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Is the venoarterial carbondioxide gradient and lactate predictor of inadequate tissue perfusion during cardiopulmonary bypass?

Venoarteriyel karbondioksit farkı kardiyopulmoner baypasta yetersiz doku perfüzyonunun laktat belirleyicisi mi?

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Background: In this study, we aimed to investigate the possible relationship between the venoarterial gradient of carbon dioxide (Dv-a PCO_2) and lactate during cardiopulmonary bypass (CPB).

Methods: Sixty consecutive patients (35 males, 53 females; mean age 64 years; range 38 to 78 years) who were scheduled for elective isolated coronary artery bypass graft (CABG) surgery were included in the study after obtaining their informed consent and the approval of the ethics committee of the hospital. All patients were followed up by the same surgical and anesthesia team. The adequacy of tissue perfusion during CPB was evaluated by the venoarterial partial carbon dioxide gradient, lactate level, measurement of arterial and venous blood gas, urinary flow rate, and hemodynamic parameters. The measurements were performed in four periods: before CPB (T_1), at the beginning of CPB (T_2) at 36 ºC and 32 ºC of hypothermia (T_3) and at the end of rewarming (T_4) at 37 ºC. The relationship between tissue perfusion parameters was assessed by Pearson's correlation analysis.

Results: There was a significant correlation between Dv-aPCO_2 and the venous lactate level (r=0.54, p=0.046) as well as between Dv-aPCO_2 and the arterial lactate level (r=0.55, p=0.042) during the T_2 and T_4 periods of CPB. There was also a significant correlation between Dv-aPCO_2 and arterial base excess (BE) (r=0.64, p=0.013) and between Dv-aPCO_2 and arterial HCO_3 (r=0.54, p=0.048) during the T_3 and T_4 periods.

Conclusion: Our study results suggest that in the hypothermia period, the increase in the venoarterial carbon dioxide gradient (Dv-aPCO_2) is not inversely associated with insufficient blood flow during CPB and there was a significant correlation between Dv-aPCO_2 and the tissue perfusion parameters during the periods other than hypothermia.

Key words: Cardiopulmonary bypass; tissue perfusion; venoarterial carbondioxide gradient.

Amaç: Bu çalışmada kardiopulmoner baypas (KPB) sırasında venoarteriyel karbondioksit farkı (Dv-a PCO_2) ve laktat arasındaki muhtemel ilişkisi araştırıldı.

Çalışma planı: Hastanemiz etik kurulu onayı ve hasta onamları alınan elektif izole koroner arter baypas greft (KABG) cerrahisi yapılacak 60 ardışık hasta (35 erkek, 53 kadın; ort. yaş 64 yıl; dağılım 38-78 yıl) çalışmaya alındı. Tüm hastalar aynı anestezi ve cerrahi ekip tarafından izlendi. Kardiopulmoner baypas süresince doku perfüzyonun yeterliliği venoarteriyel parsiyel karbondioksit farkı, laktat düzeyi, arteriyel ve venöz kan gazı ölçümü, idrar çıkış hızı ve hemodinamik parametrelerin analizi ile değerlendirildi. Ölçümler kardiopulmoner baypas öncesi (T_1), KPB başlangıcında 36 ºC'de (T_2), hipotermide 32 ºC'de (T_3) ve yeniden ısınmanın sonunda 37 ºC'de (T_4) olmak üzere dört periyotta yapıldı. Doku perfüzyon parametreleri arasındaki ilişki, Pearson korelasyon analizi ile değerlendirildi.

Bulgular: Kardiopulmoner baypasın T_2 ile T_4 periyotları arasında doku perfüzyon parametrelerinden Dv-aPCO_2 ile arteriyel laktat düzeyi (r=0.55, p=0.042) ve Dv-aPCO_2 ile venöz laktat (r=0.54, p=0.046) arasında anlamlı ilişki vardı. T_3-T_4 periyotları arasında da Dv-aPCO_2 ile arteriyel base excess (BE) (r=-064, p=0.013,), Dv-aPCO_2 ile arteriyel HCO_3 (r=-0.54, p=0.048) arasında anlamlı ilişki vardı.

Sonuç: Çalışma bulgularımız, hipotermi döneminde, karbondioksit çözünürlüğündeki değişikliğe bağlı olarak, KBP sırasında venoarteriyel karbondioksit farkındaki (Dv-aPCO_2) artışın yetersiz kan akımı ile ters orantılı olmadığını ve hipotermi periyodu dışındaki dönemlerde, Dv-aPCO_2 ile doku perfüzyon parametreleri arasında anlamlı bir ilişkinin olduğunu göstermiştir.

Anahtar sözcükler: Kardiyopulmoner baypas; doku perfüzyonu; venoarteriyel karbondioksit farkı.

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Most cardiac surgery is currently being performed under cardiopulmonary bypass (CPB). The purpose of CPB is to supply adequate oxygen (O_2) to the tissues and to remove the carbon dioxide (CO_2) that is produced in the tissues from the body. The adequate supply of O_2 to the tissues during CBP depends on maintaining the parameters of the hematocrit (Hct), partial pressure of oxygen (pO_2), mean arterial pressure (MAP), and pump flow values at acceptable limits. However, even when this is possible, sometimes tissue hypoxia occurs during CPB because of the preoperative cardiovascular status and the accompanying preexisting pathologies of other systems.[1,2] Therefore, it is necessary to monitor the adequacy of tissue perfusion using various parameters during CPB and to adjust the hemodynamic parameters according to changing conditions. Blood lactate levels, arterial and venous oxygen saturation, the rate of urinary output, and base excess (BE) have to be monitored during CPB for the adequacy of tissue perfusion. For example, knowing the blood lactate level is vital for monitoring the adequacy of tissue perfusion during CPB.[3,4] However, it is known that changes in the levels of blood lactate are affected by several factors during CPB.[5-8]

Partial pressure of carbon dioxide (pCO_2) in venous blood and the partial pressure of veno-arterial carbon dioxide ($D_{v\text{-}a}pCO_2$) gradients increase due to cessation of circulation, traumatic shock, or inadequate circulation resulting from severe sepsis or a decrease in systemic or pulmonary circulation.[9] During CPB, similar states in systemic and pulmonary circulation have been encountered, and the term "sepsis-like syndrome" has been used for CPB.[10]

Other parameters such as lactate, the veno-arterial carbon dioxide (CO_2) gradient, and mixed venous oxygen saturation (SvO_2) are not accepted as definitive indicators for tissue perfusion, and they all have their own deficiencies. However, they are currently accepted as indirect tissue perfusion indicators. In our study, our aim was to search for any correlations and changes between lactate, the veno-arterial CO_2 gradient, and SvO_2 during the non-physiological state of circulation, or CPB.

PATIENTS AND METHODS

Sixty consecutive patients (35 males, 53 females; mean age 64 years; range 38 to 78 years) who were scheduled for elective isolated coronary bypass were accepted into the study with the approval of the hospital ethics committee and with the informed consent of the patient. There were no exclusions. The demographic data of the patients is shown in Table 1. All of the patients were premedicated with alprazolam 0.5 mg (Xanax) taken orally the night before surgery. Midazolam 125 mic/kg intramuscular (IM) was given 30 minutes before surgery. A 16 G intravenous (i.v.) cannula was used for the i.v. lines of all of the patients admitted to the operation room, and isotonic saline infusion 100 ml/hour i.v. was started. Hemodynamic monitorization of the patients was done with a two-channel electrocardiogram (ECG) (Siemens 7000 model) DII, V5 derivations, a pulse oximeter, invasive arterial pressure (with a catheter placed in the radial artery by an 18 G cannula and an Edwards Lifesciences TruWave Disposable Pressure Transducer, ICU Medical, Inc. San Clemente, CA 92673 USA), and central venous pressure. Induction of anesthesia was performed with midazolam 50 mic/kg and pancuronium 2 mg, followed by fentanyl 25-35 mic/kg and pancuronium in total 0.1 mg/kg. Endotracheal intubation was done after at least five minutes of mask ventilation. Desflurane 3-4% in oxygen 50% and N_2O 50% were used for patients whose hemodynamic parameters were appropriate (systolic blood pressure >120 mmHg, ejection fraction >40%). Anesthesia was maintained using oxygen 50% and air 50% in other patients. Midazolam and vecuronium infusions, both 80 mic/kg/hour, were started. Furosemid 0.5 mg/kg i.v. bolus was given. Beta-blocker agents or vasodilators were used to control hypertension. Heparin 4 mg/kg was given after the left internal thoracic artery had removed, and activated coagulation (ACT) was maintained at between 450-600 seconds. Cardiopulmonary bypass was started following cannulation. The hematocrit values were kept at >18%, with the MAP remaining between 50-80 mmHg, and the pump flow between 2-2.5 $L/m^2/min$ throughout the operation. A fresh gas flow was provided at 1.35 $L/m^2/min$ in order to remove the carbon dioxide which had accumulated in the reservoir during CPB. Moderate hypothermia (32°) was applied to all patients. Antegrade cold crystalloid cardioplegia (7-10 ml/kg) was used after cross-clamping. When the extracorporeal circulation was terminated, midazolam and vecuronium infusions were set at 50 mic/kg/hour. These infusions

Table 1. The demographic and operative data of the patients

Parameters	%	Mean±SD
Age (years)		64±10
Female sex	40	
Basal surface area		1.86±0.18
Cardiopulmonary bypass time (minutes)		72±35
Crossclamp time (minutes)		38±18
Fluid balance at the end of operation (ml)		635±773

SD: Standard deviation.

Table 2. Hemodynamic parameters and blood gas analysis

	T1 (Before CPB)		T2 (CPB, Normothermia)		T3 (CPB, Hypothermia)		T4 (CPB, rewarming)	
	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD
Dv-a PCO_2 (mmHg)		7.96±1.6		5.89±2.1		5.74±2		7.24±2.6
Lactate (mmol/l)		0.9±0.16		0.9±0.2		1.02±0.3		1.6±0.6
Actual base excess		0.2±2		2±1.6		1±1.7		-1.9±2.4
Arterial HCO_3		25±1.7		26±1.7		25±1.2		23±1.9
SaO_2 (%)	99.9		99.9		99.9		99.9	
SvO_2 (%)		74±6		74±7		76±10		59±11
Hematocrit (%)		35±4.7		25±4.3		28.5±4.2		30±5
Mean arterial pressure		80±12		68±13		68±14		71±11
Pump flow		–		2.25±0.1		2.15±0.2		2.15±0.1

CPB: Cardiopulmonary bypass; SD: Standard deviation.

were stopped following skin closure. The efficiency of tissue perfusion was monitored throughout the CPB via the $D_{v\text{-}a}PCO_2$ gradient (by blood samples from the venous and arterial lines of CPB), lactate levels, blood gas analysis of venous and arterial blood, urinary output, and assessment of hemodynamic parameters.

Measurements were conducted at four periods: before CPB (T_1), at the beginning of CPB at 36 °C (T_2), at hypothermia at 32 °C (T_3), at the end of rewarming at 37 °C (T_4).

Data was reported as a percentage or as a mean ± standard deviation (SD), and t-tests were used for continuous variables. The variables were considered significant if *p* values were less than 0.05. During the assessment of the correlation between the tissue perfusion parameters, the differences between the changes in hemodynamic parameters between the periods were found and compared according to Pearson's correlation.

RESULTS

The demographic and operative data of our patients is given in Table 1.

There was no significant correlation between the parameters in any of the periods. The values of $D_{v\text{-}a}PCO_2$ were 5.89±2.1 5.74±2 and 7.24±2.6 in the T_2, T_3, T_4 periods, respectively while the lactate values during the same periods were 0.9±0.2 1.02±0.3 and 1.6±0.6. The hemodynamic and blood gas values are given in Table 2.

The T_2 and T_3 periods were compared with regard to the correlation of the change of tissue perfusion parameters between periods, and Table 3 reveals that there was no significant correlation between $D_{v\text{-}a}PCO_2$ and lactate values. The results in which both the changes in venous lactate (r=0.54, p=0.046) and arterial lactate (r=055, p=0.042) values along with those of $D_{v\text{-}a}PCO_2$ showed significant correlation when the T_2 and T_4 periods were compared. These results are provided in Table 4. A significant correlation was found between $D_{v\text{-}a}PCO_2$ and arterial base excess (BE) values (r=-0.64, p=-0.019) when the T_3 and T_4 periods were compared, and these results are shown in Table 4.

DISCUSSION

The main source of carbon dioxide in our body is CO_2, and it is generated as the byproduct of aerobic metabolism and is produced after the buffering process of acids, such as lactic acid, is induced as the result of anaerobic metabolism. The solubility of CO_2 is 20 times more than that of O_2, so it is more significant for CO_2 to be carried in a dissolved state.[11-13] The main route of excretion for CO_2 in circulation is the lungs, and under normal conditions, the value for $D_{v\text{-}a}PCO_2$ is 2-5 mmHg. The increased load of CO_2 is balanced by

Table 3. The correlations of changes in the tissue perfusion parameters in between the T_2 and T_3 of cardiopulmonary bypass

Parameters	*p*	Coefficient of Pearson correlation
Arterial-venous lactate	0.001	0.87
Mixed venous saturation-arterial HCO_3	0.005	0.7
Arterial base excess-arterial HCO_3	0.046	0.54

Table 4. The correlations of changes in the tissue perfusion parameters in between T_2 and T_4 periods of cardiopulmonary bypass

Parameters	*p*	Coefficient of Pearson correlation
$D_{v\text{-}a}PCO_2$-arterial lactate	0.042	0.55
$D_{v\text{-}a}PCO_2$-venous lactate	0.046	0.54
Arterial-venous lactate	0.001	0.88
Venous lactate-base excess	0.013	-0.64
Arterial HCO_3-arterial base excess	0.001	0.87

Table 5. The correlations of changes in tissue perfusion parameters in between the periods T_3 and T_4 of cardiopulmonary bypass

Parameters	*p*	Coefficient of Pearson correlation
$D_{v\text{-}a}PCO_2$-arterial base excess	0.013	-0.64
$D_{v\text{-}a}PCO_2$-arterial HCO_3	0.048	-0.54
Arterial lactate-venous lactate	0.001	0.90
Arterial base excess-arterial HCO_3	0.001	0.90
Venous lactate-arterial base excess	0.002	-0.75
Venous lactate-arterial HCO_3	0.005	-0.70

the elimination of CO_2 through the lungs. However, it is necessary to increase the transfer of CO_2 to the lungs in order to be able to increase the elimination of CO_2.

In low perfusion states when there is no hypoxia, studies have shown that more CO_2 than normal enters the circulation in the peripheral tissue and causes venous hypercapnia due to the increased circulation time. In turn, this causes the $D_{v\text{-}a}PCO_2$ values to increase.[12,13]

In hypoxic situations in which there is insufficient blood flow, CO_2 production is a result of the tamponade of the acids coming out. This method has less CO_2 production; thus, it is more difficult for the produced CO_2 to enter circulation. Because of this, it is takes more effort to detect the CO_2 produced under hypoxic conditions. High venous flow is needed to wash out the CO_2 produced in the tissue under hypoxic conditions, and it is not possible to detect the produced CO_2 under hypoxic conditions by $D_{v\text{-}a}PCO_2$.[14]

The increase in veno-arterial CO_2 gradient is not only related to the inadequate blood flow but also to CO_2 production and elimination. In septic shock, which is typical in hyperdynamic cardiac failure, the $D_{v\text{-}a}PCO_2$ values have been shown to increase due to systemic hypoperfusion.[15]

The increase in $D_{v\text{-}a}PCO_2$ values in septic shock is due to several factors. First, there is the impairment of ventricular contractility due to the circulating mediators of the patients in septic shock. As a result, there is a decrease in systemic vascular resistance (SVR); consequently the heart cannot supply the increasing demand. The second factor is the rise in production of CO_2 due to the hyperdynamic state. In addition, there is the CO_2 produced during the buffering of the acids along with the increased need for the buffering of the higher amount of lactic acids during septic shock.[16] Finally, there is the change in CO_2 elimination through the lungs because of respiratory failure due to sepsis.

Mecher et al.[9] stated that in 37 patients in septic shock, 19 had $D_{v\text{-}a}PCO_2$ values of >6 mmHg with low cardiac output, but after fluid replacement, the low cardiac output improved, and the $D_{v\text{-}a}PCO_2$ values decreased. Bakker et al.[16] followed 64 septic patients and detected low cardiac output in 15 who had an increase in $D_{v\text{-}a}PCO_2$ and $PvCO_2$ values. The authors deduced that there is a close relationship between the low cardiac output and $D_{v\text{-}a}PCO_2$ and $PvCO_2$. Bakker et al.[16] also showed that there was no statistically significant difference between the $D_{v\text{-}a}PCO_2$ values of patients who were ventilated mechanically and those who were breathing spontaneously (p=0.055). The values of $D_{v\text{-}a}PCO_2$ also increased more in patients with high mortality, and this relationship with $D_{v\text{-}a}PCO_2$ is stronger than the parameters related to oxygen and $D_{a}\text{-}PO_2$.

Our study was designed to detect inadequate blood flow during CPB with $D_{v\text{-}a}PCO_2$, especially in septic patients, when taking into consideration the efficiency of the use of $D_{v\text{-}a}PCO_2$ for this purpose. When we compared the $D_{v\text{-}a}PCO_2$ values with the other oxygenation parameters and blood lactate levels[3,4] in the normothermic-hypothermic period of CPB (T_2 versus T_3), no significant correlation was found

between the changes in lactate $D_{v-a}PCO_2$ and SvO_2 values (Table 3).

The expected correlation between the T_2 and T_3 periods could not be detected because of the increased solubility of CO_2 (dissolving of CO_2 and becoming a liquid form) attributable to hypothermia and the relationship between the total CO_2 content. The PO_2 had also been disrupted.[17] Although venous hypercapnia was expected during the hypothermic period of CPB due to inadequate blood flow, it did not occur because of the increased solubility of CO_2. This results indirectly in the increase in $D_{v-a}PCO_2$ not occurring. This physiological change in CO_2 due to temperature difference modifies and reduces the efficiency of $D_{v-a}PCO_2$ to show the inadequate perfusion in the hypothermic period of CPB. Therefore, it is not possible to say that the adequacy of tissue perfusion can be monitored safely only via the monitorization of $D_{v-a}PCO_2$ during all periods of CPB. Likewise, when evaluating the other indirect parameters of the adequacy of tissue perfusion, such as SvO_2, along with the changes in the values of lactate during the hypothermic periods of CPB, the SvO_2 and lactate levels changed in parallel directions. However, the decrease in SvO_2 was expected to be parallel to the increase in lactate. In order to explain this difference in hypothermia, what the SvO_2 reflects and how it works should be precisely known.

Mixed venous oxygen saturation is commonly used to assess the balance of total body oxygen delivery to oxygen demand during cardiopulmonary bypass. Given an adequate and stable arterial oxygen content and metabolic rate, SvO_2 of more than 60% implies adequate systemic oxygen delivery.[17] Despite the general acceptance of this fact, major postoperative end-organ complications potentially secondary to undetected regional ischemia during bypass continue to be reported, for example acute mesenteric ischemia, gastrointestinal bleeding, and acute pancreatitis.[18] Mixed venous oxygen saturation may not accurately represent major end-organ venous desaturation and acidemia because it represents pooled venous blood from all organs.[19]

In addition to this deficiency in the ability of SvO_2 to detect the adequacy of tissue oxygenation, when CPB and hypothermia are added to the scene, the interpretation of SvO_2 becomes even more confusing.

During CPB practice, this change in the redistribution of blood flow along with any associated negative outcomes has led clinicians to prefer to work with the highest blood flow, MAP and hematocrit values during CPB. In addition, with hypothermia, as stated above, the total body O_2 consumption (VO_2) decreases more than the O_2 supply, and an increase in the SvO_2 is observed, especially in the hypothermic period of CPB. However, there are regional hypoperfusion areas. This situation decreases the reliability of SvO_2.

Lactate is considered to be the gold standard of the tissue perfusion indicators. Microcirculation fails in nonpulsatile flow and during hypothermia, however redistribution occurs, especially during the hypothermic period of CPB, and although tissue hypoxia exists blood lactate levels may stay within normal range similar to other tissue perfusion parameters.[3-8] However, when the regional perfusion improves, there is an increase in blood lactate levels (wash-out). In order to diagnose poor tissue perfusion in time, all of the indirect tissue perfusion parameters should be closely monitored and evaluated during CPB since they work in conjunction with each other.

In conclusion, our results showed that $D_{v-a}PCO_2$ and the other indirect parameters of tissue perfusion are not adequate if evaluated alone. Every parameter has its own intrinsic value, but each also comes with its own deficiencies. Therefore, monitorization of the adequacy of tissue perfusion should prove to be more accurate when all of the parameters are evaluated together.

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