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Dissociation Between Measures of Macrocirculation and Microcirculation in Patients Undergoing Cardiac Surgical Procedure

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ABSTRACT

BACKGROUND In the postoperative period of cardiac surgical procedure, there is an imbalance in the ratio of oxygen supply to oxygen consumption that leads to organic dysfunction and death. There is evidence of microcirculation involvement in cardiac surgical procedure, and a dysregulated inflammatory response similar to sepsis can occur.

METHODS We present a cohort of 280 consecutive adults who were monitored in the postoperative period after cardiac surgical procedure. We performed serial measurements of macrocirculatory indices, indices of global oxygenation, CO_2-derived indices, and perfusion indices in the first 24 hours postoperatively.

RESULTS We identified a dissociation between circulatory macrohemodynamic parameters/global oxygenation indices and the CO_2-derived indices. The CO_2-derived indices constitute a surrogate for microcirculatory flow and indicate the presence of anaerobic metabolism.

CONCLUSIONS A better understanding of these clinical variables will help establish optimal management protocols. It will also aid in the identification of patients in subpopulations with organic dysfunction despite conventional circulatory parameters within normal limits who can be overlooked if this exhaustive hemodynamic evaluation is not performed.

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In the postoperative period of cardiac surgical procedure, there is an intense physiologic stress, the consequence of a dysregulated systemic inflammatory response associated with extracorporeal circulation and tissue injury,[1] leading to an imbalance between tissue oxygen consumption and oxygen supply. The hemodynamic assessment of these patients generally includes macrocirculatory parameters, venous oximetry, and biochemical data of poor tissue perfusion. However, mixed venous saturation (Svo_2) does not reflect tissue hypoxia when oxygen consumption is affected by mitochondrial dysfunction or when microcirculatory failure is present,[2] and hyperlactatemia may result from mechanisms as a

IN SHORT

- There is a dissociation between the macrocirculatory and microcirculatory parameters in the first 24 hours after cardiac surgical procedure with extracorporeal circulation.
- The predominant hemodynamic profile is the presence of low microcirculatory flow in a state of predominantly anaerobic metabolism, similar to sepsis.

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surgical stress response, use of β-adrenergic drugs,[3] and even sepsis.

Similar to sepsis, a dysregulated systemic inflammatory response can result in microcirculatory alterations (heterogeneity of capillary flow and a decrease in functional capillary density). In this context, indices derived from carbon dioxide (CO_2) could provide useful information. These include the central venous-to-arterial P_{CO_2} difference (Pv-a$_{CO_2}$), which, when ≥6 mm Hg, indicates a state of low flow at the capillary-cell interface,[4] and the difference between venous-arterial CO_2 and arterial-venous O_2 content (Cv-a$_{CO_2}$/a-v$_{O_2}$D ratio), a surrogate for the respiratory quotient (ratio of CO_2 production to oxygen consumption); an increase above values of 1 indicates anaerobic production of CO_2.[5]

Our hypothesis was that when the patient is in a dysregulated systemic inflammatory state similar to sepsis, patients who undergo cardiac surgical procedure should show a similar hemodynamic behavior in the first 24 hours.

PATIENTS AND METHODS

This cross-sectional study investigated 280 consecutive adult patients who were admitted to the critical care unit at the Instituto Nacional de Cardiología Ignacio Chávez in Mexico City, Mexico, from June 1 to December 30, 2022, after cardiac surgical procedure. We performed serial measurements on admission and at 6, 12, and 24 hours of the macrocirculatory parameters (cardiac index, systemic vascular resistance index, and central venous pressure), global oxygenation indices (Sv_{O_2}, arterial-to-venous O_2 difference [a-v$_{O_2}$D], and oxygen extraction rate [O_2ER]), CO_2-derived indices (Pv-a$_{CO_2}$ and Cv-a$_{CO_2}$/a-v$_{O_2}$D ratio), and perfusion indices (capillary refill time and lactate levels). The formulas used are presented in Supplemental Table 1. The local institutional research and ethics committees waived approval for this study.

We performed the Shapiro-Wilk test of normality for continuous variables and report them as median and interquartile ranges because all of them were nonparametric. Comparisons of continuous variables were made by the Kruskal-Wallis test. We report categorical variables as frequencies and percentages and used the χ^2 or Fisher exact probability tests, as appropriate, to compare expected values. All statistical analyses were performed with Stata version 14 software (StataCorp LP), and P values $< .05$ were considered statistically significant.

RESULTS

DEMOGRAPHIC AND SURGICAL CHARACTERISTICS. Most patients were male (54.3%), with a median age of 57 (range, 45-65) years and New York Heart Association functional class II (51.6%). Their most frequent comorbidities were hypertension (41.1%), diabetes (24.8%), and atrial fibrillation (22.3%), and 9.6% of patients had previous cardiac surgical procedure. The most frequent cardiac surgical procedure was aortic valve replacement (25.9%), followed by coronary artery bypass graft (15.6%). The median extracorporeal circulation time was 145 minutes; for aortic clamping, it was 101 minutes. The most frequent postsurgical syndrome was hypovolemia (40.8%), followed by mediastinal bleeding (11.7%; Supplemental Table 2).

HEMODYNAMIC PARAMETERS. The hemodynamic parameters are presented in Table 1 and the Figure.

Macrohemodynamic Variables. The cardiac index remained above 1.8 $L \cdot min^{-1} \cdot m^{-2}$ throughout the first 24 hours. There was a tendency for the central venous pressure to increase throughout the first 24 hours, whereas the systemic vascular resistance index was above its maximum reference value (2400 $dynes \cdot s \cdot cm^{-5} \cdot m^2$) only in the first 12 hours.

Venous Oximetry. On arrival, there was high Sv_{O_2} (normal value, 65%), probably in relation to high doses of drugs necessary for the exit of the extracorporeal circulation, as well as high levels of fractional inspired oxygen during the transfer from the operating room. The a-v$_{O_2}$D and O_2ER were within normal limits on arrival (3-5 mL/dL and 20%-30%, respectively). For the remainder of the first 24 hours, all these parameters remained within their normal reference range, except for the O_2ER, which rose uniquely at 6 and 24 hours.

CO_2-Derived Indices. The Pv-a$_{CO_2}$ was elevated at admission and remained elevated during the rest of the first 24 hours (normal value, <6 mm Hg). The Cv-a$_{CO_2}$/a-v$_{O_2}$D ratio remained above its reference range of 1 throughout the first 24 hours, reaching its maximum values at admission and 12 hours (1.72 and 1.64, respectively).

Perfusion Indices. The capillary refill time was elevated at arrival (normal value, <3 seconds) but normalized during the first 24 hours. Serum lactate levels remained above their reference range (<2 mmol/L) during the first 24 hours, with a peak between admission and 6 hours (>2.6 mmol/L).

HEMODYNAMIC PROFILE: CLASSIFICATION PROPOSAL. We performed an analysis of all patients with lactate levels ≥2 mmol/L and assigned them to 4 hemodynamic profiles: profile 1, low macrocirculatory flow with anaerobic metabolism; profile 2, low microcirculatory flow with anaerobic metabolism; profile 3, cellular (mitochondrial) dysfunction; and profile 4, alteration in lactate kinetics (clearance). Profile 2 predominated at 0, 6, 12, and 24 hours, followed by profiles 1, 3, and 4 (Table 2).

OUTCOMES. At admission, those patients in profile 2 had a greater number of stroke (3 vs 1), delirium (19 vs 2), pneumonia (13 vs 3), mediastinitis (4 vs 0), transfusion (54 vs 9), acute kidney injury (47 vs 9), renal replacement therapy (8

TABLE 1 Hemodynamic Characteristics

Variable	Admission	6 h	12 h	24 h	*P* Value
Macrohemodynamic variables					
Cardiac output, L/min	3.8 (3-4.8)	3.7 (2.8-4.6)	3.7 (3.1-4.6)	3.8 (3.1-4.5)	.61
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.3 (1.8-2.8)	2.2 (1.7-2.7)	2.1 (1.8-2.7)	2.2 (1.9-2.6)	.39
Central venous pressure, mm Hg	8 (6-11)	9 (8-12)	10 (8-12)	11 (8-12)	<.001
Systemic vascular resistance, $dynes \cdot s \cdot cm^{-5}$	1425 (1107-1858)	1396 (1115-1821)	1423 (1111-1806)	1408 (1138-1817)	.98
Systemic vascular resistance index, $dynes \cdot s \cdot cm^{-5} \cdot m^2$	2446 (1864-3125)	2402 (1891-3108)	2391 (1948-3007)	2377 (1957-2972)	.95
Venous oximetry					
Mixed venous O_2 saturation, %	77 (70-82)	68 (62-75)	68 (62-75)	67 (62-73)	<.001
Arteriovenous O_2 difference, mL/dL	3.8 (2.8-4.9)	4.5 (3.5-5.6)	4.3 (3.4-5.2)	4 (3.3-5)	<.001
O_2 extraction ratio, %	24 (18-30)	31 (24-38)	30 (25-37)	31 (25-37)	<.001
CO_2-derived indices					
Venous-to-arterial CO_2 pressure difference, mm Hg	6 (4-9)	7 (5-9)	7 (5-9)	6 (4-8)	<.001
Venous-arterial CO_2 to arterial-venous O_2 content difference ratio	1.72 (1.09-2.54)	1.54 (1.14-2.09)	1.64 (1.22-2.02)	1.51 (1.06-2.02)	.03
Perfusion indices					
Capillary refill time, s	3 (2.1-4)	2.3 (2-3)	2 (2-2.8)	2 (2-2.4)	<.001
Lactate, mmol/L	2.6 (1.8-4)	2.6 (1.7-4.1)	2.3 (1.6-3.5)	2 (1.5-2.7)	<.001

Values are reported as median (interquartile range).

vs 3), liver injury (25 vs 5), postoperative atrial fibrillation (17 vs 4), and in-hospital mortality (9 vs 2) events. There were no clinically significant differences in intensive care unit days, mechanical ventilation time, Sequential Organ Failure Assessment score (at 24 and 72 hours), and total hospitalization time (Supplemental Table 3).

COMMENT

Microcirculation distributes blood flow to different organs, adapting the flow and oxygen supply to local metabolism to maintain its function. Cardiac surgical procedure with extracorporeal circulation and its consequent systemic inflammatory response can cause damage to microcirculatory flow.[6]

Resuscitation based on the normalization of systemic macrohemodynamic variables does not always lead to improvement in microcirculatory perfusion and cellular oxygenation.[7] The use of CO_2-derived indices can help establish microcirculatory flow alterations in the presence of normal macrocirculatory and global oxygenation parameters, in addition to indicating the predominance of anaerobic status.

Regarding the evaluation of macrohemodynamic parameters in our study population, the median values of all determinations were within normal ranges, except for a slight elevation of the systemic vascular resistance index at admission and 12 hours. All global oxygenation indices were normal on admission, with the exception of the O_2ER, which rose discretely above its reference value at 6 and 24 hours, suggesting discrete peripheral compensatory extraction in this period. Notably, CO_2-derived indices were *always* above their normal range, which confirms that a state of low flow and anaerobiosis predominates during the first 24 hours. Finally, the median lactate level remained above 2 mmol/L, leading us to conclude that a state of low flow predominates at the cellular capillary interface with anaerobic hyperlactatemia in the presence of normal macrocirculatory parameters. We interpret that microcirculation dysfunction is responsible for this clinical behavior.

The group that predominated in the 4 hemodynamic moments (arrival and 6, 12, and 24 hours) consisted of patients with Svo_2 >65%, Pv-aco_2 ≥6 mm Hg, and Cv-aco_2/a-vo_2D ratio >1. In this state, there is a persistence of an anaerobic condition, which is commonly found in patients with dysregulated inflammatory response states. A relevant number of patients during the first 24 hours (10%) also presented with Svo_2 >65% and Pv-aco_2 <6 mm Hg but with a Cv-aco_2/a-vo_2D ratio >1, indicating the probability of alteration at the cellular level (mitochondrial cytopathy). In sepsis and septic shock, these profiles have been associated with morbidity and death comparable to that of patients who do not meet macrohemodynamic goals. The greatest number of adverse outcomes stood out when the patients presented profile 2 on admission, which could be related to the peak of inflammatory response after the bypass circulation. A proposal for how to approach and intervene in these patients, based on the previously described parameters, is

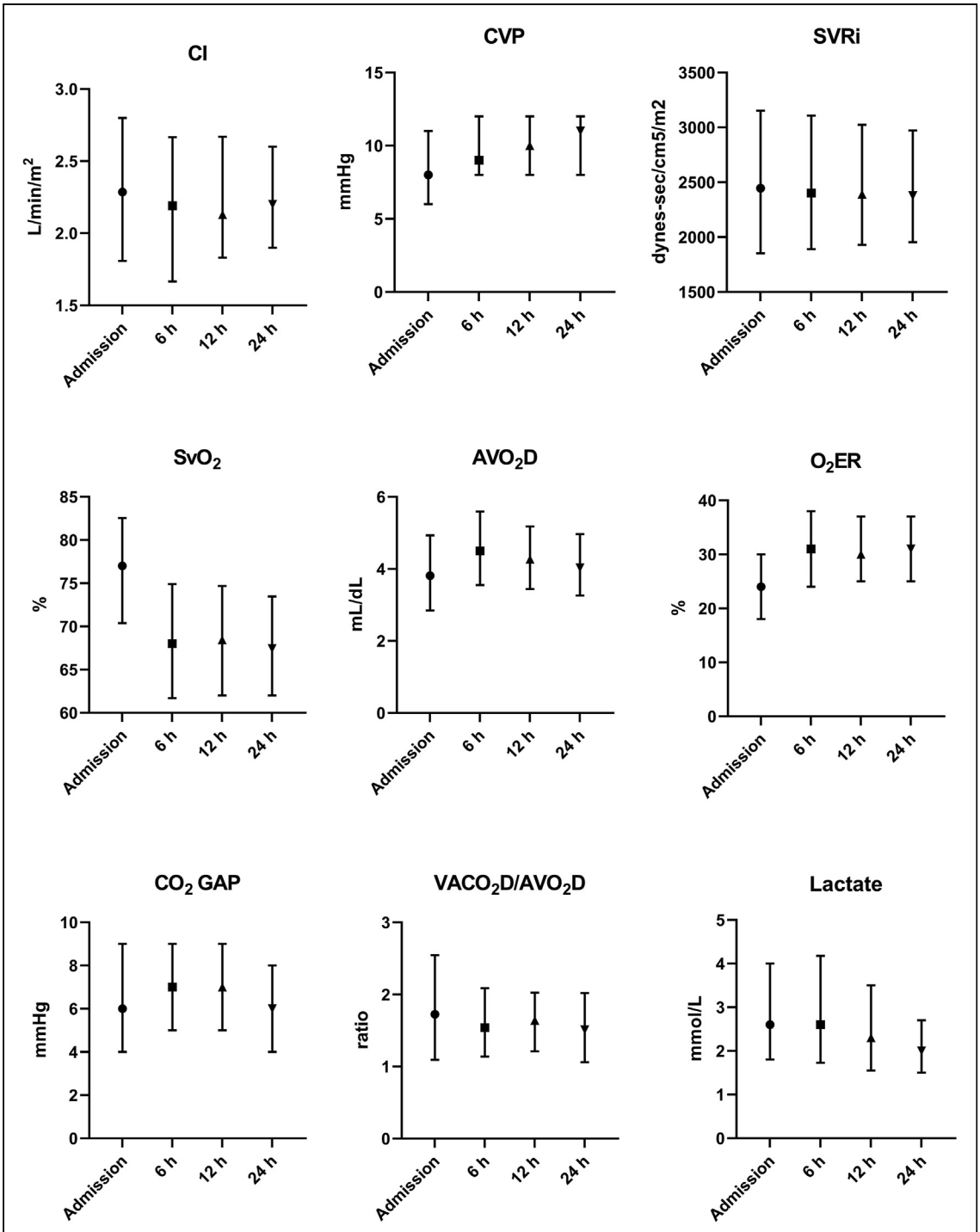

FIGURE Linear graph showing trends in macrocirculatory measurements, venous oximetry, CO_2-derived indices, and lactate. AVO_2D, arterial-to-venous O_2 difference; CI, cardiac index; CO_2 GAP, central venous-to-arterial P_{CO_2} difference; CVP, central venous pressure; O_2ER, oxygen extraction rate; SvO_2, venous oxygen saturation; SVRi, systemic vascular resistance index; $VACO_2D/AVO_2D$ ratio, venous-arterial CO_2 to arterial-venous O_2 content difference.

included in the Supplemental Figure. Further studies will be required to evaluate the impact of these circulatory alterations on postoperative complications and mortality. Currently, studies evaluating and intervening on the basis of these variables (direct and indirect evaluation of microcirculation) are under development.[8,9]

In conclusion, we found a dissociation between macrocirculatory parameters and global oxygenation

TABLE 2 Proposed Hemodynamic Profile and Its Pathophysiology

Hemodynamic Profile	0 h (n = 201)	6 h (n = 200)	12 h (n = 171)	24 h (n = 154)	Pathophysiology
Profile 1	12 (6)	67 (33.5)	56 (32.7)	49 (31.8)	Low macrocirculatory flow with anaerobic metabolism
Svo_2 <65%					
Pv-aco_2 ≥6 mm Hg					
Cv-aco_2/a-vo_2D ratio >1					
Lactate ≥2 mmol/L					
Profile 2	112 (55.7)	77 (38.5)	65 (38)	52 (33.8)	Low microcirculatory flow with anaerobic metabolism
Svo_2 >65%					
Pv-aco_2 ≥6 mm Hg					
Cv-aco_2/a-vo_2D ratio >1					
Lactate ≥2 mmol/L					
Profile 3	36 (17.9)	20 (10)	21 (12.3)	14 (9.1)	Cellular/mitochondrial dysfunction
Svo_2 >65%					
Pv-aco_2 <6 mm Hg					
Cv-aco_2/a-vo_2D ratio >1					
Lactate ≥2 mmol/L					
Profile 4	31 (15.4)	21 (10.5)	21 (12.3)	23 (14.9)	Alteration in lactate kinetics (clearance)
Svo_2 >65%					
Pv-aco_2 <6 mm Hg					
Cv-aco_2/a-vo_2D ratio <1					
Lactate ≥2 mmol/L					

Values are reported as number (percentage). Cv-aco_2/a-vo_2D ratio, venous-arterial CO_2 to arterial-venous O_2 content difference; Pv-aco_2, central venous-to-arterial Pco_2 difference; Svo_2, venous oxygen saturation.

indices compared with CO_2-derived indices (out of range) in the first 24 hours after cardiac surgical procedure involving extracorporeal circulation. This finding highlights the predominantly anaerobic environment at this time, which could be attributed to microcirculatory disorders. This situation could be a useful indicator for clinicians who target resuscitation on the basis of these parameters and not on "traditional" indicators, in addition to their prognostic implication.

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.atssr.2023.09.009] on http://www.annalsthoracicsurgery.org.

The data that support the findings of this study are available on request from the corresponding author (D.M.-S.).

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DISCLOSURES

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