Different effects of prostacyclin and phentolamine on delivery-dependent O_2 consumption and skin microcirculation after cardiac surgery

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Inadequate tissue oxygen uptake autoregulation has been reported during the first hours after extracorporeal circulation for cardiac surgery. In the present study, we examined whether a dependence of oxygen consumption ($\dot{V}O_2$) on oxygen delivery (DO_2) can be detected 24 hr after cardiac surgery using two different vasodilating agents. Cardiac output in triplicate was measured by thermodilution. Oxygen saturation of arterial and mixed venous blood was measured using a CO-oximeter. Oxygen consumption was assessed from the reverse Fick equation. In addition skin blood flow was assessed continuously by laser Doppler flowmetry. To investigate the $\dot{V}O_2/DO_2$

relationship in 15 patients an increase in cardiac output and DO_2 of at least 15% was achieved by systemic vasodilatation with iv prostacyclin ($5-10 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or phentolamine ($5-10 \text{ g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Infusion of phentolamine produced a $29 \pm 2\%$ (mean $\pm$ SE) increase in DO_2 which was associated with a $20 \pm 6\%$ increase in $\dot{V}O_2$. In contrast, prostacyclin produced a $22 \pm 3\%$ increase in DO_2 without change in $\dot{V}O_2$. Phentolamine did not alter skin microvascular blood flow, whereas prostacyclin increased skin microvascular blood flow by $33 \pm 3\%$. The results of the present study demonstrate a supply-dependency of $\dot{V}O_2$ in clinically stable patients 24 hr after cardiac surgery, suggesting the presence of an inadequate tissue O_2 uptake autoregulation. The type of the vasodilator used to increase DO_2 seems to play an important role in detecting such a supply-dependency of $\dot{V}O_2$, as well as changes of skin blood flow.

Key words

HORMONES: prostacyclin;
MEASUREMENT TECHNIQUES: Doppler ultrasound;
OXYGEN: consumption, delivery;
SYMPATHETIC NERVOUS SYSTEM: pharmacology,
phentolamine.

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The present study was supported in part by grants from the Swiss National Fund for Scientific Research no 3.749.0.87 and 32.29956.90, and the Carlos and Elsie de Reuter Foundation for Medical Research no 120.

Accepted for publication 23rd August, 1992.

On a déjà rapporté une incompétence de l'autorégulation de la captation tissulaire de l'oxygène pendant les heures qui suivent la chirurgie cardiaque sous circulation extracorporelle. Au cours de la présente étude, nous recherchons si une dépendance entre oxygène consommé ($\dot{V}O_2$) et l'oxygène disponible (DO_2) peut être détectée 24 h après la chirurgie cardiaque pendant la perfusion de deux vasodilatateurs différents. Des mesures triples du débit cardiaque sont effectuées par thermodilution et la consommation de l'oxygène est évaluée par l'équation de Fick. La saturation en oxygène dans le sang artériel et veineux est déterminée à l'aide d'un cooxymètre. De plus, le débit sanguin cutané est évalué continuellement par débitimétrie au laser (effet Doppler). Pour examiner la relation entre $\dot{V}O_2$ et DO_2 chez 15 patients, une augmentation du débit cardiaque et de la DO_2 d'au moins 15% provoquée par vasodilatation systémique avec prostacycline iv ($5-10 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) ou phentolamine ($5-10 \text{ g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). La perfusion de phentolamine augmente de $29 \pm 2\%$ (moyenne $\pm$ ET) la DO_2 sans changement de la $\dot{V}O_2$. La phentolamine n'altère pas le flux sanguin microvasculaire alors

que la prostacycline l'augmente de $33 \pm 3\%$. Les résultats de l'étude démontrent une dépendance entre apport et consommation d'oxygène chez des patients stables cliniquement 24 hre après une chirurgie cardiaque, suggérant ainsi une perte d'autorégulation de la captation oxygénée. Le type de vasodilatateur utilisé pour augmenter la DO_2 semble jouer un rôle important dans la détection d'une interdépendance entre l'apport et la consommation d'oxygène de même que le débit sanguin cutané.

The first hours after cardiac surgery and cardiopulmonary bypass represent a period at risk for cardiovascular decompensation, most likely due to the discrepancy between increasing metabolic needs and impaired cardiac function.¹⁻³ Inadequate microvascular perfusion during the first hours after open heart surgery was shown to decrease skeletal muscle partial pressure of oxygen (O_2).⁴ Despite normal systemic blood flow and arterial O_2 tension, a delivery-dependent oxygen consumption ($\dot{V}O_2$) has been observed in patients early after cardiac surgery,⁵ suggesting inadequate regional O_2 uptake regulation.

Bihari *et al.* have proposed that such an inadequate tissue regulation resulting in a covert O_2 debt could be detected by transiently increasing oxygen delivery (DO_2) to tissues; in response to this "dynamic oxygen flux test," $\dot{V}O_2$ did increase.⁶ The concept of delivery-dependent oxygen consumption, i.e., the fact that some patients are "flow dependent" with increases in DO_2 above normal leading to parallel increases in $\dot{V}O_2$ is now widely accepted. A supply-dependency of $\dot{V}O_2$, i.e., a covert O_2 debt, has previously been reported in patients presenting with increased plasma lactate concentrations immediately after cardiopulmonary bypass and in patients with sepsis or an adult respiratory distress syndrome.^{5,7} It is not known for how long such a covert O_2 debt persists after cardiac surgery, and in particular whether it is still present in patients which are weaned from mechanical ventilation and breathing spontaneously.

The method and drug administered to increase DO_2 for the "oxygen flux test" may be important. In patients with chronic heart failure, changes in $\dot{V}O_2$ have been shown to depend on the type of vasodilator used and not on absolute changes in DO_2 .^{8,9} The first objective of the present investigation was to compare changes in DO_2 and $\dot{V}O_2$ induced by intravenous phentolamine, an arteriolar vasodilator, versus prostacyclin, a prostaglandin with preferential vasodilator effect on the microcirculation, in patients studied 24 hr after open heart surgery and weaned from mechanical ventilation. The second objective was to determine whether changes in DO_2 and $\dot{V}O_2$ induced by these vasodilators correlate with their effect on the

microcirculation assessed by continuous skin microvascular blood flow laser Doppler flowmetry.

Methods

Patients

The investigation was approved by the committee for ethics in human research of our institution and informed consent was obtained from every patient. Fifteen patients, age 59 ± 8 yr (mean $\pm$ SE), mean body weight 75 ± 8 kg, admitted to the surgical intensive care unit after elective open heart surgery were included in the study and investigated 18 to 24 hr after end of surgery (Table I). Their tracheas were extubated and the patients were breathing spontaneously with supplemental O_2 given by face mask at an inspired O_2 fraction of 0.35. All were in a stable clinical and haemodynamic condition for at least four hours before beginning the study. Blood haematocrit was between 30 and 35% and cardiac filling pressures, i.e., central venous pressure and pulmonary capillary wedge pressure, were between 8 and 14 mmHg. No patient received vasoactive or inotropic drugs during the study period.

Measurements

The following variables were measured: heart rate, mean systemic arterial and mean pulmonary arterial blood pressure, central venous pressure and pulmonary capillary wedge pressure using calibrated quartz pressure transducers (1290 A Hewlett Packard) positioned at the mid-axillary line. Cardiac output was measured three times at end-expiration by the same operator by thermodilution with ice-cold injectate and using a bedside Edwards computer (type 9520 A). The coefficient of variation for cardiac output measurements was less than 5%. Systemic (SVRI) and pulmonary vascular resistance index (PVRI) were calculated using standard formulae. Arterial and mixed venous blood samples were drawn for measurement of total haemoglobin concentration by spectrophotometry, O_2 tension and pH were measured using standard electrodes (ABL 330, Radiometer, Copenhagen, Denmark) and corrected for the patient's rectal temperature. Oxygen saturation of haemoglobin in arterial (SO_2) and mixed venous blood (SvO_2) were measured using a CO-oximeter (Corning 2005, Ciba-Corning, Switzerland). Plasma lactate concentrations were measured by absorption spectrometry (Boehringer UV test, Mannheim, FRG).

Skin microvascular blood flow was measured continuously using a laser Doppler flowmeter (LDF) probe (Periflux PF2B, Perimed, Sweden) placed on the inner thigh.¹⁰ This non-invasive method gives similar measurement of microcirculatory flow when compared either to

TABLE 1 Clinical characteristics of patients

Patient number	Age (yr)	Sex (M/F)	Weight (kg)	Preoperative LVEF (%)	ECC (min)	Operation
1	42	M	95	26	214	CABG (3 vessels)
2	75	M	82	60	179	CABG (3 vessels)
3	57	M	90	20	103	CABG (3 vessels)
4	64	M	80	59	126	AVR
5	64	M	66	58	170	MVR
6	66	M	72	75	173	CABG (2 vessels)
7	24	M	63	65	190	MVR and AVR
8	67	F	75	36	120	CABG (3 vessels)
9	63	M	91	55	120	CABG (3 vessels)
10	56	M	85	49	140	CABG (3 vessels)
11	58	M	70	30	103	CABG (3 vessels)
12	83	F	44	49	152	AVR
13	59	M	88	50	114	MVR
14	39	M	74	63	208	CABG (3 vessels)
15	69	F	56	57	115	CABG (2 vessels)

LVEF: left ventricle ejection fraction; ECC: duration of extracorporeal circulation (min);

CABG: coronary artery bypass graft; AVR: aortic valve replacement; MVR: mitral valve replacement.

$^{133}\text{xenon}$ washout measurements¹¹ or capillaroscopy.¹² It has the advantage of providing a continuous assessment of the microcirculatory flow and has been shown to be useful in investigating the skin microcirculation in man.¹¹⁻¹³ According to the Doppler principle, moving blood cells in the superficial region of the skin change the frequency of the back-scattered light. The LDF signal is a function of the product of the number of red blood cells and their mean velocity. In the present study, the change in LDF signal was expressed as a percentage of the maximal internal calibration signal.¹¹

Study protocol

After two control measurements separated by a time interval of 30 min (control 1 and 2), patients were randomly assigned to receive a 30-min infusion of either prostacyclin, 5–10 ng · kg⁻¹ · min⁻¹ (Flolan®, Wellcome, Rheinfelden, Switzerland), or phentolamine, 5–10 g · kg⁻¹ · min⁻¹ (Regitine®, Ciba-Geigy, Basel, Switzerland). Drug dosage was adapted to obtain an increase in cardiac output of at least 15%. Haemodynamic and respiratory measurements were repeated after 30 min of constant drug infusion. The infusion was then stopped. Sixty minutes later, control measurements were repeated and thereafter the second vasodilator administered and all measurements repeated. The $\dot{V}O_2$ was calculated by multiplying cardiac output by arterial O_2 content using standard formulae. The $\dot{V}O_2$ was derived from the reverse Fick equation. The oxygen extraction ratio ($O_2\text{ER}$) was expressed as the ratio of $\dot{V}O_2$ to DO_2 .

All recorded variables (mean ± SE) were compared within each treatment using a one-way analysis of variance

for repeated measurements followed by Bonferroni's multicomparisons test. Comparison between both treatments was performed with the two-tailed Student's paired *t* test. The Pearson's least square correlation coefficient was used to detect any significant association between changes in DO_2 , $\dot{V}O_2$ and in haemodynamic, respiratory or biochemical variables. A *P* value < 0.05 was considered as statistically significant.

Results

Clinical characteristics of the patients included in the present study are reported in Table 1. Mean duration of extracorporeal bypass and aortic cross-clamping were 153 ± 12 and 100 ± 9 min, respectively. Mean values for systemic and pulmonary haemodynamic variables are presented in Tables II and III. Arterial lactate concentrations were above the normal range >1.9 mmol · L⁻¹ in three of 15 patients. All patients presented an increased alveolo-arterial O_2 gradient/inspired O_2 fraction ratio ($P(A-a)O_2/FiO_2$), an elevated venous admixture, but normal values of DO_2 and $\dot{V}O_2$. There were no differences in any of the recorded variables between the two control measurements taken before administration of either vasodilator. The sequence of drug administration had no influence on the effects of the vasodilators on DO_2 and $\dot{V}O_2$. No change in arterial plasma lactate concentrations was observed after administration of either of the vasodilators (Table II).

Prostacyclin infusion

The 30-min *iv* infusion of prostacyclin produced a $22 \pm 3\%$ increase in DO_2 (from 8.8 ± 0.3 to 10.8 ± 0.4 ml ·

TABLE II Haemodynamic variables and plasma lactate concentrations

	Prostacyclin			Phentolamine		
	Control 1	Control 2	Vasodilatation	Control 1	Control 2	Vasodilatation
Heart rate (beats · min ⁻¹)	90 ± 4	90 ± 4	95 ± 4	87 ± 4	88 ± 4	101 ± 4*
MAP (mmHg)	77 ± 2	77 ± 2	69 ± 2*	81 ± 2	81 ± 3	69 ± 2*
CVP (mmHg)	12 ± 1	12 ± 1	13 ± 1	11 ± 1	11 ± 1	11 ± 1
MPAP (mmHg)	22 ± 2	22 ± 2	22 ± 1	22 ± 2	23 ± 1	20 ± 2
PCWP (mmHg)	13 ± 1	13 ± 1	14 ± 1	13 ± 1	13 ± 1	13 ± 1
Cardiac index (L · min ⁻¹ · m ⁻²)	2.6 ± 0.1	2.6 ± 0.1	3.4 ± 0.1*	2.5 ± 0.1	2.5 ± 0.1	3.4 ± 0.2*
SVRI (dynes · sec · cm ⁻⁵ · m ⁻²)	2218 ± 118	2188 ± 94	1452 ± 51*	2498 ± 153	2455 ± 141	1533 ± 73*
PVRI (dynes · sec · cm ⁻⁵ · m ⁻²)	252 ± 36	257 ± 32	193 ± 27*	280 ± 26	286 ± 31	171 ± 27*
Arterial lactate (mmol · L ⁻¹)	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	1.6 ± 0.2	1.7 ± 0.1	2.0 ± 0.3

x ± SE; n = 15; MAP: mean arterial pressure; CVP: central venous pressure; MPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index.
Control 1: beginning of the study; control 2: 30 minutes later.
*Significantly different from control 2 values (*P* < 0.05).

TABLE III Body temperature, respiratory variables, oxygen transport, oxygen consumption and oxygen extraction ratio during short *iv* infusions of prostacyclin and phentolamine

	Prostacyclin			Phentolamine		
	Control 1	Control 2	Vasodilatation	Control 1	Control 2	Vasodilatation
Rectal temperature (°C)	37.4 ± 0.2	37.4 ± 0.2	37.3 ± 0.1	37.4 ± 0.1	37.4 ± 0.1	37.2 ± 0.1
pH (units)	7.39 ± 0.01	7.39 ± 0.01	7.40 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.40 ± 0.01
PaCO ₂ (mmHg)	44 ± 1	44 ± 1	42 ± 1	44 ± 1	44 ± 1	42 ± 1
PaO ₂ (mmHg)	89 ± 5	92 ± 4	63 ± 3*	98 ± 6	98 ± 5	69 ± 2*
SaO ₂ (%)	95.1 ± 0.3	95.3 ± 0.3	90.6 ± 0.9*	95.3 ± 0.3	95.4 ± 0.2	92.7 ± 0.5*
SvO ₂ (%)	62.1 ± 1.3	63.0 ± 1.3	63.6 ± 1.5	62.8 ± 1.1	63.0 ± 1.1	63.2 ± 1.1
P(A-a)O ₂ /F _i O ₂ (mmHg)	359 ± 15	351 ± 15	427 ± 11*	339 ± 17	339 ± 17	413 ± 9*
Venous admixture (%)	19.1 ± 1.2	18.7 ± 1.0	31.8 ± 1.5*	18.3 ± 1.1	18.0 ± 0.9	26.3 ± 1.3*
Oxygen transport (ml · min ⁻¹ · kg ⁻¹)	8.7 ± 0.4	8.8 ± 0.3	10.8 ± 0.4*	8.4 ± 0.4	8.5 ± 0.4	10.8 ± 0.4*
Oxygen consumption (ml · min ⁻¹ · kg ⁻¹)	3.0 ± 0.2	3.0 ± 0.1	3.2 ± 0.2	2.9 ± 0.1	2.9 ± 0.1	3.5 ± 0.1*
Oxygen extraction ratio (%)	35.1 ± 1.3	34.5 ± 1.3	30.1 ± 1.2*	34.7 ± 1.2	34.7 ± 1.1	32.2 ± 1.1

x ± SE; n = 15; SaO₂: arterial O₂ saturation of haemoglobin; SvO₂: mixed venous O₂ saturation of haemoglobin; P(A-a)O₂/F_iO₂: alveolo-arterial O₂ gradient/inspired O₂ concentration ratio; Control 1: beginning of the study; control 2: 30 minutes later.
*Significantly different from control 2 values (*P* < 0.05).

kg⁻¹ · min⁻¹, *P* < 0.05), without change in $\dot{V}O_2$ (Figure 1). The SVRI, PVRI, and mean arterial pressure decreased significantly (Table II), as it did in PaO₂, SaO₂, whereas P(A-a)O₂/F_iO₂ and pulmonary venous admixture increased (Table III).

Phentolamine infusion

The 30-min infusion of phentolamine produced a 29 ± 2% increase in DO₂ (from 8.5 ± 0.4 to 10.8 ± 0.4 ml · kg⁻¹ · min⁻¹, *P* < 0.05), which was not different from the increase in DO₂ produced by prostacyclin, but was associated with a 20% increase in $\dot{V}O_2$ (from 2.9 ± 0.1 to 3.5 ± 0.1 ml · kg⁻¹ · min⁻¹, *P* < 0.05) (Figure 1). The mean of the individual patient slopes of the relationship between the

changes in $\dot{V}O_2$ and DO₂ were three times greater for phentolamine than for prostacyclin (23.0 ± 4.4 vs 7.6 ± 5.5, *P* < 0.05, respectively). As with prostacyclin, SVRI, PVRI, and mean arterial pressure decreased (Table II), as did PaO₂, SaO₂, whereas P(A-a)O₂/F_iO₂ and pulmonary venous admixture were increased (Table III).

Skin blood flow

Under control conditions, the LDF signal assessing skin perfusion was 40 ± 10% of the maximal internal calibration signal. No differences were observed between the two control periods before administration of each vasodilator. Prostacyclin produced a 33 ± 3% mean increase in skin perfusion whereas phentolamine did not cause any change

FIGURE 1 Percentage changes (mean $\pm$ SE) in oxygen delivery (DO_2) and whole body oxygen consumption ($\dot{V}O_2$) produced by 30-min infusions of prostacyclin (open bars) and phentolamine (hatched bars) in 15 patients studied 24 hr after cardiac surgery. * $P < 0.05$ between prostacyclin and phentolamine infusion.

FIGURE 2 Percentage increase (mean $\pm$ SE) of the laser Doppler flowmetry signal produced by 30-min intravenous infusions of prostacyclin (open bar) and phentolamine (hatched bar). * $P < 0.05$ between prostacyclin and phentolamine infusion.

in skin microcirculation (Figure 2). After stopping prostacyclin, the LDF signal recovered its control value within 10 ± 3 min.

Discussion

The present study demonstrates that increasing DO_2 by phentolamine but not by prostacyclin increases O_2 uptake in patients studied 24 hr after cardiac surgery and who had been weaned from mechanical ventilation. The type of vasodilator used to increase DO_2 may thus play an important role in detecting an abnormal tissue $\dot{V}O_2$ auto-

regulation. Changes in $\dot{V}O_2$ produced by either vasodilator were not explained by changes in skin microvascular blood flow measured by laser Doppler flowmetry.

Our results indicate a supply-dependency of $\dot{V}O_2$ when DO_2 was increased by phentolamine in patients even when in stable clinical condition with normal systemic haemodynamics. Phentolamine does not change $\dot{V}O_2$ in healthy animals¹⁴ or human volunteers.¹⁵ Phentolamine has been reported to induce a O_2 supply-dependency in mechanically ventilated patients immediately after cardiopulmonary bypass with plasma lactate concentrations above 2.5 mmol $\cdot$ L⁻¹.⁵ In patients with normal plasma lactate concentrations, $\dot{V}O_2$ was related to DO_2 only when DO_2 decreased below 300 ml $\cdot$ min⁻¹ $\cdot$ m⁻².⁵

It would probably have been more appropriate to measure $\dot{V}O_2$ by indirect calorimetry to avoid the problem of mathematical coupling because of the shared variables – cardiac output and O_2 content. However, we believe that this potential error, if at all, in the context of the present situation, because both drugs increased DO_2 to a similar extent, but only phentolamine increased $\dot{V}O_2$ by 20%, a value more than twice as much as the error measurement of $\dot{V}O_2$. Accuracy of $\dot{V}O_2$ measurement depends largely on the coefficient of variation of cardiac output, which has recently been estimated to be $4.3 \pm 3.3\%$ in 33 patients with acute myocardial infarction,¹⁶ allowing a coefficient of variation for calculated $\dot{V}O_2$ of $8.5 \pm 4.4\%$.

The supply-dependency of $\dot{V}O_2$ during phentolamine infusion found in the present study is possibly due to inadequate tissue $\dot{V}O_2$ autoregulation. Our patients did not present clinical or biochemical evidence of anaerobic metabolism. In particular, arterial plasma lactate concentrations were above the normal range only in three of fifteen patients. Nevertheless, our patients could have had an elevated lactate production if lactate clearance was correspondingly increased. For instance, more than 50% of lactate produced may be simultaneously used by peripheral skeletal muscles.¹⁷ Moreover, during O_2 depletion, the balance of oxidation could shift from cytochrome A_3 to non-ATP-producing oxidase systems, which does not necessarily result in accumulation of lactate.¹⁸ Therefore, patients studied 24 hr after open heart surgery may have an inadequate tissue $\dot{V}O_2$ that is not reflected by the clinical and biochemical cardiopulmonary variables generally recorded in clinical practice.

We used laser Doppler flowmetry, a non-invasive measurement of the skin microvascular blood flow, to explain the differential effect on $\dot{V}O_2$ produced by prostacyclin and phentolamine after cardiac surgery. In physiological conditions, prostacyclin has been shown to increase both the perfusion of the dermis in healthy volunteers¹⁹

and the gastric mucosal blood flow in rats.²⁰ Moreover, prostacyclin preferentially vasodilates arterioles and venules, and increases the density of perfused capillaries,²¹ whereas alpha-adrenergic blocking agents are arteriolar vasodilators only.²² The data of the present study are in accordance with the results of previously cited studies showing an increased microcirculatory blood flow secondary to the administration of prostacyclin but not of phentolamine. However, we observed no relationship between changes in skin microcirculatory flow and oxygen transport and utilization during the infusion of either vasodilator in patients after cardiac surgery. Our data confirm studies in critically ill patients where changes over time of laser Doppler signal occurred independently of changes in cardiac index and DO_2 .^{23,24} In one of these studies, a multivariate data analysis demonstrated that only 20% of the variability of the laser Doppler signal depends on changes in systemic haemodynamic variables.²³ Also, our data suggest that the supply-dependency of VO_2 found in postoperative cardiac patients could probably not be explained by a maldistribution of blood flow to the microcirculation. Indeed, there is little evidence that phentolamine, like other conventional vasodilators, could reduce a maldistribution of blood flow in the microcirculation.²⁵ Increased circulating endogenous catecholamines produced in response to cardiopulmonary bypass could open physiological arteriovenous shunts leading to an increased anaerobic metabolism.^{26,27} Administration of the alpha-adrenergic blocking agent phentolamine could antagonize the effects of increased endogenous catecholamines present after cardiac surgery, resulting in a better tissue DO_2 and utilization.²⁸

In conclusion, the results of the present study demonstrate a supply-dependency of VO_2 during phentolamine infusion in patients studied 24 hr after cardiac surgery and weaned from mechanical ventilation, suggesting the presence of an inadequate tissue VO_2 autoregulation. The type of the vasodilator used to increase DO_2 seems to play an important role in detecting such a supply-dependency of VO_2 . These findings may have some importance in cardiac surgery patients with severely limited DO_2 , in which the presence of an oxygen debt may be not reflected by clinical and biochemical cardiopulmonary variables generally recorded in clinical practice.

Acknowledgements

We gratefully acknowledge the technical assistance of Julian Lopez.

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