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

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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.