP was measured with a second Millar catheter (Model SPC-471A) placed in the right atrium. The location of the catheters was standardized by monitoring vascular pressure waveforms on a pen recorder.

SAP was measured in the carotid artery, with a pressure transducer (Statham Model P23Db; Hato Rey, PR).[24] This transducer was positioned at the point of the shoulder. All pressure transducers were calibrated with a mercury manometer. A multichannel pen recorder (Beckman Model R-612) was used to record pressures and ECG. An open flow technique was used to determine oxygen consumption.[24]

Hematology. Venous blood samples were immediately placed in a tube containing EDTA. Hematocrit was determined in quadruplicate by spinning samples in a microhematocrit centrifuge (12000 rpm) for 10 min. Hemoglobin concentration was determined as the cyanomethemoglobin derivative.[10] Blood viscosity was analyzed with a Sonoclot Coagulation Analyzer (Sienco, Inc., Morrison, CO). The instrument was calibrated with standard viscosity fluids after every 10 samples.

Standard exercise test. Each exercise test was run on the level and consisted of a 3 min warm-up followed by 2 min of exercise at speeds that elicited 50, 75, and 95–100% of each individual's $\dot{V}O_2max$. Running speeds were selected to include low, moderate, and maximal or near maximal work rates. Steady state oxygen consumption was obtained within the 2 min time period at all running speeds.

Measurement of cardiac output. $\dot{Q}$ was determined by the direct Fick method.[24] Anaerobic arterial and mixed venous blood samples were analyzed for oxygen content with a Lex-O_2-Con (Lexington Instruments Model TL, Chestnut Hill, MA). SV was calculated from $\dot{Q}$ and HR, measured from ECG. TPR was calculated from $\dot{Q}$ and mean SAP.

Table 1. *Resting hematological values*

Parameter	Control	Furosemide	Dextran infusion
PV (l)	28.9±1.3	26.5±1.5*	35.3±1.6*
TBV (l)	41.7±2.4	37.2±2.1*	46.4±1.8*
RCV (l)	12.8±1.2	10.7±0.9*	11.1±0.8
PCV ($l\,l^{-1}$)	0.35±0.01	0.33±0.02	0.27±0.02*
Hb ($g\,l^{-1}$)	137 ±3.0	135 ±6.0	105 ±7.0*
Vis (centipoise)	1.2 ±0.1	1.1 ±0.1	1.1 ±0.1

Values are means ± SE for 6 subjects. PV, plasma volume. TBV, total blood volume. RCV, red cell volume. PCV, packed cell volume. Hb, hemoglobin. Vis, viscosity. Significantly different from control: * $p<0.05$.

Measurement of plasma volume. A modified Evans blue dye dilution method[9] was used to measure the PV of each horse on three occasions: 1) under control conditions; 2) immediately after DI, and 3) 3 hours after FUR. *In vitro* experiments determined the accuracy of this method for measuring PV to be ±2%.[11] Total BV and red cell volume were calculated using venous hematocrit.[9]

Plasma volume expansion. PV was expanded by infusing 6% dextran solution in 0.9% saline (mean molecular weight 70000; Gentran, Baxter Healthcare, Morton Grove, IL) through the open lumen Millar catheter placed in the pulmonary artery. The amount of infusion was selected to increase the PV 25% above the estimated normal PV (i.e. 4% of body weight), an increase similar to that previously reported in response to exercise training in horses.[16]

Plasma volume reduction. Furosemide (Lasix; National Laboratories) was administered intravenously ($1\ mg\ kg^{-1}$) 3 hours prior to the exercise test.

Statistical analysis. A split-plot, repeated measures analysis assigned in Latin squares fashion was used to determine statistical significance of the effects of DI and FUR (whole plot treatment, subplot running speed). A one-way analysis of variance was used to determine differences in PV measured at rest. The null hypothesis was rejected when $p<0.05$. Results are presented as means ± SE.

RESULTS

Control studies

Control study hemodynamics at rest and during exercise are summarized in Tables 1 and 2. The two Quarter horses ran at speeds that averaged 6.0, 8.5 and 12 $m\ s^{-1}$ compared to average running speeds of 8.6, 11.3, and 13.8 $m\ s^{-1}$ for the Thoroughbreds. $\dot{V}O_2$ under control conditions averaged 1.6±0.1 $l\ min^{-1}$, at rest and 28.9±2.0, 43.4±3.9, and 61.3±2.0 $l\ min^{-1}$ respectively at 50, 75, and 95–100% of $\dot{V}O_2$ (Table 2). Following FUR and DI, $\dot{V}O_2$ at rest and during exercise did not differ significantly from the corresponding CON values.

Effects of plasma volume expansion on the hemodynamic responses at rest and during exercise

Rest Infusion of 6.4±0.3 l of the dextran solution resulted in a 22% increase in PV measured at rest (Table 1). BV increased by only 4.7 l, because the volume of circulating red blood cells at the time of measurement was 1.7 l lower than the control. Differences in red cell volume may have been related to anxiety of the horses that caused red blood cells to be released from the spleen.

In conjunction with the significant increase in plasma volume, both hematocrit and hemoglobin were reduced, whereas viscosity of venous blood remained unchanged (Table 1). With the horses standing quietly,

Table 2. *Hemodynamic responses at rest and during exercise following plasma expansion and furosemide administration*

Parameter	Rest	50%	75%	95–100%
Control				
$\dot{V}O_2$ (l min^{-1})	1.6 ±0.1	28.9 ±2.0	43.4 ±3.9	61.3 ±2.0
RAP (mmHg)	6 ±1	20 ±3	28 ±3	40 ±3
SV (ml)	850 ±76	1 228±90	1 426±111	1 443±46
HR (b min^{-1})	39 ±1	167 ±5	183 ±2	203 ±3
$\dot{Q}$ (l min^{-1})	33.2±2.8	205 ±19	261 ±21	293 ±8
BP (mmHg)	115 ±7	151 ±7	165 ±5	186 ±6
TPR (dyn s^{-1} cm-S)	292 ±40	61 ±4.6	52 ±2.7	51 ±1.5
Ca-vO_2 (ml dl^{-1})	4.9 ±0.4	14.3 ±0.6	18.0 ±0.9	20.9 ±0.5
PCV (l l^{-1})	0.35±0.01	0.45 ±0.01	0.50 ±0.01	0.49 ±0.02
Vis (centipoise)	1.18±0.05	1.32 ±0.08	1.53 ±0.05	1.76 ±0.11
Furosemide				
$\dot{V}O_2$ (l min^{-1})	1.6 ±0.3	29.4 ±1.4	42.8 ±1.9	57.6 ±2.1
RAP (mmHg)	3 ±1*	12 ±1*	17 ±2*	31 ±3
SV (ml)	671 ±57	1 208±70	1 247±84*	1 356±76
HR (b min^{-1})	39 ±2	159 ±7*	182 ±4	205 ±3
Q (l min^{-1})	26.3±2.3	192 ±12*	227 ±14*	278 ±13
BP (mmHg)	111 ±5	140 ±4	158 ±4	176 ±6*
TPR (dyn s^{-1} cm-S)	285 ±65	59 ±1.8	57 ±2.3	51 ±2.1
Ca-vO_2 (ml dl^{-1})	5.2 ±0.2	15.0 ±1.0	18.6 ±0.7	20.9 ±1.1
PCV (l l^{-1})	0.33±0.02	0.44 ±0.02	0.60 ±0.02	0.52 ±0.02
Vis (centipoise)	1.13±0.09	1.67 ±0.23	1.69 ±0.06	1.93 ±0.12
Dextran infusion				
$\dot{V}O_2$ (l min^{-1})	2.0 ±0.3	30.8 ±2.0	47.1 ±2.3	62.2 ±2.1
RAP (mmHg)	10 ±2*	25 ±3*	31 ±3	45 ±4
SV (ml)	1 058±74	1 467±85*	1 543±72	1 670±54
HR (b min^{-1})	51 ±7*	165 ±5	186 ±3	203 ±4
$\dot{Q}$ (l min^{-1})	54.0±11.2*	242 ±16*	287 ±15	339 ±10*
BP (mmHg)	124 ±4	152 ±7	165 ±6	184 ±6
TPR (dyn s^{-1} cm-S)	221 ±41	50 ±1.4	46 ±1.6	44 ±1.3
Ca-vO_2 (ml dl)	4.0 ±0.4*	12.7 ±0.4	16.4 ±0.5*	18.4 ±0.3
PCV (l l^{-1})	0.27±0.02*	0.40 ±0.01*	0.45 ±0.02*	0.48 ±0.02
Vis (centipoise)	1.08±0.01	1.37 ±0.06	1.55 ±0.11	1.88 ±0.12

Values are means ± SE; $n=6$. Measurements taken at rest and while exercising at 50, 75 & 90–100% of $\dot{V}O_2$ max following control, furosemide, and plasma expansion. $\dot{V}O_2$, oxygen uptake. RAP, mean right arterial pressure. SV, stroke volume. HR, heart rate. Q, cardiac output. BP, mean systemic arterial blood pressure. TPR, total peripheral resistance. Ca-vO_2, arterial venous oxygen content difference. PCV, packed cell volume. Vis, viscosity. Significantly different from control at same running velocity * $p<0.05$.

DI significantly increased RAP, $\dot{Q}$, and HR over control values. There were no significant differences in blood pressure or TPR (Table 2).

Exercise Both hematocrit and arterial oxygen content (CaO_2) were significantly lower than control values during exercise. These data indicate that a significant portion of the dextran was retained within the vascular system during exercise. Despite reductions in hematocrit, viscosity of venous blood was not altered.

RAP during exercise increased after DI (Table 2). There was a small variation in

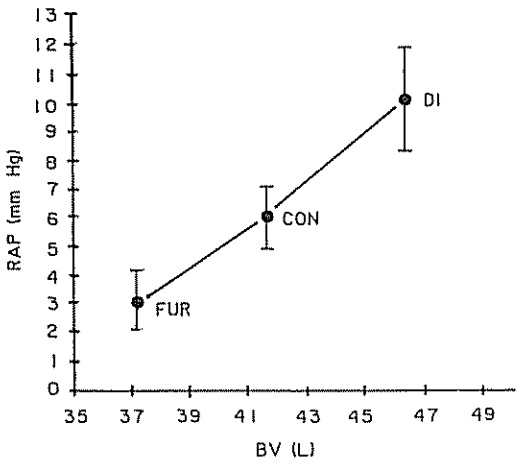

Fig. 1. Relationship between right atrial pressure (RAP) and total blood volume (BV) measured at rest under control (CON) conditions and following furosemide (FUR) administration and dextran infusion (DI). Values are means ± SE; $n=6$.

RAP within individual horses for repeated bouts of the same exercise. In a previous study, RAP measurements were essentially the same (within 1 mmHg) under similar conditions. This increase was associated with significant elevations of SV and $\dot{Q}$ (Table 2) and reductions in TPR arterial venous oxygen content difference ($Ca\text{-}vO_2$), CaO_2, and venous oxygen content (CvO_2). The increases in $\dot{Q}$ following DI were attributed to the increases in SV, because mean exercise HR was unchanged at all exercise intensities. TPR decreased in direct proportion to the increase in $\dot{Q}$, because blood pressure was identical to the control. A decline in $Ca\text{-}vO_2$ occurred in conjunction with the increase in $\dot{Q}$. The decline in $Ca\text{-}vO_2$ was associated with declines in both arterial and venous blood oxygen contents.

Effects of plasma volume reduction on the hemodynamic responses at rest and during exercise

Rest. Three hours after furosemide administration, PV was reduced by 8.3% (28.9±1.3 vs 26.5±1.5 l). Red cell volume was also significantly lower than the control (12.8±1.2 vs 10.7±0.9 l), resulting in an 11% decline in BV (Table 1). Hematocrit, hemoglobin, and viscosity were not significantly altered because a decline in circulating red cell volume occurred in conjunction with the decline in PV.

A decrease in PV following FUR resulted in a decrease in resting RAP (Fig. 1, Table 2) from 6±1 to 3±1 mmHg. There was a tendency for SV and $\dot{Q}$ to decrease and $Ca\text{-}vO_2$ to increase, with little or no change in HR, blood pressure, and TPR (Table 2). Unlike DI, which increased PV to a greater degree than FUR decreased it, FUR caused no significant alterations in the hemodynamic responses measured at rest.

Exercise. RAP was reduced an average of 34% during exercise (Table 2). Exercise SV declined significantly at 75% VO_2max (1427±111 to 1251±84 ml). The 8% decline in $\dot{Q}$ during exercise with FUR was attributed to a decrease in SV because HR was unchanged. Associated with the decrement in $\dot{Q}$ was a significant reduction in CvO_2.

Unlike DI, FUR resulted in blood pressures that were consistently lower than control during exercise at all running speeds (Table 2); however, TPR was not altered.

DISCUSSION

Effects of blood volume manipulation on Mean right atrial pressure

The present findings indicate that BV manipulation has profound effects on the cardiovascular system at rest and during exercise. Altering BV at rest in these six horses by infusing dextran or administering furosemide produced corresponding changes in RAP such that the relationship between BV and RAP was nearly linear (Fig. 1).

Stroke volume. Resting SV was altered proportionally to the change in RAP (Fig. 2). Apparently, altering BV has a direct effect on SV by altering RAP or central venous filling pressure, which presumably increases ventricular filling when compliance of the myocardium is not limiting. Although the

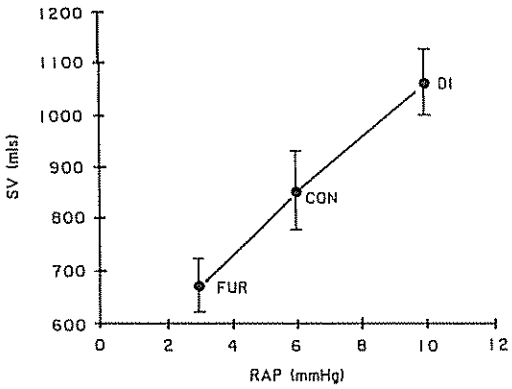

Fig. 2. Relationship between resting stroke volume (SV) and mean right atrial pressure (RAP) at control (CON) and following furosemide (FUR) administration and dextran infusion (DI). Values are means ± SE; $n=6$.

relationship between SV and RAP during exercise (Fig. 3) was not linear as that at rest, factors other than ventricular filling, such as afterload and contractility, also influence SV and may account for such differences. Because HR remained unchanged by either treatment, changes in $\dot{Q}$ during exercise can be attributed to changes in SV.

In addition, DI, which acutely increased BV 20% (an amount similar to that reported in response to short-term exercise training),[16] produced an increase in SV similar to that reported in response to 5–10 weeks of exercise training in the horse.[8] This finding supports a previous hypothesis[11] that the increase in SV typically displayed after moderate endurance training does not necessarily indicate that intrinsic myocardial adaptations have occurred, since this magnitude of increase could also result from extramyocardial adaptations that increase ventricular filling (e.g., hypervolemia).

Mean systemic arterial blood pressure. Following DI, the increase in $\dot{Q}$ was associated with a significant decline in TPR that served to keep blood pressure at its control value. Although maintenance of blood pressure may involve a variety of feedback responses, our data suggests that the increase in RAP following DI may have elicited a decline in peripheral vascular resistance by two different routes. First, low pressure receptors may be stimulated and influence the vasomotor center of the brain in response to changes in RAP.[22] Changes in central venous filling pressure caused alterations in vascular resistance in the splanchnic area,[12] skin, and muscle,[3,6,25] which could account for the observed response. Similar results were found when BV was lowered in human subjects by detraining; the subjects displayed a marked increase in TPR during exercise and subsequent reversal of this increase with acute PV expansion.[3]

Secondly, ANF (atrial natriuretic factor) is released in response to atrial stretch and has the ability to relax vascular smooth muscle. ANF may also be involved in reducing peripheral vascular resistance when RAP is increased.[19,23]

In addition, local autoregulatory controllers of vascular resistance may contribute to the observed responses. However, local responses are believed to alter blood flow to match the metabolic needs of the nearby tissue. Since each of the subjects exercised at the same intensity, with unaltered VO_2's following each treatment, we would not expect local autoregulation of vascular resistance to differ between treatments.

Furosemide results in a reduction in $\dot{Q}$ during exercise that was not completely

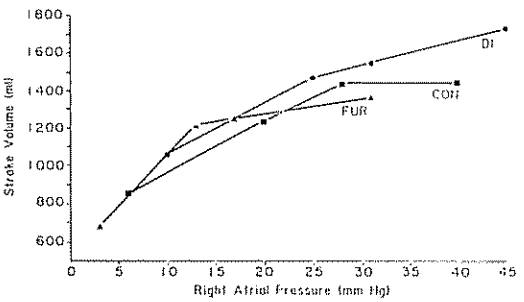

Fig. 3 Ventricular function curves showing stroke volume as a function of right atrial pressure at rest and during three levels of exercise measured under control (CON) conditions and following furosemide (FUR) administration and dextran infusion (DI).

matched by an increase in TPR. Therefore, blood pressure decreased by an average of 9 mmHg during exercise. The decline in RAP associated with FUR may elicit reflex mechanisms that attempt to keep blood pressure constant, but this activity is countered by the drug's direct effect on vascular smooth muscle. Furosemide increases synthesis and inhibits degradation of prostaglandin E and I_2, both potent vasodilators.[1,2] In addition, furosemide also influences sodium and chloride flux across cell membranes and indirectly affects vascular smooth muscle tone.[14] If the observed decline in blood pressure was due to furosemide's direct effect on vascular smooth muscle, it would be of interest to repeat this experiment using a method to reduce BV that does not alter vascular tone and observe the effects upon blood pressure and peripheral vascular resistance.

In summary, changes in circulating BV resulted in proportional changes in RAP. Through its direct effect upon SV and its reflexively mediated effect on TPR, RAP plays a key role in determining cardiovascular responses to exercise.

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