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Component reductions in oxygen delivery generate variable haemodynamic and stress hormone responses

A. Dyson[1], N. Ekbal[1], M. Stotz[1,2], S. Barnes[1], J. Carré[1], S. Tully[1], S. Henderson[1], L. Barrett[1] and M. Singer[1]*

[1] Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, London, UK
[2] Centre for Perioperative Medicine and Critical Care Research, Imperial College Healthcare NHS Trust, St Mary's Hospital, London, UK

* Corresponding author. E-mail: m.singer@ucl.ac.uk

Editor's key points

- Oxygen delivery is affected by cardiac output, haemoglobin, and oxyhaemoglobin saturation, but changes in one of these alone may have differing effects.
- Rats were subjected to circulatory, anaemic, or hypoxic hypoxia either rapidly or over 30 min.
- The different causes of decreased global oxygen delivery had varying effects.
- Rapid or slower insults also had differing effects.

Background. In clinical practice, global oxygen delivery (DO_2) is often considered as a whole; however pathological and adaptive responses after a decrease in individual constituents of the DO_2 equation (cardiac output, haemoglobin, oxyhaemoglobin saturation) are likely to be diverse. We hypothesized that an equivalent decrease in DO_2 after reductions in each separate component of the equation would result in different haemodynamic, tissue oxygenation, and stress hormonal responses.

Methods. Anaesthetized, fluid-resuscitated male Wistar rats were subjected to circulatory, anaemic, or hypoxic hypoxia (by haemorrhage, isovolaemic haemodilution, and breathing a hypoxic gas mix, respectively), produced either rapidly over 5 min or graded over 30 min, to a targeted 50% decrease in global oxygen delivery. Sham-operated animals acted as controls. Measurements were made of haemodynamics, skeletal muscle tissue oxygen tension, blood gas analysis, and circulating stress hormone levels.

Results. Whereas haemorrhage generated the largest decrease in cardiac output, and the greatest stress hormone response, haemodilution had the most marked effect on arterial pressure. In contrast, rapid hypoxaemia produced a minor impact on global haemodynamics yet induced the greatest decrease in regional oxygenation. A greater degree of hyperlactataemia was observed with graded insults compared with those administered rapidly.

Conclusions. Decreasing global oxygen delivery, achieved by targeted reductions in its separate components, induces varying circulatory, tissue oxygen tension, and stress hormone responses. We conclude that not all oxygen delivery is the same; this disparity should be emphasized in classical teaching and re-evaluated in patient management.

Keywords: cardiac output; haemodynamics; haemoglobin; stress hormones; tissue oxygenation

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Oxygen transport from the atmosphere to mitochondria, where the bulk of the body's oxygen consumption takes place, is an adaptive and highly regulated series of physiological processes. The quantity of oxygen delivered by the macrocirculation to tissues depends on the product of arterial oxygen content and cardiac output. The main arteries of the macrocirculation offer little resistance to blood flow, allowing oxygen to be transported over large distances by bulk flow. Blood flow, and thus oxygen delivery, within organ systems is then fine-tuned by the microcirculation. This is a finely regulated system as oxygen must not only be delivered, but also distributed within the organ to meet the specific metabolic demands of each cell.[1] In 1920, Sir Joseph Barcroft[2] published a classification of the 'hypoxias' that describe a decrease in each component of the oxygen delivery equation:

$$\text{Oxygen delivery } (DO_2) = [1.39 \times \text{Hb} \times Sa_{O_2} + (0.003 \times Pa_{O_2})] \times \text{Cardiac output}$$

where Hb is haemoglobin, Sa_{O_2} the saturation of Hb with arterial O_2, and Pa_{O_2} the arterial O_2 tension.

The decrease in cardiac output, haemoglobin, and the proportion of haemoglobin that is oxygen bound was described as circulatory, anaemic, and hypoxic hypoxia, respectively. This equation has become an integral part of conceptual teaching and a cornerstone of acute haemodynamic

management with a key treatment goal being rapid restoration[3] or even 'supra-normalization'[4 5] of oxygen delivery values through supplementation of oxygen, fluid and blood transfusion, and inotropic drugs. However, while oxygen delivery is routinely considered a whole entity, the pathological and adaptive responses after a decrease in each constituent part are likely to be diverse. We were unable to find any prior study that specifically addresses this question for equivalent, component-specific decreases in oxygen transport with concurrent measures of circulatory, regional oxygenation and endocrine patterns. In this study, we investigated the effects on global haemodynamics, stress hormone responses, and regional tissue oxygenation after reductions in the individual components of the oxygen delivery equation targeted to achieve a 50% decrease in total oxygen delivery.

Methods

All experiments were performed under a UK Home Office licence and local ethical committee approval. Male Wistar rats (~300 g body weight) were anaesthetized with isoflurane (2–5% in room air), although remained spontaneously breathing throughout. Adequate depth of anaesthesia was ensured throughout by assessing the stability of arterial pressure, heart rate, and lack of flexor responses to a paw-pinch. Rectal temperature was maintained at 37°C by placing the animals on a heated mat. Cannulation of the left common carotid artery was performed for arterial pressure monitoring, blood sampling, and of the right internal jugular vein to enable fluid administration. A tracheostomy was performed and connected to a T-piece to maintain anaesthesia and to vary the fraction of inspired oxygen. A midline laparotomy was performed. The bladder was cannulated for drainage and quantification of urine output. Ultrasonic flow probes (Transonic Systems, Ithaca, NY, USA) were placed around the left renal artery and descending aorta to measure macrovascular blood flows.[6] An oxygen sensor (Oxylite™, Oxford Optronix, Oxford, UK), pre-calibrated by the manufacturer, was inserted into the left vastus lateralis muscle for continuous monitoring of tissue P_{O_2} (tP_{O_2}), as previously described.[7 8]

After surgery, isoflurane was reduced to 1.2% for the remainder of the experiment. Euvolaemia was achieved by administering 4 ml kg^{-1} n-saline (0.9% sodium chloride; Baxter Healthcare, Thetford, Norfolk, UK) followed by a continuous infusion of 15 ml kg^{-1} h^{-1}. This regimen had been previously determined from pilot studies where neither arterial pressure nor aortic blood flow altered by more than 10%. After a minimum of 30 min stabilization, baseline haemodynamic and arterial blood gas values were recorded ($t=0$).

The animals were pre-assigned to six study groups. Sham-operated controls ($n=9$) were monitored for a further 60 min. In separate studies, we attempted to decrease the three components of the oxygen delivery equation by ~50% (Fig. 1).

A reduction in cardiac output (using descending aortic blood flow, as a surrogate) was achieved by blood withdrawal from the arterial line over either 5 min (rapid haemorrhage; $n=9$) or 30 min (graded haemorrhage; $n=6$) until a 50% reduction in flow relative to baseline was observed.

A decrease in arterial oxyhaemoglobin saturation was achieved by decreasing the fraction of inspired oxygen ($F_{I_{O_2}}$). This decrease was verified by measuring the arterial oxyhaemoglobin saturation (Sa_{O_2}) in arterial blood samples (~0.1 ml), collected into heparinized capillary tubes for blood gas analyses (ABL800FLEX, Radiometer, Copenhagen, Denmark). For rapid hypoxaemia ($n=9$), the $F_{I_{O_2}}$ was reduced promptly to 0.125 and maintained until the end of the experiment. For graded hypoxaemia ($n=6$), the $F_{I_{O_2}}$ was reduced to 0.16 for the first 15 min, 0.14 for the next 15 min, and 0.115 for the final 30 min.

A graded reduction in haemoglobin ($n=9$) was achieved by repeated removal of 10% of the estimated circulating blood volume (based on 70 ml kg^{-1}) and replacing it with n-saline at twice the volume of shed blood. This haemodilution was performed over 1 min and repeated three times at 10 min intervals for 30 min. Haemoglobin levels were measured in arterial blood at 30 min. We were unable to construct a model of rapid reduction in haemoglobin (i.e. over 5 min) as this resulted in early mortality in all pilot studies performed. Global oxygen delivery was calculated as the product of descending aortic blood flow and arterial oxygen content $[(Hb \times Sa_{O_2} \times 1.39) + (Pa_{O_2} \times 0.023)]$.

Urine output was measured over the last 30 min of each experiment. Arterial blood samples were obtained at baseline, 30 min, and at experiment-end (60 min) for measurement of haemoglobin, Sa_{O_2}, and Pa_{O_2} in sham and intervention groups. At 60 min, whole blood was removed from the arterial line for measurement of glucose and lactate levels and plasma was frozen for batched measurement of norepinephrine (ELISA, Labor Diagnostika Nord, Nordhorn, Germany), vasopressin (ELISA, Assay Designs, Ann Arbor, MI, USA), and corticosterone (colorimetric immunoassay, R&D Systems, Minneapolis, MN, USA). Plasma was treated according to the assay manufacturer's instructions and diluted appropriately. For all hormone analyses, samples from the study and manufacturers' standards were processed in duplicate.

Statistics

All haemodynamic and blood gas analysis data are presented as mean (standard deviation), unless otherwise stated. Statistics on parametric data were performed using repeated-measures two-way analysis of variance followed by Tukey's *post hoc* test. Data for hormone measurements, arterial lactate and glucose, and urine output were all non-parametric and are shown as median, inter-quartile range, and range. These data were analysed using a Kruskal–Wallis test followed by Dunn's test for *post hoc* comparisons. All statistical analyses were performed using Prism 5.0 software (GraphPad Software, San Diego, CA, USA). Probability values of <0.05 were considered significantly different.

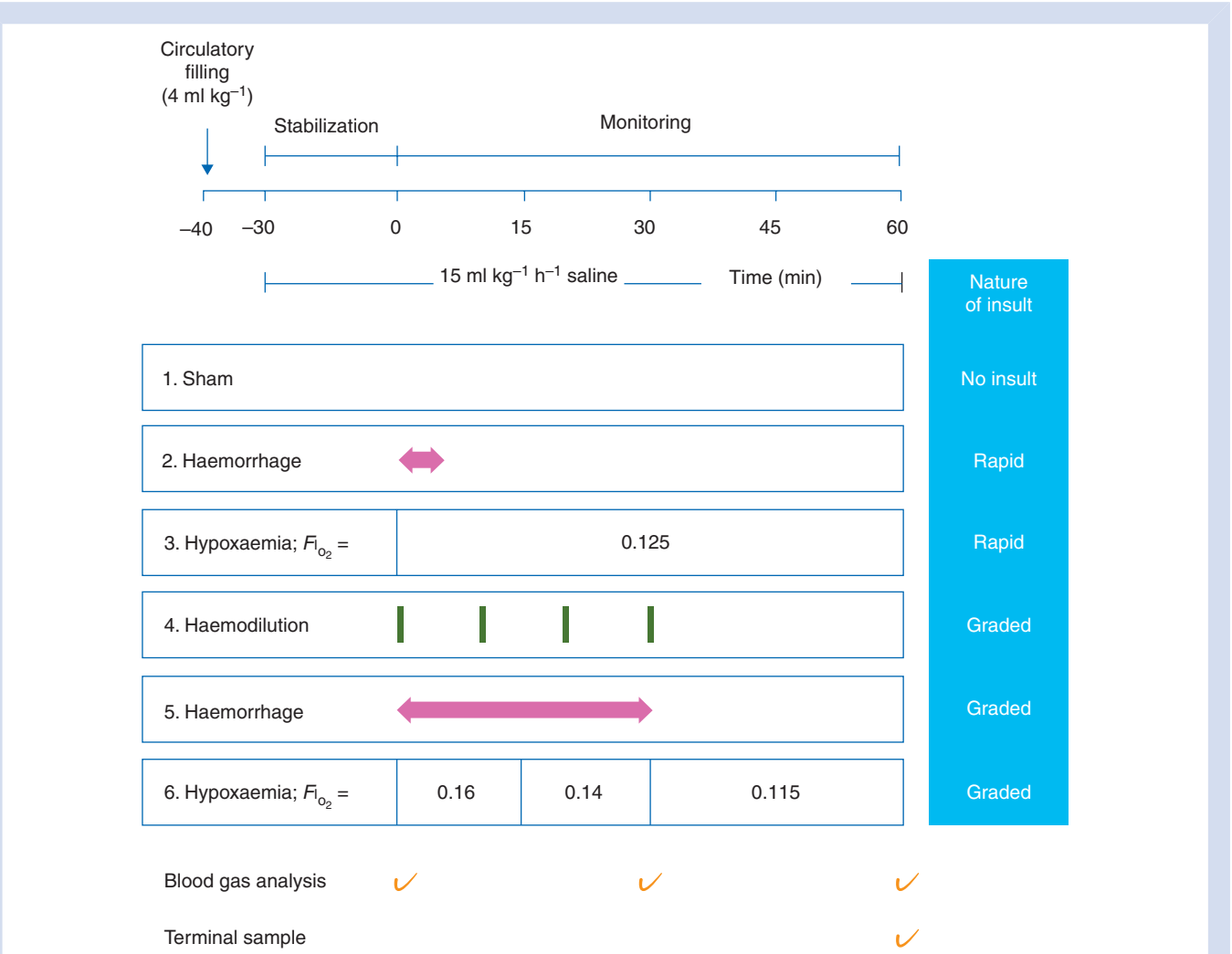

Fig 1 Schema of experimental design for each of the models. $F_{I_{O_2}}$, inspired oxygen concentration.

Results

All animals, except those subjected to a rapid haemodilution in the pilot studies, survived for the duration of the experiment. Cardiorespiratory stability was maintained in the sham-operated group over the time course of the experiment. Only aortic blood flow decreased from baseline at 60 min (Fig 2B; $P<0.05$ *vs* baseline). Haematocrit was also maintained, further supporting maintenance of intravascular filling and the absence of significant capillary leak. There was also no significant change in O_2 delivery in this group. All other sequential haemodynamic, regional tissue oxygenation, and blood gas measurements remained constant (Figs 2 and 3). At baseline, i.e. after volume optimization and a stabilization period, none of the groups showed statistically significant differences for any variable measured with the exception of muscle tissue P_{O_2} in the graded hypoxaemia group (Fig. 3F; $P<0.05$ *vs* sham).

Each cardiorespiratory insult caused diverse changes to haemodynamics, regional tissue oxygenation, blood gas analyses, and hormone levels. The targeted 50% decrease in global oxygen delivery was achieved for all insult groups ($P<0.05$ *vs* sham; Fig. 2E and I) with the exception of graded hypoxaemia (Fig. 2E). Here, despite reducing the $F_{I_{O_2}}$ to 0.115 for the final 30 min, the reflex increase in blood flow prevented achievement of the targeted decrease in global oxygen delivery. All other cardiorespiratory insult groups showed no significant change in global oxygen delivery at 60 min.

Rapid haemorrhage caused the expected early decreases in arterial pressure, aortic blood flow (to the targeted 50% reduction), renal blood flow, and tissue oxygen tension (Figs 2J and 3G–I). Arterial pressure and tissue oxygen tension subsequently increased, likely due to compartmental fluid redistribution, whereas aortic blood flow only improved marginally. By 30 min, aortic blood flow was 43% lower than baseline in rapidly haemorrhaged animals (Fig. 2J). *Graded haemorrhage* caused a more gradual decrease in arterial pressure (Fig. 3D) and aortic blood flow (Fig. 2F) to the same level achieved with rapid blood loss. Arterial pressure, but not aortic blood flow, recovered to near-baseline values, while the effects on both renal

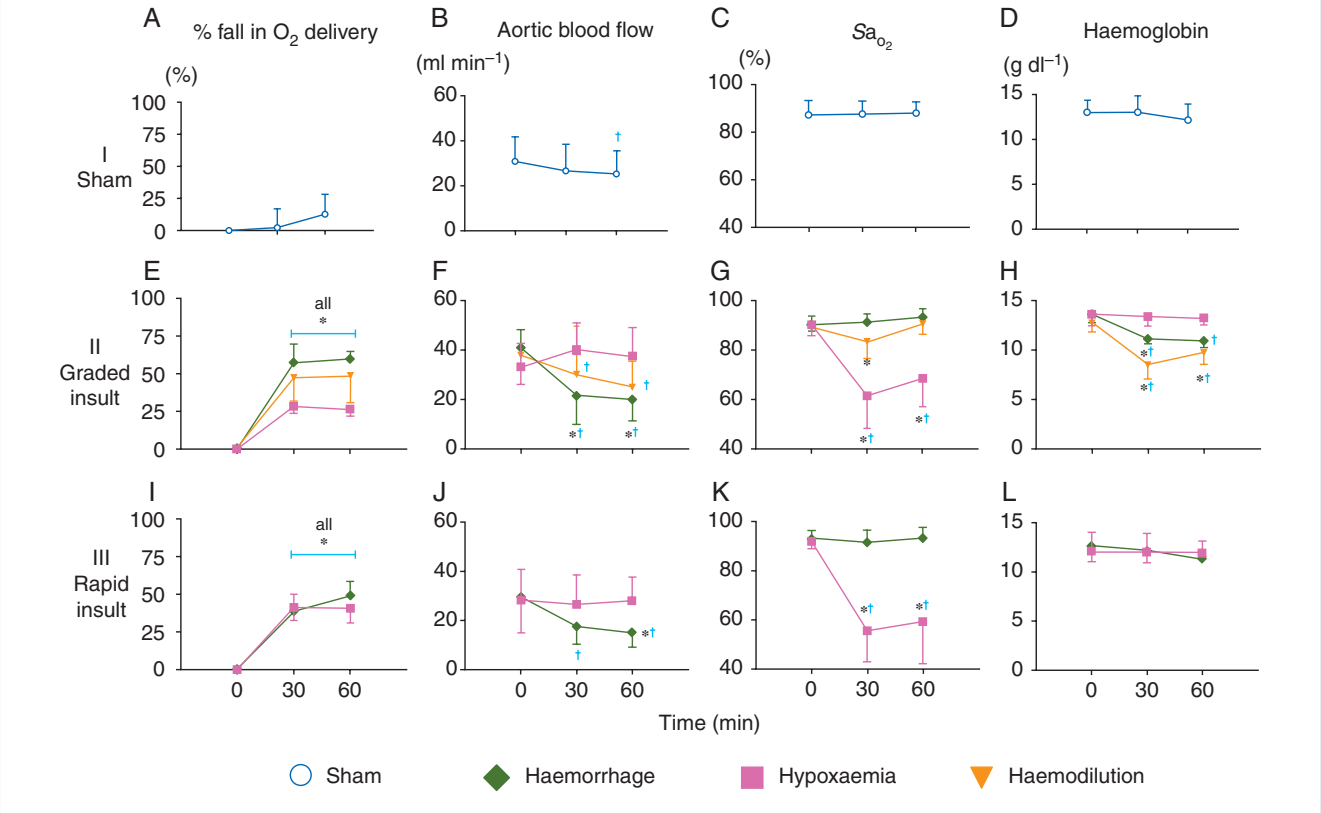

Fig 2 Changes in oxygen delivery and the individual components of the oxygen delivery equation during rapid or graded insults (haemorrhage, hypoxaemia, haemodilution). Data are displayed as mean and SD. Significant differences are indicated as follows: †$P<0.05$ *vs* baseline value; *$P<0.05$ *vs* sham group. Sa_{O_2}, arterial oxyhaemoglobin saturation.

blood flow (Fig. 3E) and muscle tissue P_{O_2} (Fig. 3F) were less pronounced. The 50% reduction in aortic blood flow from baseline values in both haemorrhage groups were significantly ($P<0.05$) lower than that recorded in the other groups, with the exception of graded haemodilution.

Graded haemodilution significantly decreased haemoglobin levels (Fig. 2H, $P<0.05$ *vs* sham and all other groups except graded haemorrhage), aortic blood flow at 30 and 60 min (Fig. 2F, $P<0.05$ *vs* baseline value), and caused a later, yet sustained, decrease in arterial pressure (Fig. 3D) that was mirrored by a decrease in muscle tissue P_{O_2} (Fig. 3F).

Rapid hypoxaemia had no effect on either arterial pressure (Fig. 3G) or aortic blood flow (Fig. 2J), but caused a greater decrease in tissue P_{O_2} compared with the other cardiorespiratory insults (Fig. 3I). In contrast, at 30 min, *graded hypoxaemia* resulted in vasodilation with a significant decrease in arterial pressure ($P<0.05$; Fig. 3D) paralleled by an increase in aortic blood flow (increased cardiac output) ($P<0.05$; Fig. 2F). Again, haematocrit was maintained in these animals suggesting the absence of significant capillary leak. The oxyhaemoglobin saturation was significantly lower in both rapid and graded hypoxaemia models at 30 and 60 min ($P<0.05$ *vs* sham and all other groups; Figs 2G and K). Although no significant difference was seen in the final oxyhaemoglobin saturation value for rapid *vs* graded hypoxaemia, a lower $F_{I_{O_2}}$ (0.125 *vs* 0.115, respectively) was required in the last 30 min to achieve similar oxyhaemoglobin saturations in both groups.

Arterial lactate levels increased with each shock state; lactate was significantly elevated at 60 min in animals receiving graded insults or rapid hypoxaemia ($P<0.05$ *vs* sham; Fig. 4B). In contrast, urine output measured over the last 30 min of each experiment was only reduced significantly in the rapid haemorrhage group ($P<0.05$ *vs* sham, Fig. 4A). Blood glucose levels were significantly ($P<0.05$ *vs* sham) elevated at 60 min for graded haemorrhage and hypoxaemia (Fig. 4C).

Plasma hormone levels measured at experiment end (60 min) are shown in Figure 5. Norepinephrine levels increased in each shock state although were only significant in both haemorrhage groups, and after graded hypoxaemia ($P<0.05$ *vs* sham; Fig. 5A). In contrast, corticosterone (Fig. 5B) increased significantly ($P<0.05$ *vs* sham) only in animals receiving rapid haemorrhage, while vasopressin levels increased in haemorrhaged animals regardless of the duration of insult (Fig. 5C; $P<0.05$).

Discussion

While oxygen delivery is often considered and clinically managed as a whole entity, we postulated that a specific decrease in each of its separate components would generate

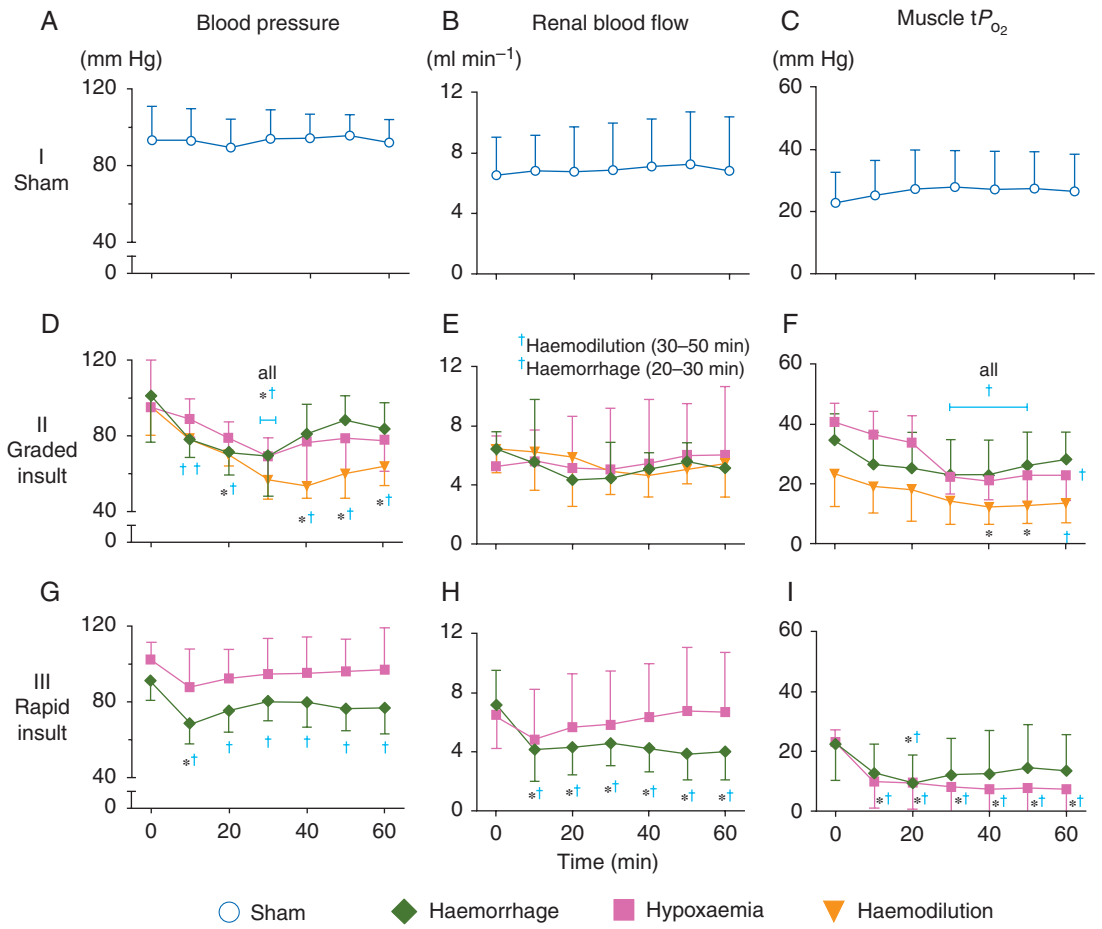

Fig 3 Changes in arterial pressure, renal blood flow, and tissue oxygen tension during rapid or graded insults. Data are displayed as mean and SD. Significant differences are indicated as follows: †$P<0.05$ *vs* baseline value; *$P<0.05$ *vs* sham group. tP_{O_2}, muscle tissue oxygen tension.

varied haemodynamic and stress responses. We confirmed this hypothesis and additionally report that the rapidity of insult development also induced varying responses. The decrease in oxygen delivery induced by rapid haemorrhage generated the largest decrease in urine output and greatest stress hormone response. In contrast, graded haemodilution had the greatest effect on arterial pressure, while rapid hypoxaemia had a relatively minor impact on global haemodynamics yet induced the largest decrease in regional oxygenation. These strikingly different responses show that oxygen delivery is not created equal and perhaps should not be the key variable used to assess management in critically ill patients.

Barcroft[2] stated that 'want' of oxygen could be divided into circulatory, anaemic, and hypoxic hypoxia. Despite this basic classification, oxygen delivery is still largely treated as a global single entity that has conceptually driven management practices over the last two decades. Strategies have been designed to increase,[4 5] global oxygen delivery under the supposition that a decrease in global oxygen delivery by whatever means would have similar effects at the end-organ level, and that restoration (or 'over-restoration') would prove beneficial.[3–5]

Targeted restoration of oxygen delivery in critically ill or high-risk surgical patients has centred predominantly upon increasing cardiac output using non-haemoglobin fluids and, if required, inotropic agents, while maintaining acceptable, levels of haematocrit and arterial oxyhaemoglobin. The early goal-directed therapy strategy for severe sepsis advocates a transfusion threshold of 30% and an oxyhaemoglobin saturation >93%.[3] Acceptance of low haemoglobin levels are predicated on the acknowledged risks of allogeneic blood transfusion[9] and recognition that anaemia is generally well tolerated in the absence of cardiorespiratory disease.[10] Transfusion thresholds of 7 g dl^{-1} are recommended for patients with established sepsis[11] and as low as 6 g dl^{-1} perioperatively in the absence of ongoing haemorrhage.[12] Notably, the degree of acute anaemia safely tolerated in cardiac surgical patients was inversely related to the patient's preoperative Hb level,[13] a factor hitherto ignored by these (inter)national guidelines that accept values ~50% below normal.

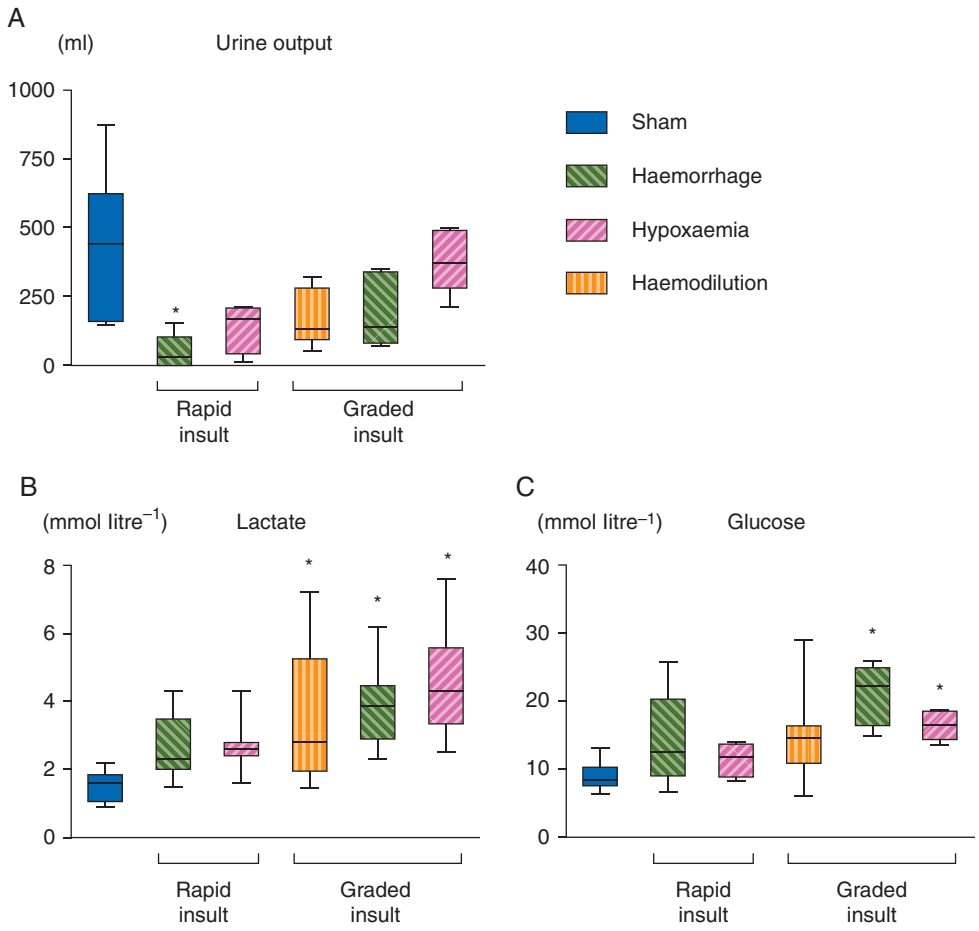

Fig 4 Changes in urine output, blood glucose, and lactate 60 min after rapid or graded insults (haemorrhage, hypoxaemia, haemodilution). Boxes represent the median, lower and upper quartiles, with whiskers indicating the minimum and maximum values. Significant differences between the groups are indicated as follows: *$P<0.05$ *vs* sham group.

Survival has been reported with haemoglobin levels as low as 1.8 g dL^{-1} in Jehovah's Witness patients refusing blood transfusion.[14] Clearly, surviving an acute 85% drop in haemoglobin levels could not be mirrored by an equivalent fall in cardiac output or oxyhaemoglobin saturation, at least at normothermia. Arterial blood gas analysis from four acclimatized healthy climbers near the summit of Mount Everest revealed reasonable mental competence despite Sa_{O_2} values of 54%.[15] This was compensated by polycythaemia (Hb averaging 19.3 g dl^{-1}), while blood lactate was barely elevated, likely due to increased utilization. In contrast, non-acclimatized people lose consciousness within 2–3 min when suddenly exposed to equivalent levels of ambient hypoxia.[16] Other than increased tissue oxygen extraction, hypoxaemia is countered acutely by vasodilatation and increased cardiac output, and chronically by polycythaemia. Anaemia generates increases in cardiac output,[17] while glycolytic ATP production increases as a compensatory mechanism in heart failure.[18]

Despite these well-recognized (patho)physiological differences, we could find no single laboratory study specifically addressing the impact of modulating the three different components of the oxygen delivery equation on haemodynamics, regional oxygenation, and stress responses. Prior studies have focused upon the relationship between oxygen delivery and consumption, with an emphasis on critical oxygen delivery (DO_2crit).[19–21] Despite different haemodynamic patterns, the DO_2crit and appearance of lactate[22 23] occurred at approximately the same degree of delivery reduction, regardless of the component affected.

We previously noted differences in haemodynamics and tissue oxygenation in rodent models of haemorrhage, hypoxaemia, and endotoxaemia.[8] Although effects were related to the magnitude of the individual insult, we noted marked regional variations depending on the insult administered. This observation prompted the current study where we targeted an approximate 50% reduction in global oxygen delivery, using short-term models to avoid confounding by established compensatory responses.

Rapid haemorrhage triggered the greatest stress hormonal response. The quantity of norepinephrine release into the

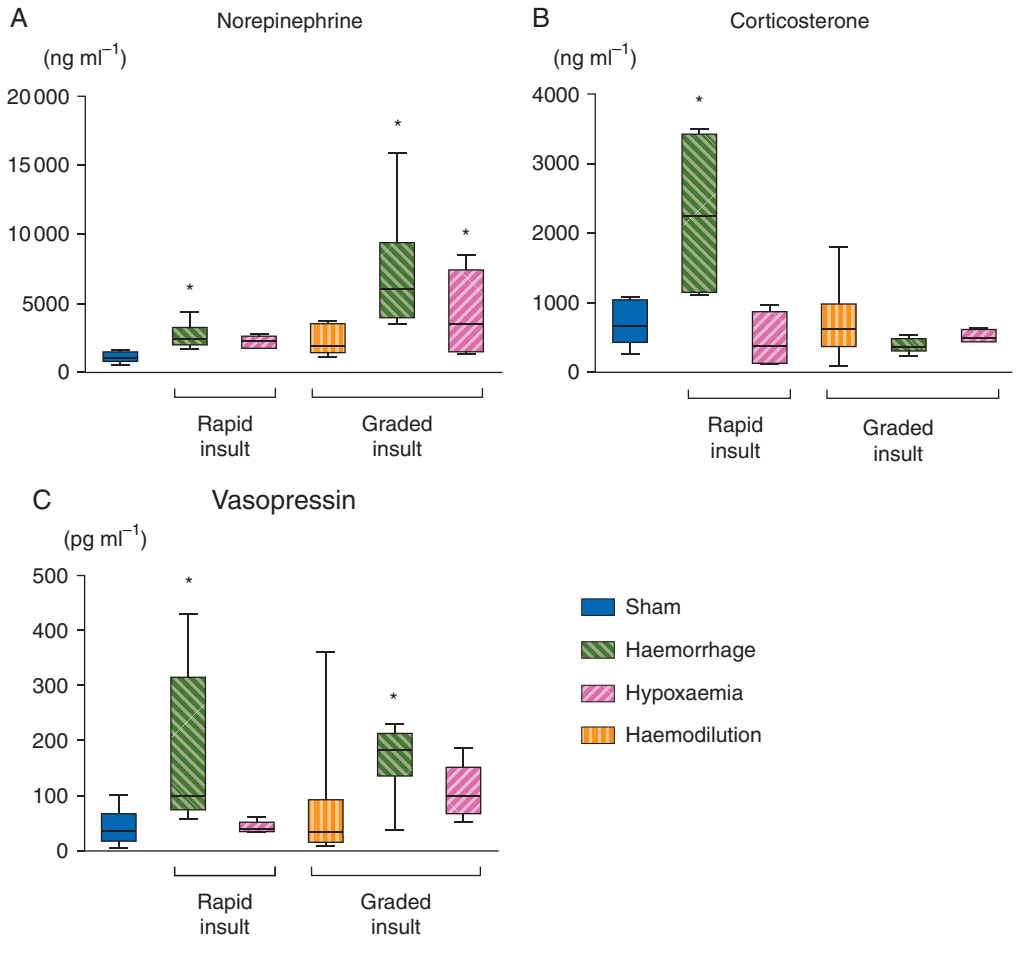

Fig 5 Changes in plasma stress hormone levels (norepinephrine, corticosterone, vasopressin) 60 min after rapid or graded insults (haemorrhage, hypoxaemia, haemodilution). Boxes represent the median, lower and upper quartiles, with whiskers indicating the minimum and maximum values. Significant differences between the groups are indicated as follows: *$P<0.05$ *vs* sham group.

circulation depends on the severity of blood loss.[24] Whereas vasopressin secretion is regulated primarily by plasma osmolarity under normal conditions,[25] loss of blood volume exceeding 10% activates baroreceptors leading to increased vasopressin release and vasoconstriction.[26] Vasopressin also increases hypothalamic sensitivity to corticotropin-releasing hormone, thereby increasing adrenocorticotropic hormone release and cortisol production.[26] The decrease in arterial pressure and flow after rapid haemorrhage and the concurrent increase in all three measured stress hormones are consistent with these known acute compensatory responses. Graded haemorrhage, although achieving similar decreases in arterial pressure and blood flow compared with rapid haemorrhage, was associated with a lesser stress hormone response, including no increase in corticosterone. Urine output also decreased to a lesser degree, while blood lactate and glucose levels were higher than with a rapid insult. Blood lactate levels represent a balance between production and utilization as a substrate. We speculate that glucose and lactate were more aggressively utilized in response to both the rapidity of haemorrhage and the longer duration of severely reduced oxygen delivery, thereby accounting for the lower levels observed at experiment-end.

Surprisingly, despite showing different haemodynamic profiles, hypoxaemia and haemodilution generated no hormonal stress response of note, with the exception of increased norepinephrine levels after graded hypoxaemia. The biological significance of this finding suggests that changes in blood flow generate the most robust endocrine responses. Haemodilution produced the most sustained hypotensive effect but only a modest increase in circulating norepinephrine levels. However, there was no vasopressin response, nor were global or regional blood flows augmented. While the decrease in arterial pressure during haemodilution may be secondary to a reduction in viscosity, haemoglobin levels had partially recovered by experiment-end. This suggests that haemodiluted animals were initially volume-expanded, perhaps underlying the failure to mount a vasopressinergic response, with subsequent capillary leak and a decrease in cardiac output.

While rapid hypoxaemia had little effect on aortic blood flow, arterial pressure, and endocrine responses, this insult

produced the largest effect on muscle tissue P_{O_2} (68% decrease from baseline) and, perhaps as a consequence, lactataemia. This is consistent with our previous observations of lower tissue P_{O_2} values across multiple organ beds during hypoxaemia compared with haemorrhage, despite equivalent, although not specifically targeted, decreases in global oxygen delivery.[8] Although graded hypoxaemia failed to reach the targeted 50% decrease in global oxygen delivery in the current study due to a compensatory increase in blood flow, tissue P_{O_2} levels still halved with a concomitant increase in blood lactate levels. This finding demonstrates the importance of radial oxygen gradients in tissue oxygen delivery.

Limitations

We used short-term models to assess the effects of modifying haemoglobin, oxyhaemoglobin saturation, or cardiac output. We did not explore whether specific responses seen with individual insults are preserved when insults are combined (e.g. hypoxaemia plus haemorrhage) or whether pre-existing comorbidities compromise the ability to respond. Indeed, in critically ill patients, a 20–30% reduction in oxygen delivery may prove fatal unless rapidly corrected.[27] Secondly, while we specifically targeted decreases in haemoglobin, Sa_{O_2}, or blood flow, compensatory changes occurred as part of the intrinsic homeostatic responses. As such, we could not construct a graded hypoxaemia model targeted to a 50% decrease in global oxygen delivery due to compensatory increases in blood flow, despite decreasing the inspired oxygen concentration to 11.5%. Hypoxic gas mixes below this threshold result in premature death.[8] Nevertheless, each of our three insults predominantly affected the separate components of the oxygen delivery equation, permitting differentiation of the response to each insult.

Thirdly, to calculate global oxygen delivery, we used descending aortic blood flow as a surrogate for cardiac output. This measurement cannot account for blood flow redistribution to vital organs such as heart and brain, and could explain the apparent decrease in cardiac output in haemodiluted animals at experiment-end. Previous reports in man have reported that proportionality was maintained between the upper and lower body in hypo- and hyperdynamic circulatory states.[28] We necessarily assumed the same applies in our model, in rats. While we did not examine either oxygen extraction ratios or changes in global oxygen consumption, measurement of skeletal muscle tissue P_{O_2} does represent the balance between local oxygen delivery and consumption.

Finally, anaesthesia is an obligatory aspect of this model. While isoflurane anaesthesia carries potential vasodilatory and negative inotropic consequences that may impact on the responses to the interventions, we have found over many years and different anaesthetic regimens (both gaseous and i.v.) that this agent offers the greatest stability. Our sham-operated model reflected this stability, albeit acknowledging the decrease in aortic blood flow seen in the sham group at the final time-point.

Conclusion

The breadth and scale of responses to manipulation of each oxygen delivery component suggest specific initial effects and a range of immediate compensatory responses. Changes in blood flow generate the most robust endocrine responses, while a rapid decrease in Pa_{O_2} has the greatest impact on tissue oxygenation. Our study highlights the fact that global oxygen delivery should not be treated as a 'whole' entity, and underlines the dilemma in optimally managing, for example, a moderately anaemic but euvolaemic patient with cardiac failure and evidence of tissue hypoperfusion. Should the low cardiac output be augmented alone or in combination with transfusion, and to what extent should both be manipulated? The concept of adequate oxygen delivery needs to be revisited and, ideally, personalized in individual patients with appropriate monitors and markers of tissue perfusion.

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Authors' contributions

A.D., M.St., and M.S. designed the study. A.D., N.E., M.St., J.C., S.B., L.B., S.H., and S.T. performed the experiments. A.D., N.E., M.St., and M.S. interpreted the data. A.D., N.E., and M.S. wrote the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interest

None declared.

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