

HYPEROXIC VENTILATION ENABLES HEMODILUTION BEYOND THE CRITICAL MYOCARDIAL HEMOGLOBIN CONCENTRATION

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Abstract

Background: When initiated in anemic hypoxia, hyperoxic ventilation (ventilation with pure O₂, FiO₂ 1.0, HV) reverses hypoxia-induced ECG-changes and enables survival for several hours. The quantification of the HV-induced gain in anemia tolerance and particularly the Hb-equivalent of HV in this situation are unknown.

Methods: Nine anaesthetized pigs were hemodiluted under normoxia (FiO₂ 0.21) by exchange of whole blood for hydroxyethyl starch (HES) until predefined, ischemia associated ECG-changes occurred (timepoint Hb_{crit}). From that time on all animals were ventilated with 100% O₂ (FiO₂ 1.0). In the case of disappearance of the ECG changes with onset of HV, the animals were further hemodiluted until ECG changes reoccurred.

Results: HV initiated in anemic hypoxia (Hb 2.3 ± 0.2 g/dl) improved ECG-readings of all animals, and allowed for a further exchange of 14 ± 11 ml/kg blood until ECG-changes reoccurred at Hb 1.2 ± 0.4 g/dl.

Conclusion: HV initiated in anemic hypoxia creates a margin of safety for myocardial tissue oxygenation and thus further increases anemia tolerance. The Hb equivalent of HV in this situation amounts to ~1g/dl.

Key words: oxygen, hemodilution, anemia, anemia tolerance, hyperoxic hemodilution

Abbreviations: HV = hyperoxic ventilation, Hb = hemoglobin concentration, Hb_{crit} = critical hemoglobin concentration

INTRODUCTION

Although safer than ever before, the transfusion of allogeneic donor blood is still associated with risks for the recipient (clerical error, bacterial and viral infection, immunosuppression, transfusion associated lung injury, TRALI). Moreover the costs of transfusion will raise in the future due to an increasing imbalance between transfusion needs and blood donations. Therefore intraoperative blood losses are primarily not replaced with whole blood, but with erythrocyte-free, i.e. crystalloidal and/or colloidal solutions; however, this approach results in dilutional anemia [6, 22, 24, 31]. As

long as normovolemia is maintained tissue oxygenation is preserved until a so called "critical" hemoglobin concentration (Hb_{crit}) i.e. critical limitation of oxygen transport is reached [22]. In this situation any further decline of RBC mass will result in anemic tissue hypoxia. From a pathophysiological point of view Hb_{crit} represents the ultimate opportunity to improve O₂-delivery before the onset of anemic hypoxia.

At Hb_{crit} hyperoxic ventilation (ventilation with pure O₂, FiO₂ 1.0, HV) has proven effective in improving tissue oxygenation [13], and prolonging survival [18]. Furthermore HV has been demonstrated an effective rescue therapy in the presence of lethal hemorrhagic shock [19], and in the presence of lethal methemoglobinemia [20]. Therefore HV is generally considered a simple and effective means to improve O₂ transport and tissue oxygenation in different pathophysiological states of anemic tissue hypoxia. The quantification of the HV-induced gain in anemia tolerance obtained with HV and particularly the Hb-equivalent of HV are however unknown yet.

We therefore investigated whether, and to which extent additional hemodilution should be realizable at Hb_{crit} under the protection of HV. We specifically focused on myocardial perfusion and oxygenation, since during hemodilution the heart represents the "motor" of compensation for dilutional anemia. Therefore in the presence of extreme hemodilution myocardial dysfunction results in a rapid onset of global tissue oxygenation and early death of the organism.

We hypothesized that HV initiated at Hb_{crit} potentially allows for additional hemodilution beyond the previous limits of anemia encountered during room air ventilation, without immediate deterioration of myocardial function.

METHODS AND STATISTICS

Results presented in this report were obtained from a comprehensive experimental study, investigating the effects of hemodilution and hyperoxic ventilation in anesthetized pigs. Parts of the data (that do however not conflict with the part of the protocol presented) have already been published [11, 12, 13]. All animals were identically instrumented with different devices

for data acquisition. Following government approval the study was conducted in 18 domestic pigs (bw 22 ± 5 kg), which were treated in accordance with the „principles of laboratory animal care“ (NIH-publication No 86-23, 1985).

ANESTHESIA

Premedication was performed with midazolam ($1-2$ mg kg^{-1}), ketamine (10 mg kg^{-1}) and atropine (0.025 mg kg^{-1}). General anesthesia was induced intravenously using fentanyl (0.05 mg kg^{-1}), methohexital (2 mg kg^{-1}) and pancuronium bromide (0.2 mg kg^{-1}). The animals were intubated and mechanically ventilated with room air (carbon dioxide pressure $35-42$ Torr, Servo 900 B, Siemens, Solna, Sweden). Throughout the experiment, animals were warmed and kept stable by continuous intravenous infusion of Ringer Solution (15 mg $\text{kg}^{-1} \text{ h}^{-1}$), midazolam (0.5^{-1} mg $\text{kg}^{-1} \text{ h}^{-1}$), morphine (80 mg $\text{kg}^{-1} \text{ h}^{-1}$) and pancuronium (0.2 mg $\text{kg}^{-1} \text{ h}^{-1}$).

INSTRUMENTATION AND MONITORING

Median sternotomy and median laparotomy were performed. The following catheters were inserted: A femoral artery (Arrow, Reading, PA, USA), a pulmonary artery catheter (7.5 F, Edwards Swan-Ganz, Baxter Healthcare, Irvine, CA, USA), two tip-manometer catheters (aorta, left ventricle, PC 350, Millar Instruments, TX, USA) and two 14G silastic catheters (left atrium, portal vein, Arrow, Reading, PA, USA). Ultrasound flow probes were placed around the aortic root and the left anterior descending coronary artery (LAD; TC208; Transsonic systems, Ithaca, NY). A urinary catheter was inserted surgically. The jejunum was exposed and the lumen was opened by antimesenteric transmural diathermic incision. The mucosa was exposed and rinsed continuously with saline at body temperature to enable tissue O_2 partial pressure measurements.

EXPERIMENTAL PROTOCOL

After surgical preparation and installation of all measurement devices the animals were allowed to stabilize for 30 min. A baseline measurement (time point: baseline) was obtained. Hemodilution was induced with hydroxyethylstarch (6% HES, 200 000/0.5, Fresenius Kabi) under room air ventilation (FiO_2 0.21) until the individual critical hemoglobin concentration (Hb_{crit}) of each animal was reached (time point: $\text{Hb}_{\text{crit } 1}$, onset of myocardial ischemia, see below: „Detection of myocardial ischemia“, and [16]). Thereafter the fractional inspiratory O_2 concentration (FiO_2) was increased to 1.0 and an equilibration period of 15 min was allowed to elapse before the third measurement (time point: HV, hyperoxic ventilation). The data obtained during these three measurement-time-points have already been described in detail elsewhere [11, 12, 13]. If ECG changes disappeared with the onset of HV, the animals were further hemodiluted with HES 6% until the same ECG-changes reoccurred (measurement $\text{Hb}_{\text{crit } 2}$, criteria see below [16]).

DETECTION OF MYOCARDIAL ISCHEMIA

The criterion for detection of the individual Hb_{crit} was defined as the onset of myocardial ischemia identified in the online-analysis of a 5-lead surface-ECG (Sirecust 1281, Siemens Munich, Germany): [1] the occurrence of arrhythmia and [2] ST-segment depression >0.1 mV (assessment by two independent investigators; lead II and V_5 ; [16]). The corresponding hb concentration is called critical myocardial hemoglobin concentration. Since all ECG-readings improved after the onset of HV at $\text{Hb}_{\text{crit } 1}$, hemodilution was continued until the ECG criteria of myocardial ischemia reoccurred. The criteria for $\text{Hb}_{\text{crit } 1}$ and $\text{Hb}_{\text{crit } 2}$ were identical.

MEASUREMENTS

Haemodynamic measurements: Cardiac output was measured beat-to-beat (aortic flow probe, transit time technique). Aortic and left ventricular pressures were registered online. O_2 consumption was calculated (see Appendix A). Tissue O_2 partial pressure (tpO_2) was measured in skeletal muscle with an O_2 -sensitive multiwire platinum surface electrode, yielding tissue pO_2 values from eight distinct spheric tissue areas each measuring $15 \mu\text{m}$ in diameter (MDO-Electrode, Eschweiler, Kiel, Germany). During each measurement timepoint 120 distinct tissue pO_2 values were recorded [3]. After offline-analysis (MIB, R. Mannhart, Steinsdorf; DASY-LAB software, Datalog, Mönchengladbach, Germany) the distribution of tpO_2 is depicted in form of sum histograms [14]. Data are presented as median and semi-interquartile range. Regional organ blood flow was determined using the fluorescent microspheres method and is given in $\text{ml min}^{-1} \text{ g}^{-1}$ tissue [5, 26, 27]. For each measurement arterial and mixed venous blood gas analysis (Chiron Diagnostics, Fernwald, Germany), and CO-oximetry (682 CO oximeter, Instrumentation Laboratory, Lexington, MA, USA) were performed. Hct was determined using a vernier caliper and lactate concentration was determined using a test kit (enzymatic ultraviolet method, Boehringer, Mannheim, Germany). O_2 transport variables and coronary perfusion pressure were calculated (see Appendix A).

STATISTICAL ANALYSIS

Statistical analysis was performed with a signed rank test for hemodynamic parameters and parameters of oxygen transport (R Version 1.8.0, R-Foundation for Statistical Computing, Vienna, Austria), Mc Nemar's test for frequency of hypoxic tpO_2 values, and a Kolmogorov-Smirnov test for the shape of tpO_2 sum histograms (Sigmastat 2.0, Jandel Scientific, San Rafael, CA, and Statistica 5.1, Statsoft, Tulsa, OK, USA). Bonferroni-Holm adjusted p-values were used to account for triple testing (the outcome results of two tests are discussed in the previous manuscripts [11, 12, 13], the result of the third test is discussed in the manuscript presented: HV vs $\text{Hb}_{\text{crit } 2}$). The overall α -error threshold was set to 5%.

RESULTS

Complete datasets were obtained in nine of 18 animals; nine animals had to be excluded from data analysis (for reasons see Table 1 and [13]). Each animal that survived time point $Hb_{crit\ 1}$ ($n = 9$) completed the whole protocol. No animal died during the second hemodilution procedure, or during the time necessary to obtain the complete dataset at $Hb_{crit\ 2}$.

Table 1. List of dropouts.

Reason for incomplete protocol	n
Ventricular fibrillation during cardiac preparation/crystal implantation	3
Sustained surgical bleeding	1
Vitium cordis (large atrioseptal defect)	1
Incomplete data acquisition	1
Premature death at critical hemoglobin concentration (myocardial ischemia)	3

HEMODILUTION BEYOND $Hb_{crit\ 1}$

Hyperoxic ventilation initiated at $Hb_{crit\ 1}$ (2.6 ± 0.3 g/dl) allowed for the additional exchange of 300 ± 250

ml (14 ± 11 ml/kg) blood for HES corresponding to 18% of total blood volume, until previously observed ECG-changes reoccurred. The second hemodilution procedure lasted approximately one hour. $Hb_{crit\ 2}$ was 1.2 ± 0.4 g/dl (min: 0.4 g/dl, max: 2.4 g/dl), therefore the Hb-equivalent of HV in this situation amounted to ~ 1 g/dl.

Hemodynamics:

At $Hb_{crit\ 2}$ myocardial function deteriorated seriously. CO, MAP, and left ventricular systolic pressure decreased (-30%, $p < 0.05$; -42 %, $p < 0.05$; -16%, $p < 0.05$; respectively), heart rate remained constant and SVRI decreased (-13 %, $p < 0.05$). While coronary perfusion pressure decreased significantly (-52%, $p < 0.05$), coronary blood flow was not affected.

OXYGEN TRANSPORT AND TISSUE OXYGENATION:

Normovolemic hemodilution from $Hb_{crit\ 1}$ to $Hb_{crit\ 2}$ further decreased arterial oxygen content by 25% ($p < 0.05$). Reduction of CaO_2 and concomitant reduction of CO resulted in a pronounced restriction of oxygen delivery (-46%, $p < 0.05$), and in a serious decline of oxygen consumption (-45%, $p < 0.05$), indicating severe O_2 supply dependency. In this situation 76% of the oxygen consumed was contributed by the plasma. However, mixed venous pO_2 did not change during the second hemodilution step. At $Hb_{crit\ 2}$ a significant deterioration of tissue oxygenation of skeletal

Table 2. Hemodynamic and left ventricular parameters.

	HV	$Hb_{crit\ 2}$
hemoglobin concentration (g/dl)	2.3 ± 0.2	1.2 ± 0.4 §
hematocrit (%)	7.7 ± 1.1	3.5 ± 0.6 §
heart rate (min^{-1})	135 ± 10	122 ± 27
mean arterial pressure (Torr)	66 ± 12	38 ± 13 §
systemic vascular resistance ($dyn\ s\ cm^{-5}\ m^{-2}$)	2349 ± 327	2039 ± 494 §
cardiac output ($l\ min^{-1}\ m^{-2}$)	4.3 ± 0.7	3.0 ± 0.8 §
left ventricular end-diastolic pressure (Torr)	6 ± 1	9 ± 4
coronary perfusion pressure (Torr)	25 ± 9	12 ± 7 §
coronary blood flow (left anterior descending) ($ml\ min^{-1}$)	92 ± 50	54 ± 46
left ventricular systolic pressure (Torr)	105 ± 9	88 ± 21 §

Table 3. O_2 -transport.

	HV	$Hb_{crit\ 2}$
hemoglobin concentration (g/dl)	2.3 ± 0.2	1.2 ± 0.4 §
arterial O_2 partial pressure (mm Hg)	464 ± 66	504 ± 73
arterial O_2 content ($ml\ dl^{-1}$)	4.4 ± 0.3	3.3 ± 0.3 §
contribution of red cells to arterial content (%)	68 ± 5	45 ± 10 §
contribution of plasma to arterial content (%)	32 ± 5	55 ± 10 §
O_2 -delivery ($ml\ min^{-1}\ m^{-2}$)	192 ± 32	103 ± 11 §

Table 4. Tissue oxygenation.

	HV	Hb _{crit 2}
O ₂ -consumption (ml min ⁻¹ m ⁻²)	125 ± 13	69 ± 15 §
contribution of red cells to O ₂ consumption (%)	55 ± 9	24 ± 17 §
contribution of plasma to O ₂ consumption (%)	45 ± 9	76 ± 17 §
arterial lactate (mmol l ⁻¹)	4.1 ± 2.4	6.1 ± 1.8
arterial base excess (mmol l ⁻¹)	-12.8 ± 5.2	-13.4 ± 4.6 §
mixed-venous hemoglobin O ₂ saturation (%)	50 ± 8	65 ± 8
mixed-venous O ₂ partial pressure (Torr)	37 ± 2	38 ± 3
regional blood flow in skeletal muscle (ml min ⁻¹ g ⁻¹)	0.9 ± 0.9	1.0 ± 0.8
tpO ₂ in skeletal muscle (Torr)	18 ± 2	6 ± 5 §

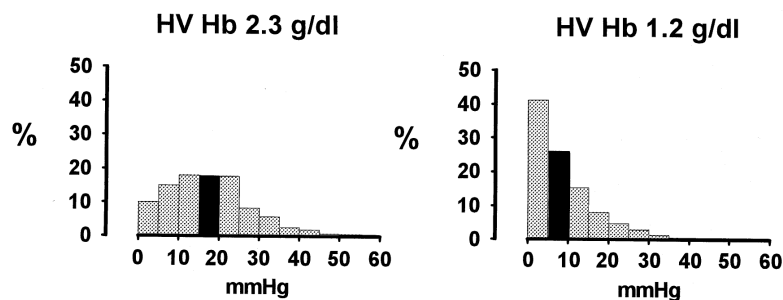


Fig. 1. Sum histograms of the distribution of tissue pO₂-values on the surface of skeletal muscle. Tissue pO₂ values are depicted as bars along the x-axis representing classes of 5 mmHg. Each bar gives the relative frequency of measured values. A histogram is characterized by its position along the x-axis, its median pO₂ value (black bar) and the frequency of hypoxic values (values <10 Torr).

muscle could be observed (Fig. 1), despite unaltered skeletal muscle blood flow (n.s.). Peripheral tissue hypoxia was indicated by a left shift of the tpO₂ sum histogram (-67%, p<0.05), and an increase in frequency of hypoxic values (<10 Torr, p<0.05) (Fig. 1).

Arterial lactate remained constant, whereas arterial base excess decreased after the second hemodilution step (-5%, p<0.05).

DISCUSSION

The main findings of the study presented are: (I) The myocardial Hb_{crit} obtained under hyperoxia was significantly lower than Hb_{crit} obtained under normoxia. (II) HV initiated at Hb_{crit} allowed for the additional exchange of about 18% of circulating blood volume with HES until the previously observed ECG changes reoccurred. (III) The Hb-equivalent of HV amounted to ~1 g/dl in this situation. (IV) At Hb_{crit 2} (critical Hb under hyperoxia) cardiovascular performance was restricted more profoundly than at Hb_{crit 1} (critical Hb under normoxia).

Tolerance of intraoperative anemia has become an integral part of clinical allogeneic blood conservation strategies. The lower the patient's Hb concentration, the less will be the net red blood cell loss per milliliter blood lost. In other words: a hemodiluted patient tolerates the same blood loss with a less pronounced decrease in Hb concentration.

In this context HV has been proven an effective method to avoid tissue hypoxia at the time point when Hb_{crit} is reached [18, 25]. However, it is unknown,

whether at Hb_{crit} an additional margin of safety is created by HV, which not only preserves tissue oxygenation at Hb_{crit}, but also enables the avoidance of transfusion of RBC despite ongoing blood loss. Maximal but still safe exertion of intraoperative anemia tolerance should allow for the delay of the onset of autologous and/or allogeneic red blood cell transfusion. At best the onset of transfusion can be delayed under the protection of HV until definite control of surgical bleeding is achieved. As a consequence a higher percentage of red blood cells transfused remains within the vasculature, and is not lost immediately by ongoing blood loss.

From both, the economical and the pathophysiological point of view, the ultimate opportunity to initiate a therapy before the onset of manifest tissue hypoxia is „critical O₂ delivery“ (DO₂ crit). At DO₂ crit the amount of O₂ delivered becomes insufficient to meet O₂ demand of the tissues. However, quantification of DO₂ crit is difficult, because it depends on various factors and varies intra- and interindividually. Common methods for the determination of DO₂ crit are detection of a sudden decay of VO₂ (by a pulmonary artery catheter, or a metabolic monitor), or monitoring of ECG or TEE. The first method identifies restrictions of whole body oxygen delivery, while the latter two focus on functional parameters of the myocardium.

In the study presented we determined DO₂ crit as the limit of coronary blood flow reserve indicated by predefined ECG changes (5-lead ECG). Since the specificity of ST-segment depression in lead II and V₅

for detection of myocardial ischemia only amounts to 80% [16], subendocardial myocardial ischemia might already be present despite the lack of pathological changes in the ECG. However, continuous ECG monitoring enables rapid evaluation of the myocardial oxygenation status, allowing a timely start of hyperoxic ventilation to avoid a rapid onset of tissue hypoxia. Furthermore ECG monitoring is the most common procedure for detection of myocardial hypoxia in the operating theatre. Determination of Hb_{crit} and DO_2 crit by a sudden decay of VO_2 is either expensive (costs of a metabolic monitor), or invasive (pulmonary artery catheter).

It has to be pointed out that our criteria for DO_2 crit solely focusses on the myocardium. Therefore it can not be deduced from our data, that the HV induced reduction of myocardial hypoxia (trigger reversal of ECG changes) is accompanied by the termination of tissue hypoxia of other organs. Furthermore we can not exclude, that some organs already suffered from tissue hypoxia, at time points when ECG changes were absent.

To our knowledge native hemoglobin concentrations of 1.2 g/dl have only been survived under room air ventilation (FiO_2 0.21) in the presence of artificial O_2 -carriers [21]. Survival of these severest degrees of anemia might also be possible in the presence of the additional amount of physically dissolved and biologically highly available oxygen [28]. However, the effects of HV are not solely beneficial in this situation: HV induces generalized arteriolar constriction, mediated by arachidonic acid metabolites and reduced endothelial NO-release [2, 4, 8, 9, 17]. This arteriolar constriction is accompanied by a reduction of cardiac output [1, 7], a reduction of functional capillary density and can therefore result in an impairment of tissue oxygenation [2, 4, 8, 9, 17]. For these reasons, HV failed to increase systemic, myocardial and intestinal DO_2 at $Hb_{crit 1}$, despite an increase of CaO_2 [13]. In contrast to these findings HV preserves survival at Hb_{crit} determined by indirect calorimetry for at least 6 hrs [18]. Therefore HV can be considered a safe and effective method to avoid formation of tissue hypoxia at Hb_{crit} [18]. Although a control group is missing in the present study, the observed reduction of ECG signs can not be attributed to any other effect than to the effective utilization of physically dissolved plasma O_2 . While the total amount of O_2 transported to the tissues surprisingly remains unchanged after HV, the amount of biologically highly available plasma O_2 increases.

Despite similar ECG changes at $Hb_{crit 1}$ and $Hb_{crit 2}$, suggesting an analogue degree of myocardial hypoxia, myocardial perfusion, myocardial function and peripheral tissue oxygenation were restricted more profoundly at $Hb_{crit 2}$ than at $Hb_{crit 1}$. Therefore cardiovascular stability and performance might differ at the two critical hemoglobin concentrations. This assumption is confirmed by the fact that CI and dp/dt_{max} were lower at $Hb_{crit 2}$ than at $Hb_{crit 1}$ indicating a deterioration of myocardial function. In fact DO_2 was also lower at $Hb_{crit 2}$ (103 ± 11 ml/dl) than at $Hb_{crit 1}$ (189 ± 40 ml/dl); particularly it has to be stated, that a DO_2 of

189 ml/dl was inherently too low for effective tissue oxygenation. Therefore the additional amount of blood exchanged until the reoccurrence of ECG-changes (ECG-equivalent ~ 1 g/dl) can not be interpreted as „additional allowable blood loss“ under the protection of HV, but should be considered as narrow margin of safety for tissue oxygenation. However, without HV a Hb of 1.2 g/dl would not have been realizable. It is known from previous studies that at a Hb of 2.9 g/dl mortality amounts to 100 % within 3 hours [18]. Survivable hemoglobin concentrations as low as those observed in the present study (1.2 ± 0.4 g/dl) are rarely reported in the literature [15, 23, 29, 31]. Nevertheless, accidental decreases of Hb to values of 1.1 g/dl or 1.2 g/dl in young patients without cardiovascular disease have been survived without sequelae [15, 28, 31]. In our model the hemoglobin concentration in one animal was 0.4 g/dl, and has been tolerated for at least 30 minutes. However, survival of a hemoglobin concentration of 0.4 g/dl for 30 minutes with no other support than normobaric hyperoxic ventilation has to our knowledge, not been reported before.

Theoretically a Hb of 1.5 g/dl can be tolerated without myocardial dysfunction presumed that the following preconditions are fulfilled: intact coronary reserve, normovolemia, normotonia, and hyperoxic ventilation) [30]. In this situation CaO_2 is equally composed by hemoglobin-bound O_2 (1.5 g/dl \times 1.34 ml/g \times $0.98 = 1.96$ ml/dl) and physically dissolved O_2 (0.003 ml/dl/mmHg \times 650 mmHg $= 1.95$ ml/dl). A CaO_2 of 4 ml/dl is supposed to be the lowest acceptable CaO_2 for sufficient myocardial oxygen supply [30]. In our experiments hemoglobin concentrations of 1.2 ± 0.4 g/dl and a CaO_2 of 3.3 ± 0.3 ml/dl were measured under hyperoxia i.e. values below the generally accepted lowest limit. Although myocardial function and integrity were intact at least during the time required for data acquisition, it was obvious that the amount of oxygen additionally provided by HV would have been insufficient to ensure long term survival at $Hb_{crit 2}$.

CONCLUSION

Hyperoxic ventilation is used to avoid immediate RBC transfusion after onset of Hb_{crit} [25]. Our data suggest that thereafter a limited additional blood loss can be tolerated, since the HV induced increase of CaO_2 compensates for the additional loss of RBC. However, once this margin of safety is exhausted, one must anticipate severe restriction of myocardial performance requiring immediate RBC transfusion.

APPENDIX

Body surface area (BSA in m^2) was calculated according to Holt et al. [10]:

$$BSA = k \times BW^{2/3}$$

where BW=body weight (in kg) and $k = 9$.

Peripheral vascular resistance index was calculated as:

$$SVRI = (MAP - CVP) \times k / CI$$

where SVRI is systemic vascular resistance, k is a constant factor necessary to adjust the formula to the different dimensions, CVP is central venous pressure.

Arterial oxygen content (CaO_2) was calculated as:

$$CaO_2 = (Hb \times SaO_2 \times 1.34) + paO_2 \times 0.003$$

Contribution of red cells and plasma to arterial O₂ content was calculated as:

$$\frac{(Hb \times SaO_2 \times 1.34)}{(Hb \times SaO_2 \times 1.34) + paO_2 \times 0.003} \quad \text{and} \quad \frac{paO_2 \times 0.003}{(Hb \times SaO_2 \times 1.34) + paO_2 \times 0.003}$$

Total body oxygen delivery was calculated as follows:

$$DO_2I = CI \times CaO_2$$

Oxygen consumption was calculated as follows:

$$VO_2I = CI \times (CaO_2 - CvO_2)$$

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