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

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Introduction

An estimated, 234 million operations are performed annually worldwide, of whom high risk surgical patients undergoing major surgery exhibit a significant risk of morbidity and mortality. Despite implementation of pulse oxymetry and capnometry in daily routine as compulsory safety measures in the 1980's, in developed countries perioperative morbidity varies between 3% and 17%, while mortality ranges between 0.4% and 0.8% in the whole surgical population. As it has been revealed in postoperative follow up studies, patients undergoing surgical procedures has higher risk of death after 1 year compared to age- and sex-matched normal populations, furthermore, patients who are higher "resource consumers", has more perioperative complications and require longer in hospital lenght of stay.

Imbalance of oxygen delivery and consumption in the high risk patients

Hemodynamic optimization is fundamental in the treatment of critically ill patients in both the operating room and in the intensive care unit. Under physiological circumstances tissue oxygenation is the net product of oxygen delivery and oxygen consumption:

$$DO_2= SV \times HR \times (Hb \times 1.34 \times SaO_2+(0.003 \times PaO_2))= CO \times CaO_2$$

$$VO_2= CO \times (CaO_2 - (Hb \times 1.34 \times SvO_2+(0.003 \times PvO_2)))= CO \times (CaO_2 – CvO_2)$$

$$OER= VO_2/DO_2$$

DO_2– oxygen delivery, SV – stroke volume, HR – heart rate, Hb – hemoglobin, SaO_2 – arterial oxygen saturation, PaO_2 – partial pressure of oxygen in the arterial blood, CO – cardiac output, CaO_2 – arterial oxygen content, VO_2 – oxygen consumption, SvO_2 – mixed venous oxygen saturation, CvO_2 – venous oxygen content.

Looking at these equations it becomes obvious that the main difference between DO_2 and VO_2 is the oxygen content (CaO_2 vs. CvO_2), especially the venous oxygen saturation, which is the most prominent parameter that is different on the venous side, therefore, theoretically it can be useful to assess the imbalance between DO_2 and VO_2, often present in the critically ill. When DO_2 is decreasing, due to several compensatory mechanisms, oxygen extraction is maintained for a considerable length of time. However, after a certain period compensatory

mechanisms become exhausted, and beyond that critical point VO_2 becomes delivery dependent.

Monitoring of tissue oxygenation

Mixed venous oxygen saturation – Central venous oxygen saturation

Mixed venous oxygen saturation (SvO_2) measured in the pulmonary artery, which detects changes in the balance between DO_2 and VO_2 of the whole body. Measurement of SvO_2 is not feasible in the everyday clinical practice, on the contrary, central venous oxygen saturation ($ScvO_2$) measured in the superior vena cava is a good alternative of SvO_2. The normal value of $ScvO_2$ ranges between 67-77%, which is 5-8% higher compared to SvO_2. Although in absolute values these parameters are not interchangeable, but their trends show good correlation in various disease states. Both increased VO_2 and decreased DO_2 can lower $ScvO_2$. Therefore, $ScvO_2$ can mirror the balance between DO_2 and VO_2.

Lactate metabolism

In a healthy person at about 1500 mmol lactate is produced daily, which is metabolized resulting in a steady state level of less than 2 mmol/l in the blood. High lactate levels are often present in critically ill patients and generally considered as a very important alarming sign of oxygen debt, hypoperfusion and shock. Hyperlactatemia can also be present when its breakdown in the Cori-cycle, in the liver and the kidneys is impaired. During the clearance, lactate oxidation and gluconeogenesis plays a major role in the liver and the kidneys. Permanent hyperlactatemia can be seen by patients with severe acute liver failure or chronic end stage liver disease. So the summation of lactate production and breakdown determines the lactate clearance throughout the time course of the diseases. Among critically ill patients high lactate levels are strong predictors of morbidity and mortality.

Venous to arterial carbon dioxide gap

Venous to arterial carbon dioxide gap (dCO_2) is an easily attainable blood gas-driven parameter, when a central venous catheter and an arterial catheter are available. It can be calculated by extracting central venous partial pressure of carbon dioxide from the arterial partial pressure of carbon dioxide. Physiologically its value is under 6 mmHg.

In anaerobic conditions, under tissue hypoxia, hydrogen ions are in minority through lactate production and mainly by the hydrolysis of adenosine triphosphate. These hydrogen ions are buffered with the bicarbonate buffer system through the carbonic anhydrase enzyme. Under sufficient flow carbon dioxide is washed out from the tissues, resulting normal venous to arterial carbon dioxide gap, while during low flow states blood has a longer transit time so it can take up more carbon dioxide. This is called the "stagnation phenomenon", hence the gap is increased.

Blood transfusion

When bleeding is persent, not only fluid, but also hemoglobin is lost. That plays a crucial role in the development of the imbalance between DO_2 and VO_2. Fluid replacement can restore the circulating blood volume, but due to hemodilution, the decreased hemoglobin level can also impair oxygen delivery. To restore DO_2, packed red blood cell has to be administered, which is also a double edge sword. On the one hand it can be life saving, but carries all the risks of allogenic blood transfusion. Therefore, physicians face two very important questions: 1) which parameter to use as transfusion trigger, and 2) how to assess the efficacy of blood transfusion?

Recent clinical investigations and experimental studies shows that alternative transfusion triggers like $ScvO_2$, electrocardiogram ST-segment analysis, or regional tissue oxymetry can help the physicians to optimize the hemoglobin level according to the needs of specific organs in the cross section of blood loss, replacement and underlying diseases.

Aims of our experiments

Despite all the above detailed pathophysiological rationale and decades of intensive research, there is no worldwide consensus about the goals, which should be targeted during fluid replacement. Therefore, we decided to design a bleeding-resuscitation experimental animal model and our aims were the following:

1. To describe the kinetics of $ScvO_2$, dCO_2 and lactate and to test their usefulness as therapeutic endpoints during a moderate hemorrhage and resuscitation animal experiment.

2. To investigate the role of dCO_2 as hemodynamic parameter and $ScvO_2$, as a marker of oxygen extraction as complementary tools for transfusion trigger during hemorrhage and fluid resuscitation

3. To compare the effects of stroke volume index-, as compared to cardiac index-guided resuscitation on $ScvO_2$ and dCO_2 in a controlled hemorrhage and fluid resuscitation model.

Materials and methods

The experiments were carried out in strict adherence to the NIH 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./142/2013.

Animals and instrumentation

Anesthesia was induced on minipigs 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/hr iv.), while analgesia was maintained with nalbuphine (0.1 mg/kg). Animals were ventilated with a tidal volume of 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. Animals were kept warm ($37\pm1^{o}C$) 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.

Stroke volume guided bleeding and fluid resuscitation: experiment-1

After catheterizations, animals were allowed to rest for 30 minutes after which baseline (T_{bsl}) hemodynamic measurements, blood gas analysis and laboratory testing were performed. After these measurements, blood was drained until the stroke volume 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 4 steps during fluid resuscitation (T_{1-4}) to reach the initial SVI by T_4. After reaching each step, 20 minutes were allowed for equilibrium, than hemodynamic and blood gas parameters were measured.

Stroke volume guided bleeding and cardiac index targeted fluid resuscitation: experiment-2

The animals were instrumented and monitored the same way as described in the previous experiment. After 30 minutes resting baseline (T_{bsl}) hemodynamic, blood gas measurements were performed. Thereafter, blood was drained until the stroke volume index dropped by 50% of its baseline value (T_0), then measurements were repeated. Pigs were resuscitated in the same pattern as in experiment-1 except, this time baseline cardiac index was target of resuscitation.

Results

Stroke volume based fluid resuscitation : experiment-1

12 animals weighing 23±5 kg underwent a 6-hr fast preoperatively but with free access to water. During bleeding 314±65 ml blood had to be drained to reach the target of 50% reduction in SVI. For resuscitation 951±307 ml crystalloid infusion was administered in total by T_4 to achieve the target value obtained at T_{bsl}.

Measures of Oxygen Debt

DO_2 decreased after bleeding and remained lower as compared to 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 to T_{bsl}. VO_2 increased after 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.

The pattern of $ScvO_2$ showed similar trends as seen in VO_2/DO_2. Levels decreased from T_{bsl} to T_0 and increased by T_4. Although $ScvO_2$ normalized by T_4, but it remained lower as compared to T_{bsl} with a mean difference of 5%.

dCO_2 increased almost two fold of its initial value during hemorrhage and decreased gradually during fluid replacement. At the end of the experiment it returned to the physiological range.

There was significant correlation between stroke volume index and $ScvO_2$ and dCO_2. There was also a strong significant negative correlation between dCO_2 and oxygen extraction.

Cardiac index based resuscitation: experiment-2

12 animals weighing 27.5 ± 5.4 kg went through the same procedure like animals in experiment-1. For a 50% decrease of SVI 479 ±101 ml blood had to be drained and 900 [850-1780] ml had to be replaced in the cardiac index based group to reach baseline cardiac index.

Measures of Oxygen Debt

During cardiac index based resuscitation at the end, DO_2 remained significantly lower at T_4 as compared to T_{bsl}. This can be partially explained by the significant and steady decrease in the hemoglobin level. VO_2/DO_2 increased after bleeding and showed a similar kinetic as in experiment-1. $ScvO_2$ was in the normal range at T_{bsl}; while after bleeding there was a drop, which remained significantly lower at the end of the experiment. The mean decrease from T_{bsl} to T_0 was 22.5% and at T_4 it was 15.1% lower as compared to T_{bsl}. dCO_2 was normal at T_{bsl}, and after bleeding it increased significantly and although it remained elevated throughout the experiment, but at T_{2-4} his difference was not statistically significant as compared to T_{bsl}.

Discussion

Changes of $ScvO_2$ during stroke volume and cardiac index controlled hemorrhage and resuscitation

The primary goal of fluid resuscitation in hypovolaemia is to maintain adequate DO_2 to the tissues. During stroke volume guided exsanguination oxygen delivery decreased significantly 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. During bleeding impaired oxygen delivery was accompanied by increased oxygen extraction, which was reflected in the changes of $ScvO_2$.

Low $ScvO_2$ is an alarming signal of inadequate oxygen delivery, therefore it is generally agreed that in the presence of this warning sign diagnostic approaches and interventions are needed. On the other side, interpretation of normal and supranormal $ScvO_2$ is more challenging. In patients under general anesthesia $ScvO_2$ is often higher than 80%, which is due to the reduced oxygen demand and consumption, hence the range of "normal" value should be considered higher in the operating room as in other scenarios.

Regarding the perioperative period, in high risk surgical patients postoperative low $ScvO_2$ was associated with increased number of complications. The best cut of value for discriminating patients who will develop complications was 73% for $ScvO_2$. Lower $ScvO_2$ was also independently associated with increased number of complications. 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. In a novel clinical study carried out by our research group, intraoperative $ScvO_2$ assisted hemodynamic optimization also resulted better organ function and 28-days survival compared to conventional treatment. Our previous animal experiments also demonstrated, that $ScvO_2$ showed good correlation with oxygen extraction.

One of the most important finding of our current study is, that $ScvO_2$ remained significantly lower at the end of resuscitation as compared to baseline with a mean of 5%, despite that stroke volume has reached its baseline value. This difference was even more pronounced during the cardiac index based resuscitation model, where $ScvO_2$ remained almost 15% below the baseline value. In both experiments, one possible factor of this difference between the baseline and final $ScvO_2$ is the significant decrease of the hemoglobin level due to

hemodilution. When bleeding is present both hemoglobin and fluid is lost which alters oxygen transport capacity. Fluid loss impairs cardiac output and decreased hemoglobin level decreases blood oxygen content. With fluid replacement only one component is treated, therefore oxygen delivery is only partially restored. This is what we saw in experiment-1, that although stroke volume was normalized but hemodilution had a significant effect on the hemoglobin levels, hence on oxygen delivery. In experiment-2 however, animals may have remained severely under-resuscitated, indicated by the very low $ScvO_2$ value at the end of the trial period. Bleeding can cause an inreased sympathetic activation, which also increases oxygen consumption and this is what we found in both experiments during the bleeding phase, which more-or-less normalized during the resuscitation phase. The net effect of reduced delivery and increased or unchanged consumption are mirrored in the lower $ScvO_2$ throughout the experiment.

These findings have very important clinical implications. Our results indicate that taking baseline $ScvO_2$, measured for example at the beginning of surgery, should not be considered as a "target" or "goal" during fluid resuscitation, because this can potentially lead to fluid overload, as "low" $ScvO_2$ may indicate inadequate resuscitation, although the circulation and stroke volume is already restored. Our results also draw the attention to the fact, that treating one single parameter, such as $ScvO_2$ in this case, can be misleading. Taking other parameters of oxygen delivery and perfusion into account and tailoring patient management in this multimodal fashion should have a very important role in the future.

Blood transfusion and $ScvO_2$

Low hemoglobin levels in the perioperative period are accompanied by increased mortality, therefore early treatment of anemia is mandatory, especially when treating high risk surgical patients. Recently, arbitrary cut off values, like the "10/30" rule, were interchanged with a restrictive concept, where hemoglobin levels between 70-90 g/l were targeted as transfusion thresholds depending on the patients' co-morbid condition. The paradigm shift was also strenghtened by the TRICC trial, a large randomized controlled study, which could not show any benefit when used liberal blood transfusion strategy compared to restrictive portocols. In the restrictive group, transfusion was indicated only below 70g/l. Patients with "special" undelying diseases like ischemic heart diseases, or brain ischemia forms another subgroup. In

these patient population tissue oxygenation should be monitored to determine the critical threshold of blood transfusion.

It is important to note, that our primary goal with blood transfusion is not to increase hemoglobin, but to increase oxygen delivery and so to restore the balance between the oxygen supply and demand. To monitor these changes $ScvO_2$ may be a valuable parameter. In a recent clinical investigation during blood transfusion, patients with low inital $ScvO_2$ level there was an improvement in their oxygen imbalance, while patients with normal $ScvO_2$ had no improvement despite the increase in their hemoglobin level.

If the patient is adequately resuscitated (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 an isovolemic anemia model, where blood loss was immediately restored with the same amount of colloid, and we found that $ScvO_2$ showed very good correlation with VO_2/DO_2. These results underscore the importance of $ScvO_2$ in the assessment VO_2/DO_2 and give the rationale for its applications an alternative transfusion trigger. However, as our results suggest, $ScvO_2$, which is a very useful indicator of the VO_2/DO_2 imbalance, on its own is unable to answer all questions during the bleeding-resuscitation process. One of the possible complementary tools to be used as resuscitation endpoint is the central venous-to-arterial CO_2 gap, the dCO_2.

Kinetics of dCO_2 during stroke volume and cardiac index based hemorrhage and fluid replacement

During stroke volume based resuscitation dCO_2 increased during bleeding, and then returned to its baseline value. After bleeding both SVI and hemoglobin levels decreased, while lactate increased more than two fold predisposing anaerob carbon dioxide production due to tissue hypoxia. With the stepwise normalization of the SVI the clearence of the carbon dioxide from the tissues resolved. On the contrary, during cardiac index guided fluid replacement in Experiment-2, dCO_2 remained higher compared to its baseline value, although this difference became non-significant after T_2. Nevertheless, out data give further support that the higher dCO_2 may indicate inadequate flow, hence in experiment-2 this could have been a warning signal of residual hypovolemia.

Several authors have reported increased dCO_2 in different low flow states. In hypoxemia-caused anaerob metabolism, hydrogen ions are buffered by bicarbonate present in the cells, and this process will generate CO_2 production. 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 cardiac output and dCO_2. It has been postulated that increased dCO_2 reflects decreased flow.

In the perioperative setting dCO_2 is a good predictive factor. Preoperatively, patients with high dCO_2 had significantly higher mortality compared to patients with normal values (36.4% versus 4.5%). High risk surgical patients admitted to intensive care unit postoperatively with high dCO_2 also developed more complications. Furthermore, the cut off value was 5.8 mm Hg. A dCO_2 >5 mm Hg had 96% sensitivity to predict the occurence of postoperative complications in patients with normal ($\geq$71%) $ScvO_2$. In critically ill patients, the dCO_2 is in good inverse correlation with the cardiac output and it has also been shown to be a good predictor a bad outcome in patients with septic shock. In a recent animal experiment, we found that adding dCO_2 to $ScvO_2$ for predicting hypovolemia-caused increase of oxygen extraction >30% improved positive predictive value from 85 to 100%.

In both current experiments dCO_2 increased significantly during bleeding reflecting inadequate flow, due to low cardiac output at T_0. When blood loss was corrected stepwise, dCO_2 decreased also gradually and returned to its baseline at the end of stroke volume based resuscitation, however when fluid therapy was targeted according to cardiac index, dCO_2 remained higher suggesting persisting "low flow" state. However, this low flow state was not indicated by the measured cardiac index, which was very similar in both groups at each measurement point and could be regarded as "normal" in both groups at the end of the experiments. Nevertheless, in the cardiac index targeted group stroke volume remained significantly lower by the end of the experiment, both compared to baseline and to the stroke volume resuscitated animals, indicating that although cardiac index "normalized", but this was due to tachycardia rather than the restoration of stroke volume.

Therefore, 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 the management of bleeding patient in the perioperative setting.

Lactate clearance as resuscitation endpoint during hemorrhage

In our experiment, lactate increased more than two fold during bleeding and further increased during the first two resuscitation steps. At the end of resuscitation it showed a 25% decrease compared to the highest value, but remained significantly higher compared to the physiological range.

Increased lactate production is mainly due to anareobic metabolism caused by tissue hypoxia. High lactate concentrations are common findings during the management of hemodynamically unstable, bleeding patients. Surgical patients admitted to the intensive care unit with high initial and 24 hours lactate level had higher mortality compared to patients with normal levels. Furthermore, there is mounting evidence, the lactate clearance is superior to single values and mirrors better the effect of therapy not only in septic, but also in surgical patients. Patients with longer duration of high lactate levels, had worse outcome, compared to patients, who responded to resuscitation and had a declining lactate levels.

In our experiment lactate levels showed a steady decline towards the end of the study protocol and it is possible that with longer observation time it would have also decreased to its normal value. However, its kinetic was slower as compared to dCO_2 and $ScvO_2$, so it can not signal when to stop fluid replacement, rather it should be applied as a very strong "retrospective indicator" of effective therapy. By and large it seems, and it also follows physiological rationale, that lactate one step behind $ScvO_2$ and dCO_2, as it only increases when there is oxygen debt and anerobic metabolism, while $ScvO_2$ and dCO_2 give signals well before oxygen debt occurs. Current guidelines consider and recommend the normalization of lactate levels within the first 6 hours after the beginning of resuscitation. Our results suggest that significant changes can take place within 15-20 minutes during resuscitation, therefore, waiting for 6 hours to assess the efficacy of resuscitation may be far too long. According to our data, changes can occur within minutes and by applying two simple blood gas tests of the arterial and central venous blood and taking all of the above mentioned indices of $ScvO_2$, dCO_2 and lactate levels into account and use them as complementary measures may provide very fast and effective measures to monitor and even guide resuscitation.

Conclusions

The main findings of our experiments are:

1) $ScvO_2$ is affected by fluid resuscitation caused hemodilution, reflected in significantly lower level at the end of resuscitation than at baseline, therefore, it cannot be used as a single parameter for resuscitation endpoint. dCO_2 mirrored both the decrease and the restoration of stroke volume during hemorrhage and volume replacement. Therefore, dCO_2 can be used as a complementary tool to assess the efficacy of fluid resuscitation and restoration of flow.

2) Lactate levels change rapidly during bleeding and resuscitation, but in general lactate levels remain higher at the end of resuscitation as compared to $ScvO_2$ and dCO_2. Our data also suggest that lactate levels change significantly within minutes, therefore can be a very useful tool in monitoring the progress of patients well within the currently recommended time frame of 6 hours.

3) During moderate hemorrhage and fluid resuscitation, normalization of the flow driven parameter of dCO_2 with other hemodynamic parameters like pulse pressure variation and stroke volume variation can indicate termination of fluid therapy, but low levels of $ScvO_2$ can be an alarming sign of persisting oxygen debt indicating blood transfusion.

4) During stroke volume guided resuscitation dCO_2 normalized with the restoration of stroke volume index and $ScvO_2$ mirrored increased oxygen extraction. When cardiac index was targeted during resuscitation, elevated levels of dCO_2 and low levels of $ScvO_2$ indicated inadequate resuscitation despite normalization of cardiac index.

Acknowledgement

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