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Role of Central Venous - Arterial pCO_2 Difference in Determining Microcirculatory Hypoperfusion in Off-Pump Coronary Artery Bypass Grafting Surgery

Mini Review

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Goal-directed therapy is based on optimizing parameters such as stroke volume, cardiac output (CO), cardiac index (CI), and/or perfusion parameters such as stroke volume variation, central venous oxygen saturation($ScvO_2$), mixed venous oxygen saturation (SvO_2), and arterial lactate [1,2]. Assessment of SvO_2 from a pulmonary artery catheter is considered as an indirect marker of global tissue oxygenation and it reflects matching between arterial oxygen delivery (DO_2) and O_2 consumption (VO_2) [3]. A low SvO_2 indicates high oxygen extraction ratio (OER) to maintain aerobic metabolism with constant O_2 consumption in response to an acute fall in DO_2. But, when DO_2 is below critical level, OER is no longer capable of upholding O_2 consumption, and global tissue hypoxia ensues, as indicated by the high lactate levels [4,5]. $ScvO_2$ can be obtained easily and trends in $ScvO_2$ closely mirrors SvO_2 [6]. Cardiac surgery induces ischemia-reperfusion injury along with systemic inflammatory response leading to capillary shunting and mitochondrial damage [7].

These changes cause disturbances in tissue oxygen extraction and leads to normal/high $ScvO_2$ values. $ScvO_2$ is measured downstream from the tissues, So, Low venous O_2 saturation from tissue with inadequate DO_2 is masked by highly saturated blood from tissue with better perfusion resulting overall normal or high $ScvO_2$ and remaining blind to local perfusion disturbances [8]. Impaired tissue oxygenation leads to increased anaerobic metabolism and production of pyruvate, which is subsequently converted to lactate. Serum lactate is a marker of global tissue hypoxia in circulatory shock. Hyperlactatemia in cardiac surgery may be due to other mechanisms like - stress response to surgery, use of β adrenergic agonist, sepsis, hyperglycaemia etc [9,10]. Therefore, after cardiac surgery, hyperlactatemia may not be a reliable means of judging the adequacy of tissue oxygenation.

Influence of Cardiac Output on P (v-a) CO_2:

Venous - to – Arterial CO_2 tension difference P (v-a) CO_2 is the gradient between PCO_2 in mixed venous blood ($PvCO_2$) and PCO_2 in arterial blood ($PaCO_2$):

P (v-a) CO_2 = $PvCO_2$ - $PaCO_2$

$PvCO_2$ & $PaCO_2$ are partial pressures of the dissolve CO_2 in the mixed venous and arterial blood, respectively.

According to the modified Fick equation P (v-a) CO_2 is related to CO_2 production (VCO_2) and inversely linked to cardiac output [11]. Under steady states of both VO_2 & VCO_2 , P (v-a) CO_2 is observe to increase in parallel with the reduction in cardiac output because of a low flow – induced tissue CO_2 stagnation phenomenon. Due to the decreasing of transit time, higher than usual addition of CO_2 per unit of blood passing the efferent micro vessels, leads to produced hypercapnia in venous blood. As long as alveolar respiration is sufficient, a gradient will occur between $PvCO_2$ & $PaCO_2$. However, under spontaneous breathing situations, hyperventilation, stimulated by the decreased blood flow, may reduce $PaCO_2$ and thus may prevent the CO_2

stagnation-induced rise in $PvCO_2$. This finding underscores the utility of calculating P (v-a) CO_2 rather than simply assessing $PvCO_2$, particularly in case of spontaneous breathing.

As per Ariza et al [12], better approximation of $PaCO_2$ under normal condition of cardiac output and arterial oxygen saturation is $PaCO_2$= 0.8 $PvCO_2$. The major determinant of increased dCO_2 is decreased tissue perfusion. So, dCO_2 can be considered as an indicator of adequate blood flow to remove CO_2. Study done by Jigisha, Hitendra et al*, the authors have done prospective observational study of 100 elective off pump CABG patients and they have evaluated the central venous to arterial PCO_2 difference (dCO_2) in patients with central venous saturation ($ScvO_2$) ≥ 70% and its relationship to the hemodynamic profile, post-operative outcome and complications. After admission in ICU arterial and central venous and mixed venous blood samples were taken to collect $ScvO_2$, Svo_2, PO_2, SaO_2, PCO_2 and lactate.

Oxygen delivery index (DO_2I), oxygen consumption index (VO_2I), arterial oxygen content (CaO_2), venous oxygen content (CvO_2) and oxygen extraction ratio (OER) were calculated using standard formulae (ANNEXURE). The dCO_2 was calculated as the difference between the PCO_2 of central venous and arterial blood. Based on the first measurement of dCO_2, the patients were divided into two groups, the high dCO_2 group (Group A, dCO_2 > 8mmHg) and low dCO_2 group (Group B, dCO_2 ≤ 8mmHg). The CaO_2 1st hour after ICU admission was significantly lower in group A, gradually CaO_2 improved over time and showed no difference at 18thhour after ICU admission. Similarly, DO_2I was also lower in group A on admission and remained lower than group B at all point of time but the difference was not significant. While comparing the CvO_2, it was significantly lower in group A at 1st hour after ICU admission and remained lower at 18th hour. OER was significantly higher in group A as compared to group B at 1st hour. VO_2I did not show a significant difference.

Annexure:

Calculation formulas

Cardiac index (L/min/m^2)

$CI = CO/ BSA(m^2)$

CI, cardiac index; CO, cardiac output

Oxygen delivery (mL/min/m^2)

$DO_2I = CaO_2 \times CI \times 10$

DO_2I, oxygen delivery; CaO_2, arterial oxygen content; CI, cardiac index

Oxygen consumption (mL/min/m^2)

$VO_2I = (CaO_2 - CvO_2) \times CI \times 10$

VO_2I, oxygen consumption; CaO_2, arterial oxygen content; CvO_2, oxygen content; CI cardiac index

Arterial oxygen content (mL/dL)

$CaO_2 = (Hb \times 1.39 \times SaO_2) + (0.0031 \times paO_2)$

CaO_2, arterial oxygen content; Hb, hemoglobin concentration; SaO_2, arterial oxygen saturation; paO_2, arterial partial pressure of oxygen: 1.39 is the oxygen-carrying capacity of hemoglobin (mL O_2/ gram Hb); 0.0031 is the solubility coefficient of oxygen in plasma (mL O_2/mmHg pO_2)

Mixed venous oxygen content (mL/dL)

$CvO_2 = (Hb \times 1.39 \times SvO_2) + (0.0031 \times pvO_2)$

CvO_2, mixed venous oxygen content; Hb, hemoglobin concentration; SvO_2, mixed venous oxygen saturation; pvO_2, mixed venous partial pressure of oxygen

Oxygen extraction rate (%)

$OER = VO_2I/DO_2I$

VO_2I, oxygen consumption; DO_2I, oxygen delivery

Post-operative outcome parameters: Cardiovascular complications were defined as new arrhythmias or a newly diagnosed myocardial ischemia detected in the electrocardiogram (new Q-wave, ST-elevations >2 mm), or a ratio of creatine kinase (CK) and its myocardial subtype (CK-MB) >10%. Neurologic complications were defined as transitory ischemic attack and postoperative delirium; pulmonary complications defined as respiratory failure and the need for reintubation, prolonged Respiratory support (>48h) or the need for continuous positive airway pressure breathing; renal complications were defined as patients requiring renal replacement therapy and continuous intravenous loop diuretics or patients with an increase of creatinine >2.0mg/dl.

The observed hemodynamic, oximetric and laboratory alterations were associated with a significantly prolonged need for mechanical ventilation (14.90 ± 10.33 vs 10 ± 9.65hrs., p=0.04) and ICU stay (5.05 ± 2.52 vs 3.75 ± 2.36days, p=0.049) in group A. Incidence of re-exploration was similar in both the groups. The total duration of hospital stay was significantly higher in group A. In the high dCO_2 group, out of 20 patients, one patient died due to multiorgan failure and septic shock, while in the low dCO_2 group, out of 45 patients, one patient died due to respiratory failure and sepsis.

Ospina-Tascon et al [13] have done post-operative observational

study on 85 patient with septic shock episode and concluded that patient with persistently high and increasing P(v-a)CO_2 had significantly higher SOFA scores at day–3 and higher mortality rate at day-28 . Interestingly, poor agreement between cardiac output and P (v-a) CO_2 was observed at different point of resuscitation. Persistence of high P(v-a) CO_2 (≥ 6mmHg) during the first 6 hours of reanimation of septic shock, patients were linked to more sever multiple organ failure and higher mortality rate. Another study by Bakker et al [14] septic patients showed that a high dCO_2 was associated with poor outcome and higher lactate levels.

There are many reasons for a high dCO_2. It has been shown that dCO_2 was related linearly to CO_2 production and inversely related to cardiac output [15]. Several studies showed that if global or regional blood flow was critically reduced or unevenly distributed as in shock, venous blood carbon dioxide increased [16,17]. Therefore, dCO_2 may increase after hypoperfusion because of a decreased washout [18]. Thus, dCO_2 also has been proposed as a marker of tissue hypoxia [19]. Durkin et al [20] described 2 different mechanisms for increased dCO_2 in patients suffering from shock. The first mechanism was related to the lower blood flow in shock patients. A longer blood transit time in the microcirculation because of decreased microcirculatory flow causes more carbon dioxide to diffuse into venous blood. Secondly, because of the increased ventilation-to-perfusion ratio, arterial partial pressure of carbon dioxide decreases as well. Another possible mechanism is a relative increase in carbon dioxide production by ischemic cells through anaerobic metabolism, which would explain the relative increase of venous-to-arterial partial pressure of carbon dioxide [20,21].

In the investigation, patients with a high dCO_2 showed a tendency towards lower CI and higher lactate level. This was in line with the results described by Durkin et al [20], e.g., related to microcirculatory hypoperfusion in the hepatosplanchnic region. Therefore, the results could be interpreted as insufficient tissue perfusion with lactic acidosis due to anaerobic metabolism. Other studies reported a correlation between dCO_2 and CI [22].These findings are comparable to results of study by Jigisha et al*. The fact that patients with high dCO_2 had significantly higher OER and decreased DO_2I, was in line with the assumption of splanchnic hypoperfusion. This finding correlated well with the significantly lower SvO_2 compared to the $ScvO_2$ at the same time point.

They were able to demonstrate that the oxygen extraction rate was the main contributing factor for an overestimation of SvO_2 by the use of $ScvO_2$ potentially because of splanchnic hypoperfusion [23]. This was also in line with data from Nygren et al, [24] who showed that patients with intestinal vasoconstriction and hypoperfusion had significantly lower SvO_2 compared to patients with normal intestinal perfusion after cardiac surgery. This was supported by the finding that after hemodynamic deterioration mesenteric blood flow decreased, resulting in venous desaturation of the lower body [25]. Therefore, it seemed quite reasonable to assume splanchnic hypoperfusion in the patients with a high dCO_2 gap. Splanchnic hypoperfusion in the high dCO_2 group also was supported by the increase of the aspartate transaminase (SGOT) on day 1 pointing towards structural liver damage. Clinically, patients with high dCO_2 required longer ICU stay, mechanical ventilation, and had a higher incidence of cardiovascular complications in the postoperative setting. Therefore, it is believed that a substantial cohort of cardiac surgical patients in the postoperative period might have been under-resuscitated if $ScvO_2 \geq 70\%$ alone was used as the goal to assess the adequacy of global and microcirculatory perfusion.

Du et al had also confirmed these findings. [26] Thus, from a physiologic point of view, it seemed reasonable to assume that hemodynamic optimization strategies minimizing dCO_2 aiming at individualized increases of global and regional/splanchnic blood flow to adjust for individual carbon dioxide production might have been more sufficient compared to strategies aiming solely at $ScvO_2 \geq 70\%$.However, more prospective studies testing this hypothesis and findings are needed. Scope: To evaluate the role of dCO_2 in non-cardiac surgical patients & pediatric cardiac surgery patients.

* Jigisha P, Hitendra K, Sunny K, Karan K, Vivek K, Ronakh R, Himani P: Central venous-arterial PCO_2 difference in determining micro-circulatory hypo-perfusion. Annals of Cardiac Anesthesia 2020; Vol 23 Issue 1: 20-26.

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