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EFFECTS OF FLUID REPLACEMENT ON RESPIRATORY FUNCTION: COMPARISON OF WHOLE BLOOD WITH COLLOID AND CRYSTALLOID

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Short title: Fluid replacement with blood, colloid or crystalloid

ABSTRACT

Background: While morbidity and mortality following fluid replacement with blood products, colloids and crystalloids have been reported, the consequences of these fluids on airway and respiratory tissue properties have not been fully characterized.

Objective: Separate assessment of airway resistance and respiratory tissue mechanics following fluid replacement with autologous blood (Group B), colloid (HES 6% 130/0.4, Group CO) or crystalloid solution (NaCl 0.9%, Group CR) after haemorrhage.

Design: Prospective, randomized study.

Setting: Experimental model of surgical haemorrhage and fluid replacement in rats.

Participants: Anaesthetized, ventilated rats randomly included in 3 groups (Group B: n=8, Group CO: n= 8, Group CR: n=9).

Intervention: Animals were bled in 6 sequential steps, each manoeuvre targeting a loss of 5% of total blood volume. The blood loss was then replaced stepwise in a 1:1 ratio with one of the three fluids.

Main outcome measure: After each step, airway resistance (Raw), tissue damping and elastance (H) were determined by forced oscillations. Oedema indices from lung weights and histology were also measured.

Results: Raw decreased in all groups following blood loss (-20.3±9.5[SD]% vs. baseline, $p<0.05$), and remained low following blood replacement (-21.7±14.5% vs. baseline, $p<0.05$), but was normalized by colloid (5.5±10.7%, NS). Crystalloid administration exhibited an intermediate reversal effect (-8.4±14.7%, NS). Tissue viscoelasticity increased following both blood loss and replacement, with no evidence of a significant difference in H between Groups CO and CR (NS). More severe oedema was observed in Groups CR and CO than in Group B ($p<0.05$), with no difference between the colloid and crystalloid solutions.

Conclusion: This model, which mimics surgical haemorrhage, yields no evidence of a difference between colloids and crystalloids with regard to the pulmonary consequences of blood volume restoration. The lung functional changes should therefore not play a key role in the optimum choice of fluid replacement therapy with these solutions.

INTRODUCTION

Blood loss during major surgery is associated with detrimental systemic and pulmonary consequences. Fluid replacement strategies under this condition are among the most polarizing issues in anaesthesia and intensive care practice. Physicians are routinely challenged with the choice of the best fluid replacement strategy for the treatment of haemorrhage from among blood products, various types of colloids or crystalloids. As an aftermath of the recent meta-analyses concerning the safety of hydroxyethyl-starch (HES) [1], this therapy should be considered with great caution, particularly in patients with increased capillary leakage. Thus, limited options are available for clinicians in fluid replacement strategies, in view of the risk of renal damage associated with the use of HES [2, 3], the appreciable costs of albumin, and the defects of haemostasis induced by gelatin solutions [4]. Crystalloids remain a rational option, but clinicians are reluctant to choose them because of the widespread belief of their fast extravasation, though this belief is based on old studies with limited evidence-based results [5-7].

We recently demonstrated that acute hypovolaemic shock and subsequent resuscitation with autologous blood affects the respiratory mechanics [8]. Although a milder, but sustained blood loss during a surgical procedure also requires fluid replacement therapy, the respiratory consequences of such a disorder have not been explored. The administration of blood products is often regarded as the gold standard therapy in this situation, with the main aim of maintaining the oxygen transport capacity. However, no evidence-based data are available that would allow a comparison of the changes in lung function between this consensual approach and goal-directed fluid therapy with colloids or crystalloids. Therefore the experimental study reported here focused on the development of a novel animal model with which to mimic continuous, hidden surgical bleeding and replacement of the lost blood. We also set out to compare the effects of blood, colloid and crystalloid solutions on the flow resistance of the airways and on the viscoelastic properties of the respiratory tissues and to attempt to relate these changes to pulmonary oedema indices. We hypothesized that the respiratory consequences of fluid resuscitation with blood differ from those observed after colloid and crystalloid solutions.

METHODS

Ethical approval for this study (no. I-74-50/2012) was provided by the Experimental Ethics Committee of the University of Szeged, Szeged, Hungary (Chairperson Prof. Gy. Szabó) on 7 December 2012, and granted by the Animal Health and Welfare Office of the local authorities in Hungary (no. XIV/152/2013, Chairperson Cs. Farle) on 9 January 2013.

Animal preparations

Anaesthesia was induced with an intraperitoneal injection of 5% chloral hydrate (400 mg/kg) in adult male Sprague Dawley rats (330 ± 38 g). Tracheal intubation was achieved with a polyethylene cannula (16-gauge, B. Braun Melsungen AG, Melsungen, Germany) after subcutaneous administration of local anaesthetics to ensure adequate analgesia around the surgical wound (lidocaine, 2-4 mg/kg). The rats were then placed in a supine position on a heating pad and the tracheal cannula was attached to a small animal ventilator (Model 683, Harvard Apparatus, South Natick, MA, USA), and mechanically ventilated with room air (70 breaths/min, tidal volume 7 ml/kg). A femoral vein was catheterized (Abocath 22 G) for drug delivery and for the fluid replacement. A femoral artery was cannulated (Abocath 22 G) and attached to a pressure transducer (Model TSD104A, Biopac, Santa Barbara, CA, USA) for continuous systemic blood pressure monitoring to assess mean arterial pressure (MAP), and to allow blood withdrawal, as part of the experimental protocol. The arterial pressure, ECG and heart rate (HR) were monitored continuously with a data collection and acquisition system (Biopac, Santa Barbara, CA, USA). Body temperature was kept in the 37 ± 0.5 °C range by using the heating pad.

Measurement of respiratory mechanics

The forced oscillation technique was applied in short (6-s-long) end-expiratory pauses interposed in the mechanical ventilation to measure the input impedance of the respiratory system (Zrs), as detailed previously [9]. Briefly, the ventilator was stopped at end-expiration and the tracheal cannula was switched from the ventilator to a loudspeaker-in-box system. The loudspeaker delivered a computer-generated small-amplitude (<1 cmH_2O) pseudorandom signal (23 non-integer multiples between 0.5 and 21 Hz) through a 100-cm-long, 2-mm-ID polyethylene tube. Two identical pressure transducers (model 33NA002D, ICSensors, Milpitas, CA, USA) were used to measure the lateral pressures at the loudspeaker end (P_1) and at the tracheal end (P_2) of the wave-tube. The signals P_1 and P_2 were low-pass filtered (5th-order Butterworth, 25-Hz corner frequency), and sampled with the analogue-digital board of a microcomputer at a rate of 256 Hz. Fast Fourier transformation with 4-s time windows and 95% overlapping was used to calculate the pressure transfer functions (P_1/P_2) from the 6-s recordings collected during apnoea. Zrs was calculated as the load impedance of the wave-tube [10]. The input impedance of the ET tube and the connections was also determined, and was subtracted from each Zrs spectrum.

A model containing a frequency-independent resistance (R) and inertance (I) and a tissue damping (G) and elastance (H) of a constant-phase tissue compartment [11] was fitted to the Zrs spectra by minimizing the weighted difference between the measured and the modelled impedance data. The tissue parameters characterize the damping (resistive) and elastic properties of the respiratory system. Raw and Iaw represent primarily the resistance and inertance of the airways, since the contribution of the chest wall to these parameters in rats is minor [12].

Lung histology

After completion of the experimental protocol, the rats were euthanized with an overdose of pentobarbital sodium (300 mg/kg iv). Midline thoracotomy was then performed and 4% formaldehyde was instilled into the right lung via the tracheal cannula at a hydrostatic pressure of 20 cmH_2O after clamping of the left main bronchus near the bifurcation. The right lung was dissected and placed into 4% buffered formalin until further processing. After complete fixation, transhilar horizontal sections (perpendicular to the longitudinal axes of the lung from the hilum) were embedded in paraffin. Two 5-μm sections were prepared in each lung specimen and were stained with haematoxylin-eosin. Digitalized images were used to obtain the oedema index around randomly selected pulmonary vessels by dividing the lumen area by the total area of the pulmonary vessel (oedema cuff area + vessel lumen area). Histological images were analysed by the same investigator in a blind fashion and in a random sequence by using JMicroVision image analysis software (version 1.2.7).

Three-to-four tissue samples were dissected from the different lobes of the non-fixated left lungs; these samples were weighed to establish the wet-to-dry weight ratio (W/D) as an index of the lung water content.

Experimental protocol

The rats were randomly assigned into one or other of the three protocol groups. The rats in Group B always received autologous heparinized blood (n = 8), while fluid replacement was performed with a colloid solution (HES 6% 130/0.4, Fresenius Kabi Deutschland GmbH, Bad Homburg v.d.H., Germany) in Group CO (n = 8), or with a crystalloid solution (NaCl 0.9%, B. Braun Melsungen AG, Melsungen, Germany) in Group CR (n = 9). The experimental protocol was started with standardization of the lung volume history through the administration of a hyperinflation via occlusion of the expiratory port of the ventilator when the animal had reached a steady-state condition (5-10 min after the starting of mechanical ventilation). The baseline respiratory mechanics was then established by measuring 3 or 4 reproducible Zrs data epochs. Haemorrhage was next induced by the withdrawal of 5% of the estimated total blood volume [13] via the femoral artery (Fig. 1). Three min later, another set of Zrs data was collected, including 3 individual measurements at 1-min intervals. The withdrawn blood was used for blood gas analyses (Cobas b221; Roche Diagnostics, Basel, Switzerland) to determine the haematocrit (Hct), pH and oxygen (PaO_2) and carbon dioxide ($PaCO_2$) partial tensions. The blood withdrawal and Zrs measurements were repeated once again in an identical manner. After completion of the first two steps of arterial haemorrhage, fluid replacement in accordance with the group allocations was performed by administering 5% of the total blood volume via the femoral vein. Three minutes after this manoeuvre, a set of Zrs data was recorded. The blood withdrawal-replacement procedure was repeated 4 more times, with the collection of Zrs data 3 min after each intervention. The total duration of resuscitation was around 90 min with each step lasting approximately 7 min. Further arterial blood gas analyses were performed from the fourth and sixth blood samples. After completion of the measurement protocol, the lungs were processed for oedema assessment, as detailed above.

Data analysis

The scatters in the parameters were expressed as SD values. The Kolmogorov-Smirnov test was used to test data for normality. Two-way repeated measures of analysis of variances (ANOVA) with the factors assessment time and group allocation was used to assess the effects of blood loss and replacement on the respiratory mechanical and haemodynamic parameters. The baseline respiratory mechanical parameters and oedema indices were compared by using one-way ANOVA tests. The Holm-Sidak multiple comparison procedure was applied to compare the different conditions (for repeated measures) or protocol groups (for independent groups). Correlation analyses between the variables were performed by using Pearson correlation tests. Statistical tests were carried out with the SigmaPlot software package (version 12.5, Systat Software, Inc., CA, USA) with a significance level of $p < 0.05$.

RESULTS

The body weights did not exhibit statistically significant differences between the protocol groups (344 ± 16.1 g for Group B, 320 ± 51.24 g for Group CO and 361 ± 20.7 g for Group CR). Table 1 demonstrates the baseline values of the respiratory mechanical parameters for the three experimental groups. No statistically significant differences were detected in the variables reflecting the airway or tissue mechanics.

The arterial blood gas parameters obtained at the beginning, at the midpoint and at the end of the experimental protocol are presented in Table 2. In Group B, Hct did not exhibit statistically significant changes throughout the protocol, whereas decreases in pH ($p < 0.001$) and PaO_2 ($p = 0.011$) were evidenced. As compared with the autologous blood, fluid replacement with colloid solution resulted in a lower Hct ($p < 0.001$), while crystalloid administration led to significant reductions in Hct ($p = 0.010$) and pH ($p = 0.009$). No difference in the changes in PaO_2 and pH was observed between the rats in Groups CR and CO. The decreases in Hct were more pronounced in Group CO than those in Group CR ($p = 0.032$).

Figure 2 depicts the changes in the airway and respiratory tissue mechanical parameters relative to the baseline. Blood withdrawal resulted in a systematic lowering of Raw. The fluid replacement with colloid in Group CO restored the baseline value of Raw, whereas the Raw remained diminished following the iv administration of autologous blood in Group B ($p = 0.005$). The changes in Raw after the iv injections of crystalloid solution in Group CR were intermediate ($p < 0.038$), with less obvious elevations in Raw after the third fluid replacement manoeuvre. Monotonous increases in G were observed throughout the protocol ($p < 0.001$), with no statistically detectable differences between the protocol groups. H was elevated in all groups, with significantly greater changes in Groups CR ($p = 0.005$) and CO ($p = 0.012$) than in Group B.

The oedema parameters obtained from the lung weights and from the histological analyses are to be seen in Fig. 3. The animals in both Groups CR and CO exhibited significantly greater wet-to-dry lung weight ratios ($p < 0.001$ for both), as also manifested in the perivascular pulmonary oedema indices ($p < 0.05$ for both).

The systemic haemodynamic changes for the 3 groups of rats are displayed in Fig. 4. The blood withdrawals caused MAP to decrease systematically, while it was restored to the previous values by fluid replacements, regardless of the group allocation. HR displayed gradual increases in all groups of rats, with significant changes from R3, W3 and R2 in Groups B, CR and CO, respectively.

The relationships between the wet-to-dry lung weight ratio and the relative change in H are presented in Fig. 5. Pooling of the data from the 3 protocol groups revealed significant correlations between the macroscopic oedema index and the increased stiffness of the respiratory system ($R = 0.55$, $p < 0.01$).

DISCUSSION

In the present study, an experimental model that mimics continuous insidious surgical bleeding and fluid replacement was applied for a direct assessment of the mechanical properties specific for the airway and respiratory tissues following a blood loss and its treatment with solutions commonly used in clinical practice. The decreased airway resistance subsequent to the haemorrhage remained low after fluid therapy with autologous blood, whereas it has re-elevated back to baseline by the administration of colloid and increased partially by fluid replacement with crystalloid. The respiratory tissues stiffened more markedly in the animals receiving colloid or crystalloid, with no difference in effect between these solutions. These adverse tissue mechanical changes were also reflected in the alterations in the oedema indices determined by lung weighing and by histology.

There has recently been an extensive debate concerning the optimum fluid replacement therapy following blood loss from the aspects of the type and the amount of the administered solution. While the lungs are primarily affected in consequence of the fluid therapy, no information is currently available on the airway and tissue mechanical changes. The administration of blood products is often considered to ensure the oxygen transport by maintaining the normal haemoglobin content. Restoration of the circulatory blood volume by blood products has a beneficial effect on the preservation of sufficient microcirculation with minimal morphologic damage or ischaemic cell injury [14, 15]. Similarly to previous findings, the blood volume loss in the present study led to bronchodilation, which is most probably due to the compensatory increase in thoracic gas volume and/or the elevated levels of circulatory catecholamines [8]. The present findings extend these results in a different model of haemorrhage without inducing the severe hypovolaemia characteristic of hidden, leaking bleeding during major surgery.

While recent studies have focused on the morbidity and mortality related to colloid or crystalloid administrations as fluid replacement therapy [1, 2, 16], the pulmonary effects of these solutions are mainly based on empirical investigations without firm evidence [5-7]. As far as we are aware, the present study addresses for the first time the respiratory mechanical changes in response to common fluid replacement strategies and attempts to establish their relationship to the oedema indices in an experimental model of surgical bleeding.

Our results demonstrate that the Raw essentially remains lowered after administration of autologous blood. The lack of a complete recovery in airway tone may be related to the relaxation potential of heparin [17]. However, a comparison of heparinized and non-heparinized colloid solutions revealed no difference in their bronchial effects (data not shown), and the potential role of heparin can therefore be excluded. Alternatively, the depressed Raw may be attributed to the presence of bronchoactive mediators in the sequestered blood, with the particular importance of the increased levels of adrenaline and noradrenaline in the withdrawn and subsequently re-administered blood [8]. Conversely, the findings revealed a complete reversal of the haemorrhage-induced bronchodilation by colloid. This suggests the importance of the interactions between circulatory changes and airway mechanics following a blood loss, with recovery of the original airway geometry through restoration by approaching the initial circulatory volume. The increases in Raw following colloid administration may be attributed to a distension of the bronchial submucosal vessels and/or to the oedema formation resulting in airway wall thickening, or an exudation into the airway lumen [18]. A similar concept can be applied to the initial results obtained with crystalloid solution, the first administration of which fully reversed the decreased Raw, when its entire volume was likely to remain in the vascular bed. This effect of the elevated intravascular volume may have been abolished in the rats of Group B due to the presence of catecholamines in the readministered autologous blood.

The tissue viscoelastic parameters following blood administration revealed slight, gradual increases, which can be attributed to the atelectasis and subsequent lung volume loss induced by the anaesthesia and mechanical ventilation in the supine position. This phenomenon was confirmed by the decrease in PaO_2, which suggests the loss of alveolar surface available for gas exchange. An important finding of the present study is the more marked gradual impairment of the respiratory tissue viscoelasticity in the animals receiving colloid or crystalloid solution (Fig. 2). This difference may arise from the variable rheological properties of the administered fluids that may contribute to the altered respiratory tissue behaviour [19], or from haemodilution-related changes in the colloid osmotic pressures. These phenomena result in oedema development affecting directly the tissue viscoelasticity. Since these adverse changes were also reflected in the oedema indices (Figs 3 and 5), the primary role of the accumulating perivascular oedema fluid in the compromised respiratory tissue stiffness can be anticipated. It is noteworthy that no evidence of a difference was found between colloid and crystalloid treatments either in the changes in the tissue mechanics or in the oedema indices. These results suggest the equivalence of these fluid replacement strategies in terms of compromising the lung tissue viscoelasticity, and as regards pulmonary oedema formation. This correspondence is also reflected in the lack of difference in the changes of blood oxygenation following the two fluid replacement regimes (Table 2). These findings are in qualitative agreement with previous results that demonstrated the lack of difference between colloid and crystalloid solutions in influencing the extravascular lung water, pulmonary leak index and lung injury score [20-22]. However, it should be borne in mind that this may hold true only in the relatively short time frame (~90 min) covered by our protocol, and systematic assessments of the prolonged effects would require further investigations.

An important methodological aspect of our protocol is related to the nature and the volume of the administered fluid. There is still a debate in the literature on the nature of fluid to be considered for resuscitation [23]. Conflicting reports aroused from recent meta-analyses with some authors suggesting the safe use of albumin in critically ill patients [24], while others do not recommend its use because of lack of robust evidence for its effectiveness to reduce mortality [25]. The very recent international consensus promotes the use of crystalloids against both HES and albumin solutions [23]. Since the aim of the present study was primarily to compare the effect of three basic fluid replacement strategies, we deliberately selected HES, as the colloid solution comparator. As concerns the crystalloid solution, various types are available for fluid replacement therapy, with slightly different ingredients resulting in somewhat variable osmolarities. Since there is an evolving debate on the choice of balanced salt solutions and normal saline, this latter offers similar osmolarity with the other 2 fluid replacement strategies. Thus, isotonic normal saline rather than the hypotonic Ringer's lactate was selected for a comparison with the slightly hypertonic HES 6% 130/0.4 [26]. As concerns the volume of crystalloid solution for fluid replacement, no evidence-based recommendations are available. Whereas textbooks conventionally state that the volume of crystalloids to be administered should be 3- to 4-fold the blood loss [27], recent studies question this, suggesting a ratio close to 1:1 [2, 7, 28]. Since the acute effect of fluid replacement was at the focus of interest in the present study, the same volume was chosen for the blood loss and replacement for both solutions (5% of the total blood volume). The rationale of this approach was confirmed by the lack of difference in MAP and HR between the protocol groups, which agrees with the concept of goal-directed therapy [28, 29].

A methodological limitation of our findings is associated with the use of total respiratory impedance data to assess pulmonary changes. While Raw accurately reflects the flow resistance of the airways, the chest wall contributes significantly to the tissue parameters G and H [12]. Nevertheless, the viscoelastic properties of the chest wall exhibited negligible changes following the induction of severe oedema with oleic acid [30]. Thus, our results are likely to reflect pulmonary changes; however, their magnitude may be somewhat underestimated due to the masking effect of the chest wall. Another methodological limitation is related to the species difference between small rodents and humans necessitating careful extrapolation of our data to a clinical situation. While rats have substantially higher Raw, G and H than humans, no major differences exist between mammalian species in the oscillatory mechanics besides scaling factor [31].

In summary, our results have provided experimental evidence of the dissociated changes in the airway and tissue mechanical properties following surgical-type bleeding and its treatment with autologous whole blood, colloid or crystalloid solution in a volume that fully restored mean arterial pressure. The measurement of respiratory mechanical, histological and gas exchange consequences of blood loss and consecutive fluid replacement strategies revealed no differences between fluid replacement with colloid and crystalloid. The two solutions demonstrated similar abilities to compromise the lung tissue viscoelasticity subsequent to mild perivascular oedema formation. These findings highlight the differences in behaviour of the respiratory system following fluid replacement with blood, colloid or crystalloid: a sustained bronchodilation is expected after the administration of autologous blood, without significant lung tissue changes, whereas colloids and crystalloids tend to restore the basal airway tone at the expense of similar deteriorations in lung tissue viscoelasticity.

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FIGURE LEGENDS

Figure 1. Scheme of the experimental protocol. BL: baseline, W1-W6 blood withdrawals, R1-R5: fluid replacements, Zrs: measurement of respiratory impedance data, BG: assessment of arterial blood gas.

Figure 2. Changes in the airway (Raw: airway resistance) and tissue mechanics (G: damping, H: elastance) relative to the baseline (BL) during blood withdrawals (W1-W6) and fluid replacements (R1-R5) with autologous blood (Group B), colloid (Group CO) or crystalloid (Group CR). BV: total blood volume. *: $p < 0.05$ vs. Group B within a condition, #: $p < 0.05$ vs. Group CO within a condition.

Figure 3. Oedema indices obtained by relating the wet lung weight to the dry weight (left) and by relating the perivascular oedema area to the total vessel area on histological sections obtained in rats receiving autologous blood (Group B), colloid (Group CO) or crystalloid (Group CR). *: $p < 0.05$.

Figure 4. Systemic haemodynamic parameters (MAP: mean arterial pressure; HR: heart rate) during blood withdrawals (W1-W6) and fluid replacements (R1-R5) with autologous blood (Group B), colloid (Group CO) or crystalloid (Group CR); BV: total blood volume. *: $p < 0.05$ vs. BL within a group.

Figure 5. Relationship between the changes in oedema index (wet weight / dry weight) and in respiratory elastance (H) in rats receiving autologous blood (Group B), colloid (Group CO) or crystalloid (Group CR).

	Raw (cmH_2O.s/l)	G (cmH_2O/l)	H (cmH_2O/l)
Group B	54.4 (7.6)	1034 (93.2)	5332 (761.6)
Group CO	52.3 (10.9)	1061 (131.3)	5293 (1139.6)
Group CR	51.7 (9.9)	912 (105.0)	4533 (546.0)

Table 1. Mean (SD) values of the airway resistance (Raw), tissue damping (G) and elastance (H) obtained under the baseline conditions in the three groups of rats.

	Hct (%)			pH			PaO$_2$ (mmHg)		
	W1	W4	W6	W1	W4	W6	W1	W4	W6
Group B	34.4	34.5	33.9	7.52	7.44*	7.43*	79.4	69.5	63.3*
	(3.4)	(5.3)	(2.4)	(0.06)	(0.06)	(0.03)	(15.7)	(17.1)	(14.3)
Group CO	32.7	31.7	24.2$^{*\#}$	7.51	7.40*	7.40*	80.4	54.9*	63.7*
	(3.6)	(3.6)	(5.0)	(0.06)	(0.03)	(0.06)	(8.7)	(7.0)	(6.7)
Group CR	33.8	31.1	28.5$^{*\#\$}$	7.51	7.42*	7.36$^{*\#}$	79.9	63.0*	64.9*
	(2.28)	(7.2)	(5.3)	(0.06)	(0.03)	(0.06)	(16.8)	(7.8)	(12.3)

Table 2. Mean (SD) parameter values derived from arterial blood samples obtained at the first (W1), fourth (W4) and last (W6) withdrawal. Hct: haematocrit, PaO$_2$: arterial partial pressure of oxygen. *: $p < 0.05$ vs. W1, #: $p < 0.05$ vs. Group B, \$: $p < 0.05$ vs. Group CO.

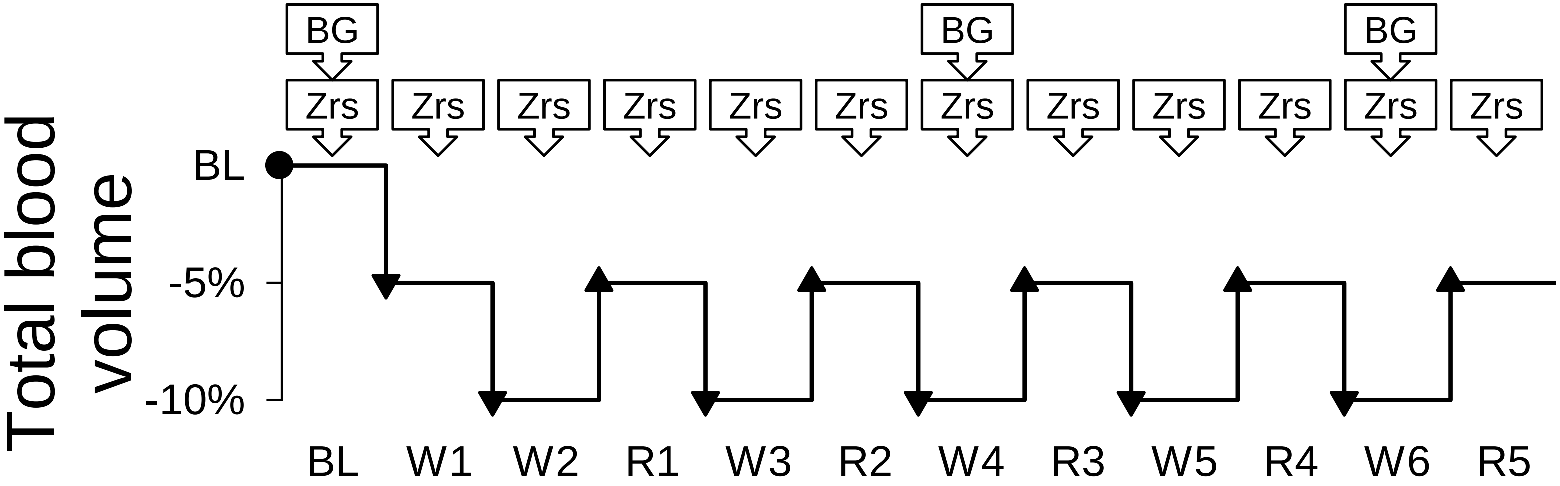
BG
BG
BG
Zrs
Zrs
Zrs
Zrs
Zrs
Zrs
Zrs
Zrs
Zrs
Zrs
Zrs
Zrs
Total blood volume
BL
-5%
-10%
BL
W1
W2
R1
W3
R2
W4
R3
W5
R4
W6
R5

Figure 1

Figure 2

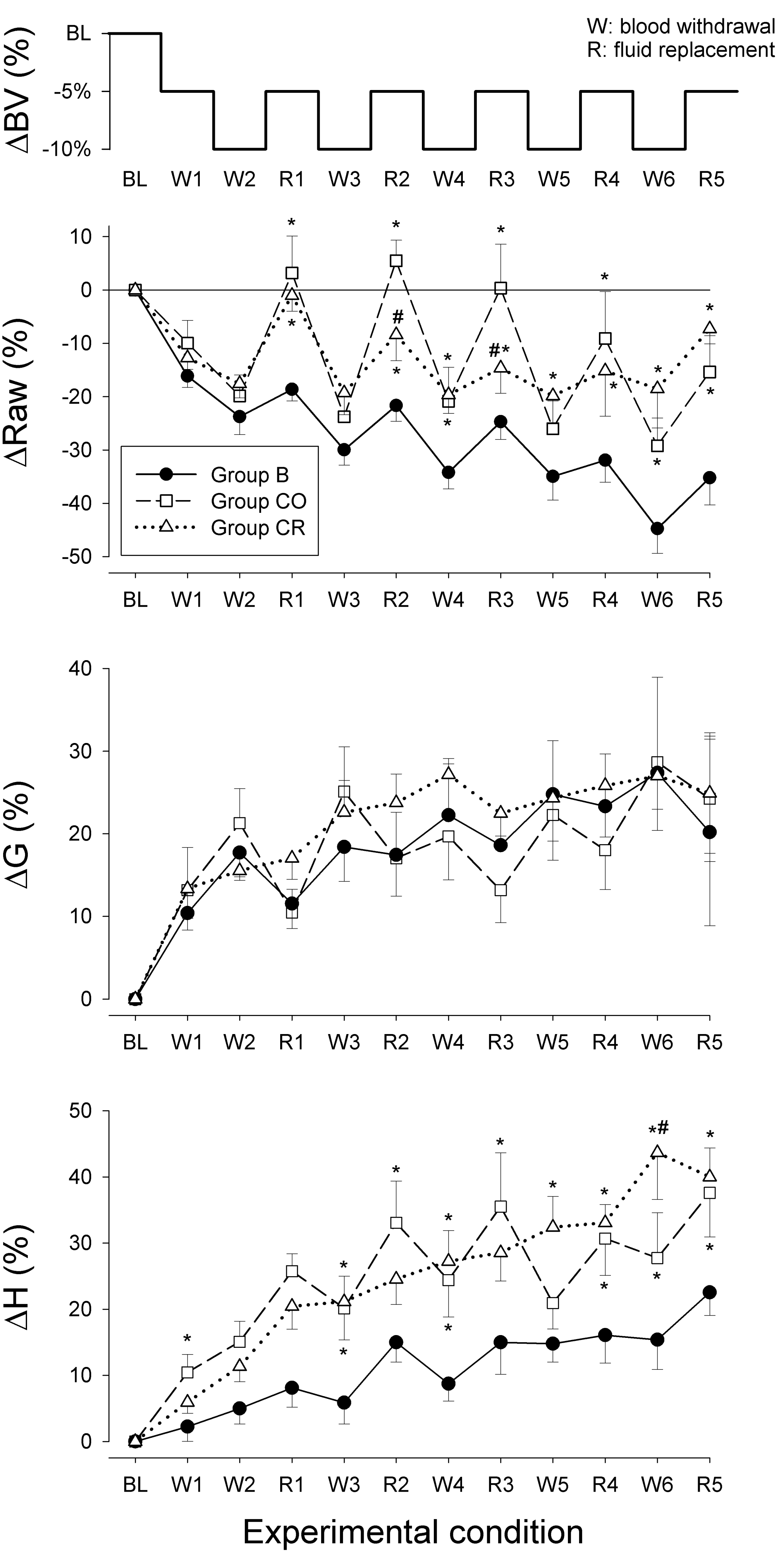

Figure 2

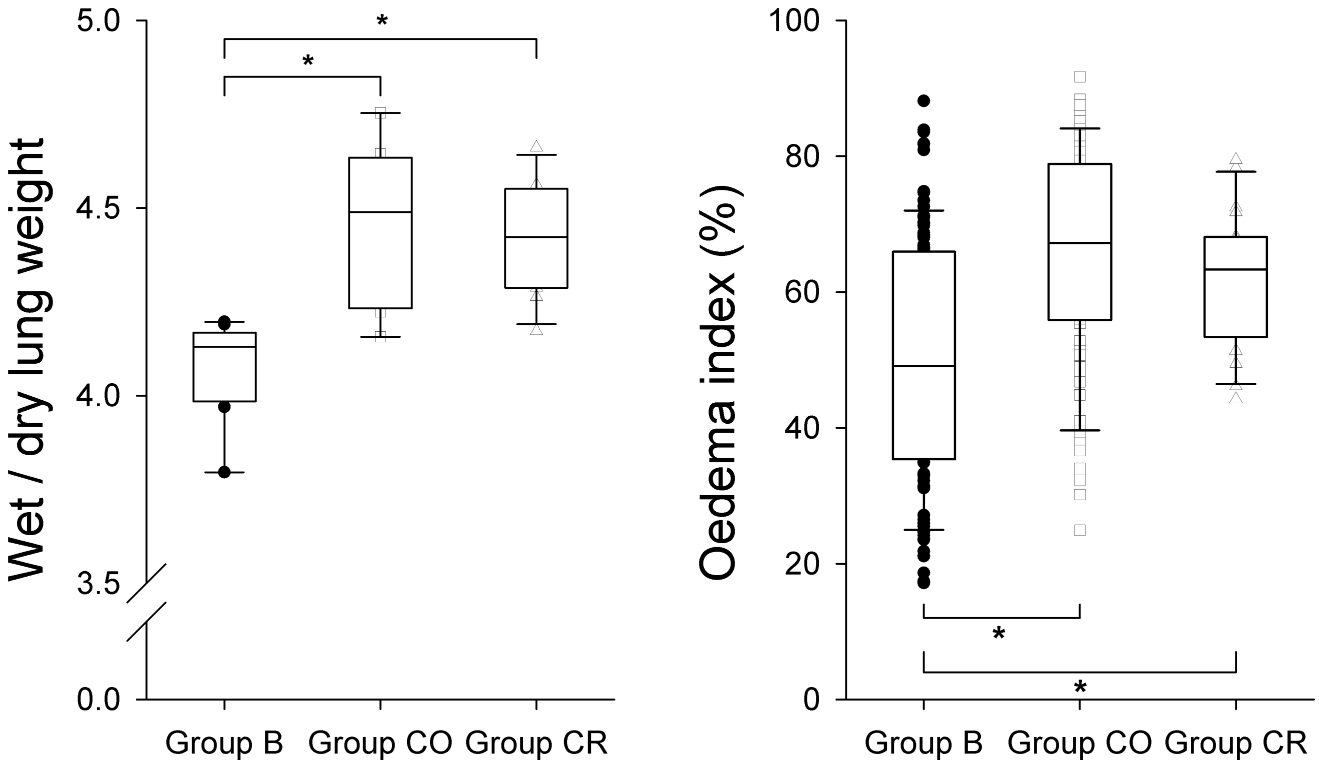
*
*
Wet / dry lung weight
5.0
4.5
4.0
3.5
0.0
Group B
Group CO
Group CR
100
80
60
40
20
0
Oedema index (%)
*
*
Group B
Group CO
Group CR

Figure 3

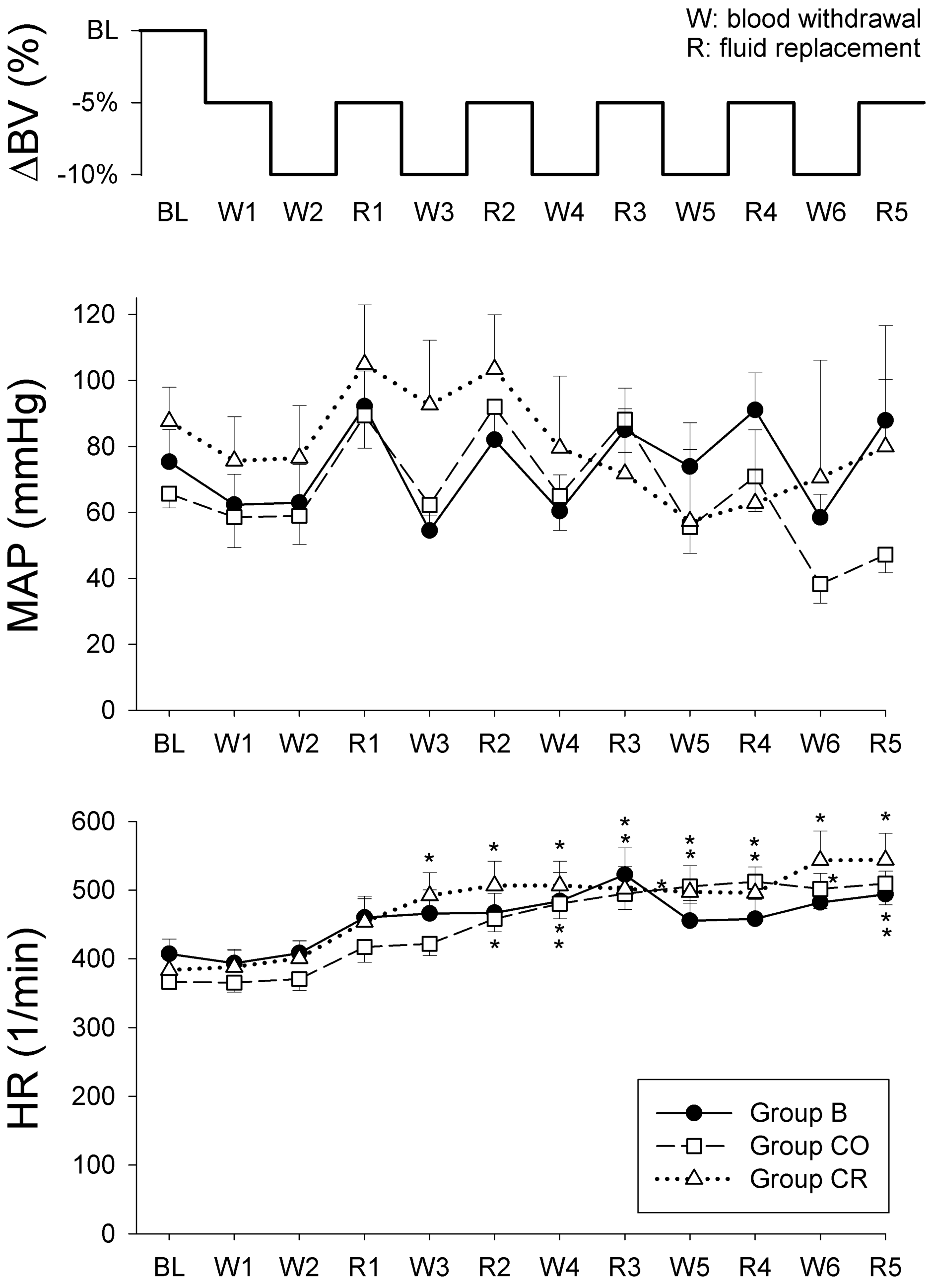
W: blood withdrawal
R: fluid replacement
ΔBV (%)
BL
-5%
-10%
BL
W1
W2
R1
W3
R2
W4
R3
W5
R4
W6
R5
MAP (mmHg)
0
20
40
60
80
100
120
HR (1/min)
0
100
200
300
400
500
600
*
Group B
Group CO
Group CR

Figure 4

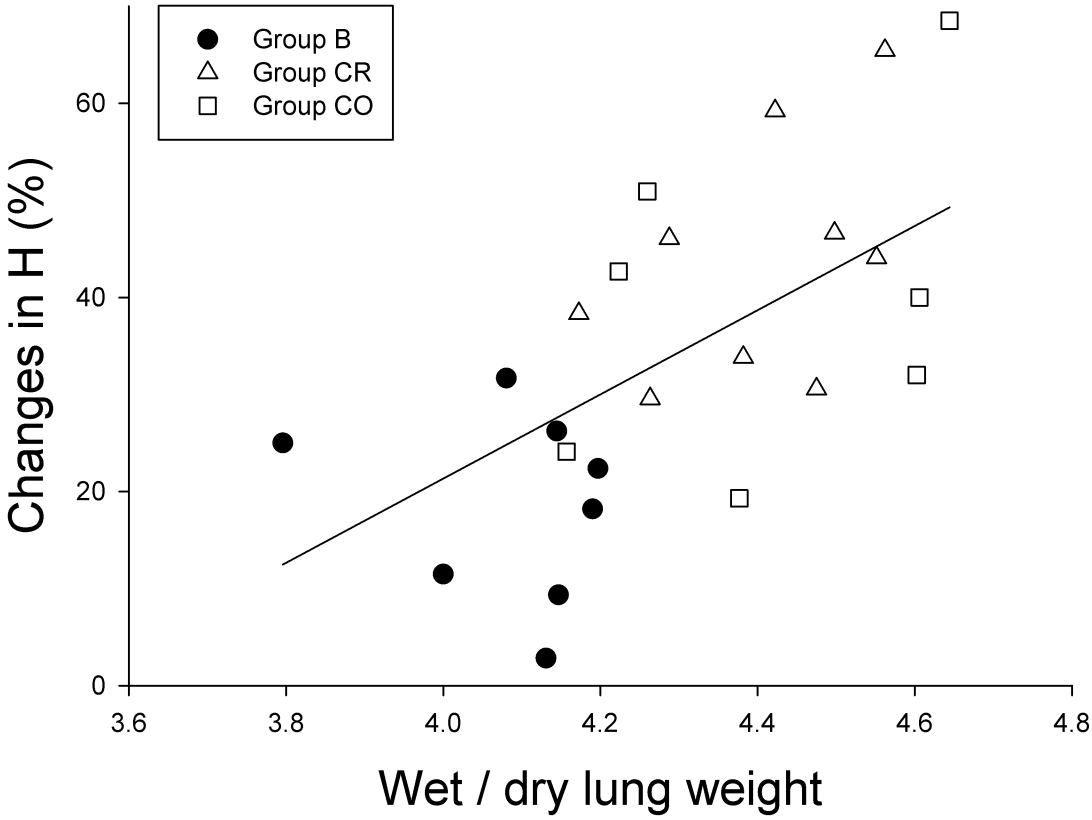
Group B
Group CR
Group CO
Changes in H (%)
0
20
40
60
3.6
3.8
4.0
4.2
4.4
4.6
4.8
Wet / dry lung weight

Figure 5