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Central venous oxygen saturation and carbon dioxide gap as resuscitation targets in a hemorrhagic shock

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Background: Fluid resuscitation is still a major challenge. We aimed to describe changes in central venous oxygen saturation ($ScvO_2$) and venous-to-arterial carbon dioxide gap (dCO_2) during an experimental stroke volume (SV) index (SVI)-guided hemorrhage and fluid resuscitation model in pigs.
Methods: Twelve anesthetized, mechanically ventilated pigs were bled till baseline SVI (T_{bsl}) dropped by 50% (T_0), thereafter fluid resuscitation was performed with balanced crystalloid in four steps until initial SVI was reached (T_4). Statistical analysis was performed with Statistical Program for Social Sciences version 18.0; data are expressed as mean ± standard deviation.
Results: After bleeding, $ScvO_2$ dropped ($T_{bsl} = 78 \pm 7$ vs. $T_0 = 61 \pm 5\%$ $P < 0.05$) and oxygen extraction ratio increased ($T_{bsl} = 0.20 \pm 0.07$ vs. $T_0 = 0.36 \pm 0.05$, $P < 0.05$). By T_4 the $ScvO_2$ normalized, but on average it remained 5% lower than at T_{bsl} ($T_4 = 73 \pm 9\%$ $P < 0.05$) and oxygen extraction also remained higher as compared with T_{bsl} ($T_4 = 0.24 \pm 0.09$ $P = 0.001$). $ScvO_2$ showed significant correlation with SVI ($r = 0.564$, $P < 0.001$). dCO_2 increased during hypovolemia (T_{bsl}:5.3 ± 2.0 vs. T_0:9.6 ± 2.3 mmHg, $P = 0.001$), then returned to normal by $T_4 = 5.1 \pm 2.6$ mmHg, and it also showed significant correlation with SVI ($R = -0.591$, $P < 0.001$) and oxygen extraction ($R = 0.735$, $P < 0.001$).
Conclusions: In this SV-guided bleeding and fluid resuscitation model, both $ScvO_2$ and dCO_2 correlated well with changes in SV, but only the dCO_2 returned to its baseline, normal value, while $ScvO_2$ remained significantly lower than at baseline. These results suggest that dCO_2 may be a good hemodynamic endpoint of resuscitation, while $ScvO_2$ is not strictly a hemodynamic parameter, but rather an indicator of the balance between oxygen delivery and consumption.

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Major surgery in high-risk patients is associated with increased risk of morbidity and mortality.[1] Perioperative hypovolemia, blood loss and hypoxia can decrease oxygen delivery, while pain and shivering can increase oxygen consumption resulting in oxygen debt.[2,3] Cumulative oxygen debt shows direct relationship with hospital mortality.[4] In hypovolemia, fluid resuscitation is the cornerstone of maintaining and correcting oxygen delivery in hemodynamically unstable patients.

However, fluid resuscitation is a double-edged sword. On the one hand, hypovolemia-induced tissue hypoxia is the major cause of post-operative organ failure,[5] while on the other hand positive fluid balance also impairs organ function and increases the number of complications.[6] It has also been shown that optimization of oxygen delivery (DO_2) during major surgery reduces post-operative complications and improves outcome in high-risk patients.[7,8]

Although cardiac output (CO) is the main determinant of oxygen delivery, the results of a recent survey from the United States and Europe demonstrated that, for example, in high-risk surgical patients intraoperative CO-monitoring has only limited availability in our everyday practice.[9] Most physicians still rely on mean arterial pressure (MAP) and central venous pressure (CVP) to guide their treatment.[9] However, it has been shown by several studies that conventional preload parameters like CVP are insufficient indicators of hypovolemia and fluid responsiveness.[10,11]

Central venous oxygen saturation ($ScvO_2$), which is a good substitute of mixed venous oxygen saturation, is a sensitive indicator of the balance between oxygen supply and demand.[12,13] There is consensus

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that low $ScvO_2$ is an important warning sign of inadequacy of DO_2.[14] Furthermore, in critically ill patients, $ScvO_2$ is often elevated because of impaired oxygen extraction, which is also associated with unfavorable outcome.[15–17] However, in patients under general anesthesia, the $ScvO_2$ can be even higher than 80%, which is due to the reduced oxygen demand and consumption (VO_2); hence, values should be interpreted differently.[18]

Another easily obtainable blood gas parameter is the central venous-to-arterial carbon dioxide gap (dCO_2). It has been shown that in sepsis, in heart failure and in severe hypovolemia, its value can be elevated.[19,20]

As the effects of a stroke volume (SV)-guided hemorrhage and resuscitation on $ScvO_2$ and dCO_2 has not been investigated yet, we hypothesized that changes in flow and VO_2/DO_2 caused by bleeding may be reflected in changes of $ScvO_2$ and dCO_2.

Materials and methods

The experiments were carried out in strict adherence to the National Institutes of Health guidelines for the use of experimental animals, and the study was approved by the Ethical Committee for the Protection of Animals in Scientific Research at the University of Szeged, with the license number: V./01882/0000/2009-V./142/2013.

Animals and instrumentation

The experiments were performed on Vietnamese mini pigs. The animals weighing 23 ± 5 kg underwent a 6-h fast pre-operatively but with free access to water. Anesthesia was induced by intramuscular injection of a mixture of ketamine (20 mg/kg) and xylazine (2 mg/kg) and maintained with a continuous infusion of propofol (6 mg/kg/h iv.), while analgesia was maintained with nalbuphine (0.1 mg/kg). A tracheal tube was inserted, and the animals' lungs were ventilated mechanically with Harvard Apparatus Dual Phase Control Respirator (Harvard Apparatus, South Natick, MA, USA). The tidal volume was set at 10 ml/kg, and the respiratory rate was adjusted to maintain the end-tidal carbon dioxide and partial pressure of arterial carbon dioxide in the range of 35–45 mmHg and the arterial pH between 7.35 and 7.45. The adequacy of the depth of anesthesia was assessed by monitoring the jaw tone. After induction of anesthesia, the right jugular vein and the right femoral artery and vein were dissected and catheterized. The central venous catheter was positioned by the guidance of intracavital electrocardiogram. Animals were kept warm (37 ± 1 °C) by an external warming device.

For invasive hemodynamic monitoring, a transpulmonary thermodilution catheter (PiCCO, PULSION Medical Systems SE, Munich, Germany) was placed in the femoral artery. The femoral artery served as the site for arterial blood gas sampling, and the central venous line was used for taking central venous blood gas samples and for the injection of cold saline boluses for the thermodilution measurements.

Hemodynamic and blood gas measurements

SV, heart rate (HR), MAP, CO, global end-diastolic volume (GEDV), SV variation (SVV), pulse pressure variation (PPV), left ventricular contractility (dPmax) and systemic vascular resistance were measured by transpulmonary thermodilution and/or pulse contour analysis at baseline and after equilibration of each step. All hemodynamic parameters were indexed for body surface area. The average of three random measurements following 10-ml bolus injections of ice-cold 0.9% saline were recorded. CVP was determined by the analysis. From the arterial and central venous blood gas samples (Cobas b 221, Roche Ltd, Basel, Switzerland) that were drawn and analyzed by cooximetry simultaneously at baseline and at the end of each step, $ScvO_2$ and dCO_2 were determined. From these parameters, the following variables were calculated:

$$DO_2 = CI \times (Hb \times 1.34 \times SaO_2 + 0.003 \times PaO_2)$$

$$DO_2 = CI \times CaO_2$$

$$VO_2 = CI \times [CaO_2 - (Hb \times 1.34 \times ScvO_2 + 0.003 \times PcvO_2)]$$

$$\text{Oxygen extraction} = VO_2/DO_2$$

Experimental protocol

The flowchart of the experiment is summarized in Fig. 1. After the catheterizations, animals were allowed to rest for 30 min, after which baseline (T_{bsl}) hemodynamic measurements, blood gas analyses and laboratory testing were performed. After these measurements, blood was drained until the SV index (SVI) dropped by 50% of its baseline value (T_0), then measurements were repeated. The difference of the $SVI_{bsl} - SVI_{T0}$ was divided into four equal target values, which was aimed to reach in four steps during fluid resuscitation ($T_{1–4}$) to reach the initial

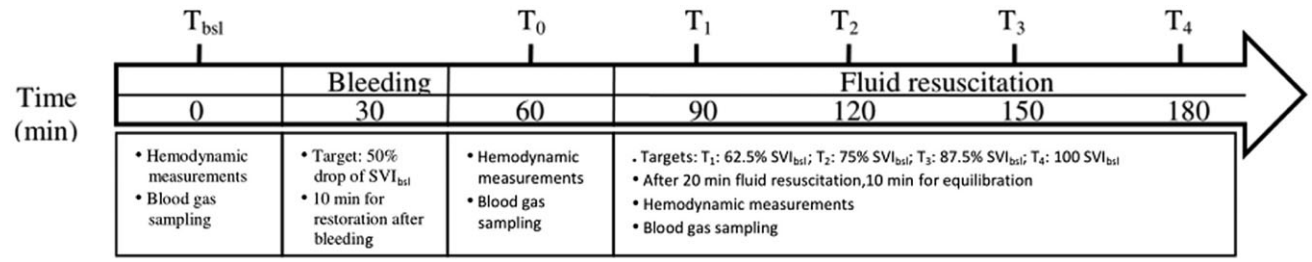

Fig. 1. Schematic diagram illustrating the flowchart of the experimental protocol. After baseline measurment, animals were bled until the stroke volume index (SVI) decreased by 50% (T_0), then measurements were repeated. The difference of the $SVI_{bsl} - SVI_{T0}$ was divided into four equal target values ($T_{1–4}$), and fluid resuscitated to reach the initial SVI by T_4.

Table 1

Hemodynamic parameters during hemorrhage and fluid resuscitation.

	T_{bsl}	T_0	T_1	T_2	T_3	T_4
Stroke volume index (ml/m^2)	26.8 ± 4.7	13.4 ± 2.3*	16.3 ± 2.6*†	19.2 ± 3.5†	22.3 ± 4.1†	26.6 ± 4.1†
Cardiac index (l/min/m^2)	2.6 ± 0.4	1.8 ± 0.3*	2.0 ± 0.4*†	2.3 ± 0.4†	2.6 ± 0.4†	2.9 ± 0.5*†
Mean arterial pressure (mmHg)	112 ± 23	74 ± 18*	73 ± 20*	78 ± 20*	84 ± 19*†	91 ± 19*†
Heart rate (beats/min)	95 ± 12	131 ± 27*	128 ± 31*	121 ± 22*	114 ± 18*†	107 ± 16*†
Central venous pressure (mmHg)	6.0 ± 1.1	4.8 ± 0.8*	5.5 ± 2.1	5.6 ± 1.5	6.0 ± 1.3	6.1 ± 1.4†
Global end-diastolic volume (ml/m^2)	309 ± 57	231 ± 61*	237 ± 54*	245 ± 45*	268 ± 48*†	287 ± 49*†
Stroke volume variation (%)	13.6 ± 4.3	22.6 ± 5.6*	21.8 ± 5*	18.6 ± 5.2†	16.6 ± 5.4†	12.2 ± 4.3†
Pulse pressure variation (%)	13.0 ± 4.5	24.5 ± 7.6*	23 ± 7.3*	18.4 ± 6.4†	16 ± 5.6†	13 ± 4.2†
Systemic vascular resistance index (dyn × s/cm^5/m^2)	3425 ± 816	3257 ± 966	2711 ± 733*†	2506 ± 680*†	2460 ± 561*†	2340 ± 526*†
dPmax (mmHg/s)	583 ± 227	596 ± 367	636 ± 413	708 ± 403	670 ± 298	657 ± 265

Data are expressed as mean ± standard deviation.
*$P < 0.05$ significantly different from T_{bsl}.
†$P < 0.05$ significantly different from T_0.

SVI by T_4. Fluid replacement was carried out with boluses of balanced cryristalloid Lactated Ringer (B. Braun AG., Melsungen, Germany). After reaching each step, 20 min were allowed for equilibrium, then hemodynamic and blood gas parameters were measured. At the end of the experiment, the animals were euthanized with sodium pentobarbital.

Data analysis and statistics

Data are presented as mean ± standard deviations unless indicated otherwise. For testing normal distribution, the Kolmogorov–Smirnov test was used. Changes in all parameters throughout the experiment were tested by repeated measures analysis of variance. For pairwise comparisons, Pearson's correlation was used. Post hoc calculation showed a power of 0.90 with an effect of 10% drop in the $ScvO_2$ following hemorrhage for a sample size of 12 and $\alpha < .05$. For statistical analysis, Statistical Program for Social Sciences version 18.0 for Windows (SPSS, Chicago, IL, USA) was used, and $P < 0.05$ was considered statistically significant.

Results

Macrohemodynamics

During bleeding, 314 ± 65 ml of blood had to be drained to reach the target of 50% reduction in SVI. For resuscitation, 951 ± 307 ml of crystalloid infusion was administered in total by T_4 to achieve the target value obtained at T_{bsl}. Hemodynamic changes during the experiment are summarized in Table 1. After bleeding, the SVI decreased by the planned 50% at T_0 and returned to its initial value by T_4. The cardiac index (CI) also decreased and reached a higher value by T_4 as compared with T_{bsl}. There was an increase in HR from T_{bsl} to T_0, which remained elevated during the whole experiment. MAP fell during the hemorrhage and remained lower until the end of the experiment as compared with T_{bsl}. GEDV decreased at T_0 and increased during resuscitation, but remained lower as compared with T_{bsl}. The CVP also decreased from T_{bsl} to T_0 and returned to its baseline value at T_4. There was a tendency of gradually increasing myocardial contractility as indicated by

Table 2

Blood gas parameters during hemorrhage and fluid resuscitation.

	T_{bsl}	T_0	T_1	T_2	T_3	T_4
Oxygen delivery index (ml/min/m^2)	419 ± 62	272 ± 56*	285 ± 58*	305 ± 47*	305 ± 55*	341 ± 62*†
Oxygen consumption index (ml/min/m^2)	77 ± 26	96 ± 19*	89 ± 15	90 ± 17	82 ± 31	82 ± 27
Oxygen extraction (VO_2/DO_2)	0.20 ± 0.07	0.36 ± 0.05*	0.33 ± 0.07*	0.31 ± 0.07*	0.28 ± 0.09*	0.24 ± 0.09*
Arterial pH	7.50 ± 0.63	7.45 ± 0.7	7.42 ± 0.6	7.38 ± 011*	7.44 ± 0.42	7.45 ± 0.43
Partial pressure of oxygen in arterial blood (mmHg)	84.5 ± 8.1	84.6 ± 9.7	84.9 ± 11.8	84.9 ± 8.8	83.0 ± 8.8	83.6 ± 8.8
Arterial oxygen saturation (%)	96.8 ± 1.0	96.2 ± 1.7	96.1 ± 1.8	96.5 ± 1.1	96.5 ± 1.3	96.4 ± 1.4
Central venous oxygen saturation (%)	78 ± 7	61 ± 5*	64 ± 3*	67 ± 7*	70 ± 9*	73 ± 9*†
Venous to arterial carbon dioxide gap (mmHg)	5.3 ± 2	9.6 ± 2.3*	8.9 ± 1.7	7.3 ± 2.7	6.7 ± 2.6	5.1 ± 2.6†
Lactate (mmol/l)	1.62 ± 0.43	3.86 ± 1.49*	4.75 ± 1.88*	4.75 ± 2.07*	4.17 ± 2.06*	3.54 ± 1.9*
Hemoglobin (g/dl)	12.05 ± 1.37	11.22 ± 1.39*	10.6 ± 1.52*	9.53 ± 1.29*	8.58 ± 1.49*†	8.45 ± 1.1*†

Data are expressed as mean ± standard deviation.
*$P < 0.05$ significantly different from T_{bsl}.
†$P < 0.05$ significantly different from T_0.

dPmax, but it did not achieve statistical significance. Pulse contour analysis driven SVV and PPV increased from T_{bsl} to T_0 and normalized by T_4. Both the SVV and the PPV showed significant negative correlation with SVI determined by thermodilution ($R = –0.53$; $P < 0.001$; $R = –0.615$; $P < 0.001$).

Blood gas parameters

Parameters of oxygen delivery and consumption are summarized in Table 2. Oxygen delivery decreased after the bleeding but remained lower as compared with T_{bsl} despite improvement during resuscitation. Hemoglobin levels also decreased from T_{bsl} to T_0 and remained lower at the end of resuscitation as compared with T_{bsl}. Oxygen comsumption increased after the bleeding, and although remained elevated until the end of the experiment, it did not reach statistical significance. Oxygen extraction (VO_2/DO_2) also increased by T_0 and improved during resuscitation; however, it did not return to its baseline value by T_4. Lactate levels increased from T_{bsl} to T_0 and remained elevated throughout, with a non-significant decrease from T_0 to T_4.

$ScvO_2$ decreased from T_{bsl} to T_0 and although increased by T_4, it remained lower, with a mean difference of 5% as compared with T_{bsl}. There was significant correlation between SVI and $ScvO_2$ and dCO_2 (Figs. 2 and 3). There was also a strong significant correlation between dCO_2 and oxygen extraction (Fig. 4).

Discussion

The main findings of our experiments are that: (1) $ScvO_2$ and dCO_2 showed good correlation with SV during bleeding-caused hypovolemia and fluid resuscitation; 2) while dCO_2, PPV and SVV together with SVI, returned to the baseline physiological value, $ScvO_2$ did not.

SV as resuscitation endpoint

Several clinical investigations found that perioperative goal-directed therapy had positive effects on overall outcome after surgery.[7,8] Most of these algorhythms focused on optimization of CO, oxygen delivery[21,22] or SV.[23,24] Although MAP and CVP remain the most often used hemodynamic parameters during high-risk surgery,[9] there is mounting evidence that neither MAP nor CVP are appropriate and reliable indices of changes in CO and SV during fluid resuscitation in the critically ill.[10,11]

During bleeding to restore homeostasis, the symphatetic nervous system becomes activated and releases epinephrine and norepinephrine. As a result, venous return will increase, while on the arterial side norepinephrine-caused vasoconstriction tries to maintain perfusion. Because of the symphatetic activation, HR and myocardial contractility will also increase. During resuscitation, our pivotal goal is to restore circulating blood volume by increasing SV to improve oxygen delivery. Recent clinical investigations[23,24] showed positive effects of SV optimization, and there is frank evidence that PPV and SV variation are well-established indicators of fluid responsiveness.[25] In our experiment, both parameters determined by pulse contour analysis became significantly elevated during hypovolemia and returned to their baseline values by the end of resuscitation.

Conventional parameters such as HR, MAP and CVP failed to follow the changes in SV; therefore,

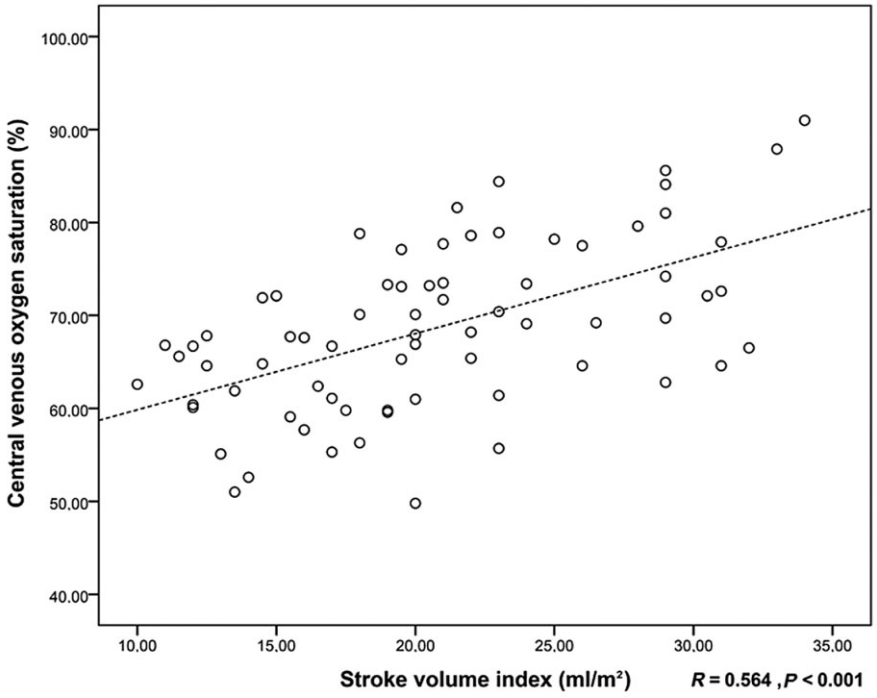

Fig. 2. Correlation between central venous oxygen saturation and stroke volume index. Data are presented as scatter with a linear regression line.

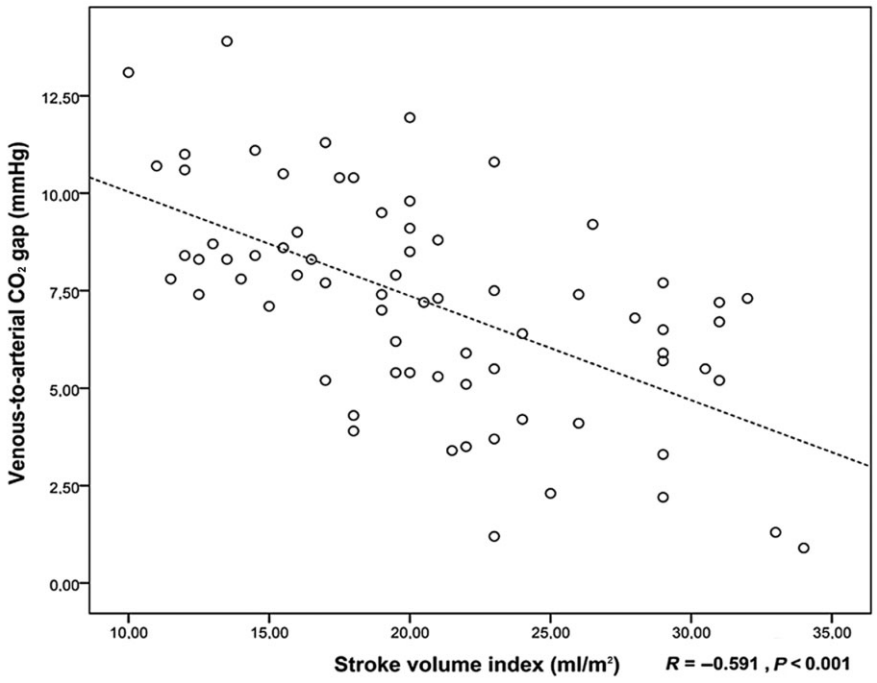

Fig. 3. Correlation between venous-to-arterial CO_2 gap and stroke volume index. Data are presented as scatter with a linear regression line.

our results do not support their routine use as accurate resuscitation endpoints. These are also in accord with the findings of several recent clinical studies.[10,11,25] It is also important to note that normalizing SVI resulted in higher CO by the end of resuscitation as compared with baseline, possibly because of the bleeding-induced sympathetic response, which caused tachycardia and a tendency of increased contractility, which was present until the end of the experiment. These results suggest the superiority of SV as primary goal of resuscitation instead of CO, as the latter may mask hypovolemia

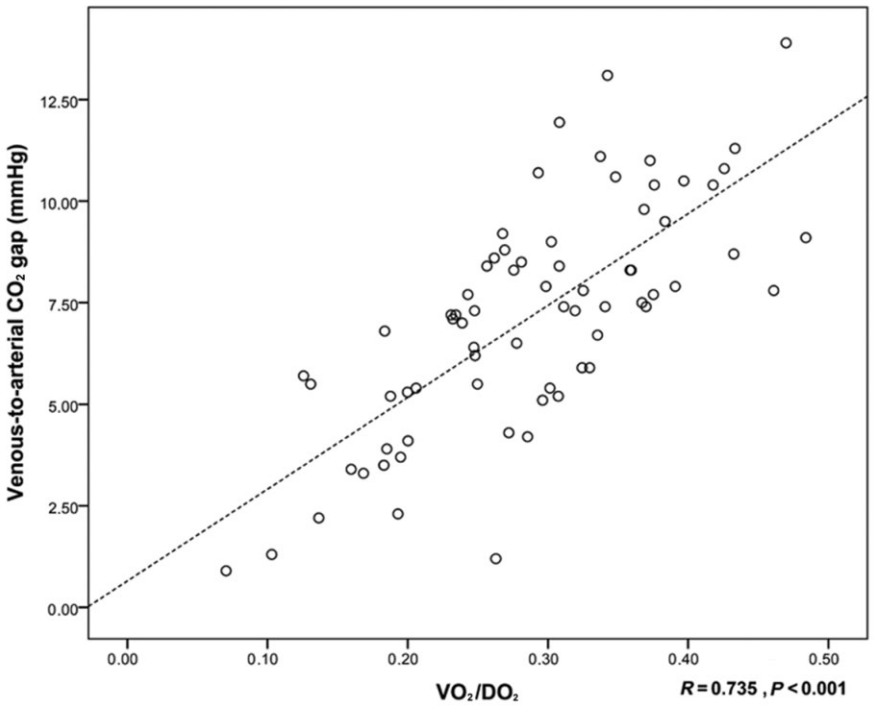

Fig. 4. Correlation between venous-to-arterial CO_2 gap and VO_2/DO_2 (oxygen extraction). Data are presented as scatter with a linear regression line.

due to the increased HR, which is not caused by hypovolemia per se, but the sympathetic response for bleeding. However, this postulate has to be tested in the future.

$ScvO_2$ as therapeutic endpoint

The primary goal of fluid resuscitation in hypovolemia is to maintain adequate oxygen delivery to the tissues. In our experiment, oxygen delivery decreased significantly during the bleeding and returned to a significantly lower value at the end of the study. This finding can mainly be explained by the lower hemoglobin levels caused by hemodilution, as other determinants of oxygen delivery returned to normal or supranormal values. During bleeding, impaired oxygen delivery was accompanied by increased oxygen extraction, which was reflected in the changes of $ScvO_2$.

Physiological mixed venous oxygen saturation ranges between 68% and 77%, and $ScvO_2$ is considered to be 5% higher.[26] However, in patients under general anesthesia the $ScvO_2$ is often higher than 80%, which is due to the reduced oxygen demand and consumption; hence, higher values should be considered as 'normal'.[18]

Regarding the perioperative period, in high-risk surgical patients postoperative low $ScvO_2$ was associated with increased number of complications.[27] In a recent study, aiming to achieve oxygen extraction < 27% as target endpoint, which means keeping $ScvO_2 > 73\%$, reduced the number of organ failures and hospital stay after surgery.[28] In our previous experiments, $ScvO_2$ showed good correlation with oxygen extraction.[29,30] However, it is an important finding of the current study that $ScvO_2$ remained significantly lower at the end of resuscitation as compared with baseline despite that SV has reached its baseline value. One possible cause of this difference between the baseline and final $ScvO_2$ is the significant decrease of the hemoglobin level due to hemodilution that was also observed in previous studies.[31] Therefore, taking baseline $ScvO_2$, measured for example at the beginning of surgery, as a target during fluid resuscitation can potentially lead to fluid overload and should not be aimed for. In contrast, if the patient is hemodynamically stabilized (i.e. PPV, SVV and dCO_2 are also normalized) but the $ScvO_2$ remains low, it can be an alarming sign that the low hemoglobin causes decreased oxygen delivery, which may require transfusion. This is in accord with our recent findings in isovolemic anemia.[29]

dCO_2 as therapeutic endpoint

Several authors have reported increased dCO_2 in different low flow states.[19,20,32,33] In hypoxemia-caused anaerob metabolism, hydrogen ions are generated by the hydrolysis of adenosine triphosphate

to adenosine diphosphate, and by the increased production of lactic acid.[20] These hydrogen ions are buffered by bicarbonate present in the cells, and this process will generate CO_2 production.[32] Arterial $PaCO_2$ is dependent on pulmonary gas exchange, and central venous $PvCO_2$ is dependent on the capability of blood flow to wash out carbon dioxide from the tissues. The Fick principle adapted to carbon dioxide demonstrates the inverse relationship between the CO and dCO_2.[34] Thus, it has been postulated that increased dCO_2 reflects decreased flow.

In our experiment, dCO_2 increased significantly during bleeding and then returned to its baseline value. After bleeding, both SVI and hemoglobin levels decreased significantly, while lactate increased more than twofold predisposing anaerobic CO_2 production due to tissue hypoxia. With the stepwise normalization of the SVI, the clearance of the CO_2 from the tissues was resolved.

In the clinical setting, dCO_2 seems to be a promising target endpoint. A $dCO_2 > 5$ mmHg had 96% sensitivity to predict the occurence of post-operative complications in patients with normal ($\geq 71\%$) $ScvO_2$.[35] In critically ill patients, the dCO_2 is in a good inverse correlation with the CO,[32] and its high value has a bad prognostic factor.[36]

However, if the flow is normal or elevated (hyperdynamic states), the CO_2 produced by anaerobic metabolism can be washed out; hence, there will be no increase in the dCO_2. This phenomenon was demonstrated by Vallet et al. on isolated hind limb of dogs. Their results suggest that dCO_2 increases only in the presence of ischamic hypoxia, but not in hypoxemic hypoxia with intact flow.[37] This also means that reaching the physiological value of the dCO_2 does not mean adequate tissue oxygenation. In a recent animal experiment, we found that adding dCO_2 to $ScvO_2$ for predicting hypovolemia-caused increase of $VO_2/DO_2 > 30\%$ improved positive predictive value from 85% to 100%.[30]

Nevertheless, our current results give further evidence that combining dCO_2 with $ScvO_2$ can be complementary tools not just in the diagnosis in hypovolemia, but also during fluid resuscitation in the perioperative setting.

PPV and SVV to guide fluid therapy

PPV and SV variation are the result of the cyclic lung–heart interactions, and they have been shown to be excellent dynamic indices of fluid responsiveness in mechanically ventilated patients with sinus rhythm.[25] In a recent study, we also found that PPV-guided fluid therapy resulted a decrease in the number of complications in patients undergoing major abdominal surgery.[38] In the current experiment, both SVV and PPV increased significantly following hemorrhage indicating hypovolemia, and at the end of fluid resuscitation they returned to normal values and correlated well with SVI. When SVI was completely restored, PPV, SVV and dCO_2 also returned to the baseline physiological value, while $ScvO_2$ remained lower. Our results give further evidence that while $ScvO_2$ is a good indicator of the VO_2/DO_2 relationship, PPV, SVV and dCO_2 are better indicators of changes in SV.

Limitations

First of all, the results can only partially be extrapolated for the real clinical settings. Reducing the SV by 50% was a strictly controlled scenario, rarely happening in the everyday practice. The observation period at the end of the experiment was also short; therefore, long-term effects of SV-based fluid resuscitation on hemodynamics and oxygen delivery and consumption were not assessed. Another limitation of the model is that bleeding was relatively fast, causing a symphatetic burst, while in the operating room intravascular volume loss and bleeding-caused hypovolemia usually occurs over a longer period of time.

Conclusion

In this experiment in an SV-guided bleeding and fluid resuscitation model, both $ScvO_2$ and dCO_2 correlated well with changes in SV. However, together with SV, PPV, SVV and dCO_2 returned to baseline normal values; $ScvO_2$ still indicated a non-optimal oxygen delivery because of low hemoglobin concentrations. These results suggest that SVI, SVV, PPV and dCO_2 are good hemodynamic endpoints of resuscitation, while $ScvO_2$ is not strictly a hemodynamic parameter, but rather an indicator of the balance between oxygen delivery and consumption.

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Conflicts of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

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