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Time course of central venous-to-arterial carbon dioxide tension difference in septic shock patients receiving incremental doses of dobutamine

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Take-home message: Central venous-to-arterial carbon dioxide tension difference (ΔPCO_2) appears to provide a good indication of the changes in VO_2 induced by dobutamine. Monitoring ΔPCO_2 could be a useful tool to assess the adequacy of oxygen supply versus oxygen demand and, therefore, may help to guide therapy with dobutamine in stable septic shock patients.

Electronic supplementary material
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Abstract *Purpose:* To assess the time course of the central venous–arterial carbon dioxide tension difference (ΔPCO_2)—as an index of the carbon dioxide production (VCO_2)/cardiac index (CI) ratio—in stable septic shock patients receiving incremental doses of dobutamine. *Methods:* Twenty-two hemodynamically stable septic shock patients with no signs of global tissue hypoxia, as testified by normal blood lactate levels, were prospectively included. A dobutamine infusion was administered at a dose of up to 15 μg/kg/min in increments of 5 μg/kg/min every 30 min. Complete hemodynamic and gas measurements were obtained at baseline, and at each dose of dobutamine. *Results:* Dobutamine induced a significant dose-dependent increase of CI from 0 to 15 μg/kg/min ($P < 0.001$). Oxygen consumption (VO_2) and VCO_2 were progressively increased by dobutamine. These increases were more marked between 10 and 15 μg/kg/min (8.3 and 8.6 %, respectively) than between the lower doses. ΔPCO_2 and oxygen extraction (EO_2) significantly decreased between 0 (8.0 ± 2.0 mmHg and 43.8 ± 13.4 %, respectively) and 10 μg/kg/min of dobutamine (4.2 ± 1.6 mmHg and 28.9 ± 7.9 %, respectively), but remained unchanged from 10 to 15 μg/kg/min (5.4 ± 2.4 mmHg and 29.5 ± 8.2 %, respectively). The central venous oxygen saturation significantly ($ScvO_2$) increased from 0 to 10 μg/kg/min and remained unchanged from 10 to 15 μg/kg/min. Time courses of ΔPCO_2, $ScvO_2$, and EO_2 were linked therefore to the biphasic changes of VO_2 and VCO_2. *Conclusion:* ΔPCO_2 is a good indicator of the change of VCO_2 induced by dobutamine. Measurement of ΔPCO_2, along with $ScvO_2$ and EO_2, may be presented as a useful tool to assess the adequacy of oxygen supply versus metabolic and oxygen demand.

Keywords Central venous-to-arterial carbon dioxide tension difference · Cardiac index · Dobutamine · Stable septic shock · Oxygen consumption · CO_2 production

Abbreviations

ACCP	American College of Chest Physicians
APACHE	Acute Physiology and Chronic Health Evaluation
CI	Cardiac index
CHF	Chronic heart failure
DO_2	Oxygen delivery
EO_2	Oxygen extraction
FiO_2	Fractional inspired oxygen level
MAP	Mean arterial pressure
ΔPCO_2	Central venous-to-arterial carbon dioxide tension difference

P[v–a]CO_2	Mixed venous-to-arterial carbon dioxide tension difference	$ScvO_2$	Central venous oxygen saturation	VO_2	Oxygen consumption
SCCM	Society of Critical Care Medicine	SOFA	Sequential Organ Failure Assessment		
		VCO_2	CO_2 production		

Introduction

Dobutamine is a synthetic catecholamine with strong inotropic effects on the myocardium owing to its predominately β_1-adrenergic properties [1]. This drug is the first choice inotrope recommended by the Surviving Sepsis Campaign [2] for septic shock patients with low cardiac index (CI), or ongoing signs of tissue hypoperfusion in the presence of adequate fluid resuscitation. The aim of dobutamine administration in these patients is the restoration of an appropriate CI to provide adequate oxygen supply in an attempt to meet the elevated tissue oxygen requirements. However, dobutamine, in parallel to its effects on systemic hemodynamics, may increase oxygen consumption (VO_2) and, therefore, tissue CO_2 production (VCO_2) through its direct cellular metabolic effects [3, 4]. According to the Fick equation applied to CO_2, the determinants of the mixed venous-to-arterial CO_2 difference (P[v–a]CO_2) are tissue CO_2 production and blood flow (cardiac output) [5, 6]. Previously, Teboul et al. [7] found that P[v–a]CO_2 was helpful in assessing the adequacy of CI versus oxygen demand when incremental doses of dobutamine were infused into stable chronic heart failure (CHF) patients. Whether such phenomena can be observed in stable septic shock patients is presently not known. Interestingly, it has been demonstrated that P[v–a]CO_2 can be substituted by the central venous-to-arterial carbon dioxide tension difference (ΔPCO_2) in critically ill patients [8, 9]. Therefore, the aim of our study was to assess the behavior of ΔPCO_2—as an index of the VCO_2/CI ratio—in hemodynamically stable septic shock patients, but with ongoing signs of tissue hypoperfusion, receiving incremental doses of dobutamine.

Materials and methods

This prospective and observational study was conducted in a single, mixed medical and surgical adult intensive care unit (ICU) with 15 beds. The study was approved by a local institutional ethics committee (comité d'éthique du centre hospitalier du Dr. Shaffner de Lens). Informed consent was obtained from the next of kin of each patient.

Patients

The study included 22 patients within 24 h of septic shock onset. The diagnosis of septic shock was defined according to the criteria of the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference [10]. As part of the routine management of septic shock in our ICU, all patients were already monitored by a transpulmonary thermodilution device (PiCCO, Pulsion Medical System, Munich, Germany) for CI measurement and were mechanically ventilated with a fractional inspired oxygen level (FiO_2) no greater than 65 %, and a respiratory rate less than 35 breaths/min using an Engström Carestation ventilator (Engström, General Electrics, Madison, Michigan, USA). Sedation was provided with propofol and analgesia with remifentanil. Patients were included in the study if, as decided by the attending physician, dobutamine administration was needed to increase CI because of the persistence of signs of hypoperfusion (oliguria, mottled skin [11], central venous oxygen saturation ($ScvO_2$) <70 % despite a hemoglobin >8 g/dl) despite achieving adequate intravascular volume and adequate mean arterial pressure (MAP) greater than 65 mmHg as recommended by the Surviving Sepsis Campaign [2]. Exclusion criteria were pregnancy, age less than 18 years old, unstable hemodynamic condition (change of vasoactive drug dosage or fluid administration within 1 h preceding the protocol), high blood lactate levels (>2 mmol/l), and uncontrolled tachyarrhythmias (heart rate >140 beats/min).

Measurements

Demographic data, septic shock etiology, the Acute Physiology and Chronic Health Evaluation (APACHE) II [12] and the Sequential Organ Failure Assessment (SOFA) scores [13] were obtained on the day of enrollment. CI was obtained with the PiCCO monitor by triplicate central venous injections of 20 ml of iced (<6 °C) 0.9 % saline solution and recorded as the average of the three measurements. In cases where the discrepancy in the CI measurements was greater than 10 %, the measurement was repeated two more times (five times in total) with elimination of the highest and lowest results. Blood gases analysis and lactate levels were measured using the GEM® Premier™ 3000 (Instrumentation Laboratory Co, Paris, France). $ScvO_2$ was determined in a sample taken from the central venous catheter with the tip confirmed by X-ray to be in the superior vena cava near or at the right atrium. ΔPCO_2 was calculated as the

difference between central venous carbon dioxide tension and arterial carbon dioxide tension. Complete hemodynamic parameters were obtained (electronic supplementary material, ESM). Oxygen delivery (DO_2) was calculated using the standard formula [14].

Transthoracic echocardiography was performed with a commercially available system. The left ventricular ejection fraction was calculated by the Simpson method [15].

Indirect calorimetry

Indirect calorimetry was obtained continuously using the new compact modular metabolic monitor E-COVX (GE Healthcare/Datex-Ohmeda, Helsinki, Finland). The characteristics of this monitor have previously been described in detail [16] (ESM).

The values of VO_2 and VCO_2 were recorded every 5 min to obtain a mean of six values collected (for each metabolic variable) over a 30-min period. Oxygen extraction ratio (EO_2) was calculated as VO_2/DO_2.

Study protocol

Additional details on the study protocol are provided in ESM. Ventilation parameters, fluid, and doses of the vasopressor and sedation drugs were kept constant in the 60-min period preceding the measurements and throughout the study period. Hypovolemia was excluded by repeated volume challenges up to a point where CI did not increase further, or when the extravascular lung water indexed to predicted body weight reached 14 ml/kg [17]. After baseline measurements, an infusion of dobutamine was started at 5 μg/kg/min and increased by 5 μg/kg/min every 30 min up to 15 μg/kg/min. After each step, all measurements (hemodynamic, indirect calorimetry) were repeated, except for echocardiography, which was only performed at baseline. The study had to be stopped if adverse effects such as arterial hypotension (MAP <60 mmHg), tachycardia (heart rate >150 beats/min), acute atrial fibrillation, or changes in the ST segment of the electrocardiogram occurred.

Statistical analysis

Statistical analysis was performed by means of SAS software (SAS Institute Inc., Cary, NC 25513). The significance level was set at 0.05. Data are expressed as mean and standard deviation.

Comparisons of hemodynamic, blood gas, and metabolic parameters according to the incremental doses of dobutamine infusion were performed using a linear mixed model. This model is an extension of the classical ANOVA that allows the handling of both fixed effect (incremental doses of dobutamine infusion) and random effect (patient); thus, this model takes into account the correlation between the measures of one patient. The Bonferroni method was used to adjust for multiple comparisons.

The relationship between VO_2 against DO_2 was assessed with a linear mixed model with random coefficients. The dependent variable was VO_2, the independent variable was DO_2, and the subject effect was considered as a random effect. The correlation coefficient between VO_2 and DO_2 was computed by the method described by Roy [18] taking into account the repeated measures.

Results

Basic characteristics of the 22 patients are presented in Table 1. The left ventricular fraction collected in these patients (40 %) characterizes the global impairment of cardiac contractility. No changes in vasopressor therapy or ventilator settings occurred during the observation period. Dobutamine infusion was well tolerated in all patients. Its hemodynamic effects are listed in Table 2. Dobutamine induced a significant dose-dependent increase in CI, which was related to combined increases in heart rate and stroke volume index. Changes in CI were paralleled by a statistically significant increase in DO_2 (Table 2). $ScvO_2$ significantly increased in parallel with increasing doses of dobutamine from 0 to 10 μg/kg/min,

Table 1 Characteristics of the patients

Age (years)	69 ± 11
Gender (men/women)	12/10
Weight (kg)	80 ± 17
APACHE II score	26 ± 10
Standardized mortality ratio (%)	57
Admission SOFA score	8 ± 3
ICU mortality, *n* (%)	10 (45)
Lactate levels (mmol/l)	1.2 ± 0.48
Urinary output (ml/kg/h)	0.36 ± 0.44
Mottled skin, *n* (%)	9 (41)
Left ventricular ejection fraction (%)	40 ± 11
FiO_2 (%)	45 ± 12
Hemoglobin (g/dl)	10 ± 2
Norepinephrine, *n* (μg/kg/min)	19 (0.48 ± 0.36)
Infection source, *n* (%)	
Pneumonia	12 (54)
Peritonitis	6 (27)
Meningitis	1 (5)
Catheter/bloodstream	1 (5)
Others	2 (9)

Values are expressed as mean ± SD unless otherwise stated
APACHE Acute Physiology and Chronic Health Evaluation, *SOFA* Sepsis-related Organ Failure Assessment, *ICU* intensive care unit, *FiO_2* fractional inspired oxygen level

Table 2 Hemodynamic, blood gas, and metabolic parameters during incremental doses of dobutamine infusion

	Dobutamine (μg/kg/min)			
	0	5	10	15
Heart rate, beats/min	88 ± 20	100 ± 19[a]	109 ± 17[a,b]	116 ± 17[a,b,c]
MAP, mmHg	81 ± 17	84 ± 18	86 ± 15	86 ± 15
Cardiac index, l/min/m^2	3.0 ± 1.1	4.0 ± 1.3[a]	4.6 ± 1.4[a,b]	5.0 ± 1.4[a,b,c]
ITBVI, ml/m^2	898 ± 137	957 ± 172	953 ± 165	969 ± 176
SaO_2, %	98 ± 2	98 ± 2	97 ± 2	97 ± 1[a]
$ScvO_2$, %	59 ± 9	68 ± 7[a]	73 ± 6[a,b]	72 ± 6[a,b]
DO_2, ml/min/m^2	357 ± 85	489 ± 115[a]	567 ± 133[a,b]	604 ± 141[a,b,c]
VO_2, ml/min/m^2	149 ± 36	155 ± 37[a]	158 ± 38[a,b]	172 ± 42[a,b,c]
VCO_2, ml/min/m^2	121 ± 30	125 ± 31[a]	129 ± 32[a,b]	140 ± 35[a,b,c]
RQ	0.80 ± 0.03	0.80 ± 0.03	0.81 ± 0.04	0.81 ± 0.05
V_E, l/min	9.3 ± 2.9	9.4 ± 2.8	9.4 ± 2.8	9.3 ± 2.9
EO_2, %	44 ± 13	33 ± 10[a]	29 ± 8[a,b]	29 ± 8[a,b]
$PaCO_2$, mmHg	37 ± 7	37 ± 6	38 ± 6	38 ± 5
$PcvCO_2$, mmHg	45 ± 6	43 ± 6[a]	42 ± 6[a]	44 ± 6[c]
ΔPCO_2, mmHg	8.0 ± 2.0	5.5 ± 1.9[a]	4.2 ± 1.6[a,b]	5.4 ± 2.4[a]
Lactate, mmol/l	1.20 ± 0.48	1.12 ± 0.46	1.14 ± 0.46	1.21 ± 0.43

Values are expressed as mean ± SD

MAP mean arterial pressure, *ITBVI* intra-thoracic blood volume index, SaO_2 arterial oxygen saturation, $ScvO_2$ central venous oxygen saturation, DO_2 oxygen delivery, VO_2 oxygen consumption, VCO_2 carbon dioxide production, *RQ* respiratory quotient, V_E minute ventilation, EO_2 oxygen extraction ratio, $PaCO_2$ arterial carbon dioxide tension, $PcvCO_2$ central venous carbon dioxide tension, ΔPCO_2 central venous-to-arterial carbon dioxide tension difference

[a] $P < 0.05$ compared with dobutamine dose of 0 μg/kg/min

[b] $P < 0.05$ compared with dobutamine dose of 5 μg/kg/min

[c] $P < 0.05$ compared with dobutamine dose of 10 μg/kg/min. Bonferonni method was used to adjust for multiple comparisons

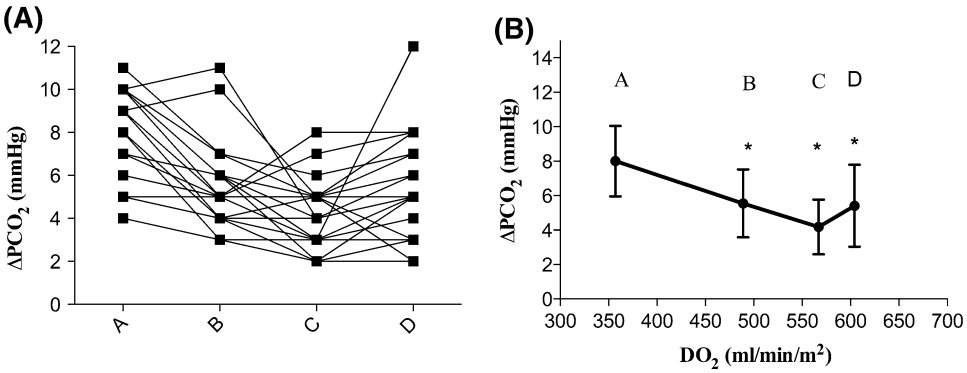

Fig. 1 **a** Individual VO_2/DO_2 slopes ($r = 0.34$). **b** Evolution of VO_2 and DO_2 during dobutamine infusion (*A* baseline; *B* dobutamine 5 μg/kg/min; *C* dobutamine 10 μg/kg/min; *D* dobutamine 15 μg/kg/min). Mean slopes = 6.4 %. Data are expressed as mean ± SD. *$P < 0.0001$ versus baseline

and remained constant thereafter when dobutamine infusion rate was further increased to 15 μg/kg/min (Table 2).

Dobutamine led to progressive increases in VO_2 and VCO_2 (Table 2). These increases were more pronounced when dobutamine was increased from 10 to 15 μg/kg/min (8.8 and 8.5 %, respectively) compared to the first two steps of dobutamine infusion (3.7 and 4 %, respectively between 0 and 5 μg/kg/min; 2.1 and 3 %, respectively between 5 and 10 μg/kg/min). The respiratory quotient remained unchanged ($\approx$0.8) testifying to the accuracy of the indirect calorimetric measurements. The EO_2 and ΔPCO_2 significantly decreased from baseline to a dobutamine dose of 10 μg/kg/min, but stayed unchanged when dobutamine was increased from 10 to 15 μg/kg/min (Table 2). The time course of individual data and mean values of ΔPCO_2 during dobutamine infusion is shown in Fig. 1a, b.

For each patient, regression lines of VO_2 against DO_2 were determined (mean $r = 0.34$) (Fig. 2a). The mean slope of the VO_2/DO_2 relationship was 6.4 ± 0.7 % (Fig. 2b).

Discussion

The main findings of our study were that (1) despite a dose-related increase in CI and DO_2, dobutamine infusion up to 15 μg/kg/min did not result in a dose-dependent decrease in ΔPCO_2, the central venous-to-arterial CO_2

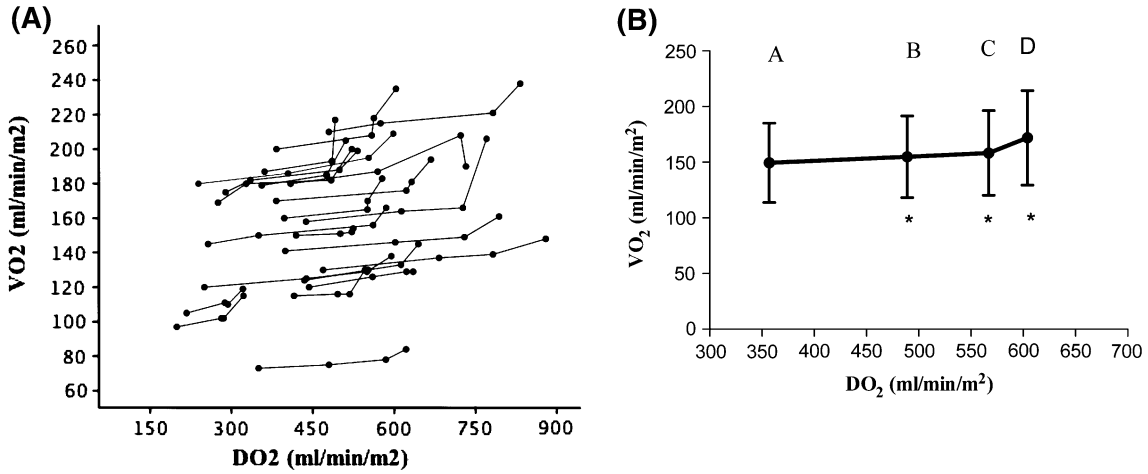

Fig. 2 **a** Individual effects of dobutamine infusion on ΔPCO_2. **b** Evolution of ΔPCO_2 and DO_2 during dobutamine infusion. *A* baseline; *B* dobutamine 5 μg/kg/min; *C* dobutamine 10 μg/kg/min; *D* dobutamine 15 μg/kg/min. Data are expressed as mean ± SD. $*P < 0.0001$ versus baseline

difference; (2) VO_2 and VCO_2 showed a statistically significant increase in parallel with the increased doses of dobutamine.

In patients with septic shock, global left ventricular hypokinesia, defined by left ventricular ejection fraction less than 45 %, has been observed in 60 % of cases during the first 3 days of hemodynamic support [19]. Dobutamine is recommended as the first-choice therapy to increase CI in the presence of signs of hypoperfusion after hypovolemia has been excluded, and adequate MAP has been achieved [2]. In our population, we observed a mean CI of 3 l/min/m^2 along with an $ScvO_2$ of only 59 % and a urinary output of 0.36 ml/kg/h before dobutamine was started. Furthermore, 41 % of patients had mottled skin (Table 1). These suggest the existence of tissue hypoperfusion associated with an inotropic defect as preload dependency was excluded by the absence of further increase of CI after repeated volume challenges. Additionally, the observed intrathoracic blood values index gave evidence against the presence of hypovolemia. Therefore, in our study, dobutamine was administered in order to increase CI in patients with established tissue hypoperfusion and cardiac dysfunction. This approach is completely different from the concept of supranormal oxygen delivery that refers to the use of dobutamine to drive up the oxygen delivery to achieve predefined supranormal hemodynamic end points for all patients at high risk of complications in an attempt to prevent organ failure and to improve outcome. Numerous controlled clinical trials of supranormal oxygen delivery involving patients with severe sepsis not only failed to demonstrate any benefit but also could be potentially harmful [20, 21].

Dobutamine may exert thermogenic effects and is able to increase both VO_2 and VCO_2. $P[v–a]CO_2$ was shown to detect changes in oxygen demand accompanying dobutamine-induced changes in CI in stable CHF patients [7]. To the best of our knowledge there is no report on the behavior of ΔPCO_2 in septic shock patients receiving incremental doses of dobutamine.

The increase in systemic blood flow can affect VCO_2 production under situations of anaerobic metabolism activation. Indeed, under conditions of oxygen supply dependency, an increase in CI may concurrently lead to (1) an increase in aerobic VCO_2 through the supply-dependent increase in VO_2 and (2) a decrease of anaerobic VCO_2 production [6, 7]. In this situation, the changes in CI may have no effect on the time course of ΔPCO_2. Therefore, to better study the effects of dobutamine-induced increase in CI on ΔPCO_2, we only included stable septic shock patients with no signs of anaerobic metabolism activation. Although the normal lactate levels after a resuscitation period up to 24 h might reflect an attenuated stress response and could not completely exclude the presence of anaerobic metabolism in our septic shock patients, the lack of previous oxygen debt was confirmed by the observation at the end of the study of a small positive slope (only 6.4 %) in the VO_2–DO_2 relationship during changes in DO_2 testifying to an oxygen supply-independency state (Fig. 2a, b) [22–25]. Further evidence of the absence of anaerobic metabolism is that EO_2 decreased and $ScvO_2$ increased appropriately (instead of remaining constant) after increasing DO_2 by dobutamine administration at between 0 and 10 μg/kg/min doses.

The change in ΔPCO_2—as an index of VCO_2/CI ratio—must be interpreted in line with changes in CI and VCO_2. During the stepwise increase of dobutamine rate from 0 to 10 μg/kg/min, CI linearly increased resulting in a decrease of ΔPCO_2, although VCO_2 slightly increased. This is explained by the relatively much higher increase

of CI compared to VCO_2 (55 vs. 7.2 %, respectively) allowing removal of both stagnated and newly produced CO_2 and resulting in a lower ΔPCO_2. Our findings are, in part, in agreement with the results of Teboul et al. [7]. Indeed, these authors studied the effects of incremental doses of dobutamine on the time course of $P[v–a]CO_2$ in ten stable CHF patients. They found that, from dobutamine doses of 0–10 μg/kg/min, $P[v–a]CO_2$ decreased in parallel with a linear increase in CI. However, in that study VO_2 and therefore VCO_2 remained constant between these doses [7]. Differences between the two studies may stem from several factors. First, the studies involved dissimilar populations of patients. Second, in our study, VO_2 and VCO_2 were directly measured by indirect calorimetry, whereas VO_2 was calculated from the reverse Fick equation in the study by Teboul et al. However, in accordance with our results, other studies [22, 24] reported a small increase in VO_2 and VCO_2 in patients with stable septic shock receiving incremental doses of dobutamine (from 0 to 10 μg/kg/min).

When dobutamine infusion rate was increased from 10 to 15 μg/kg/min, ΔPCO_2 did not change significantly, whereas CI continued to increase. It is noteworthy that the relationship between CI and ΔPCO_2 is curvilinear at constant VCO_2 [6]. In this way, a change of CI will result in the smallest change of ΔPCO_2 in the highest range of CI. However, in our study VCO_2 was not constant but significantly increased when dobutamine was increased from 10 to 15 μg/kg/min. This increase of VCO_2 was of the same magnitude as the increase of CI (8.3 vs. 7.5 %, respectively), which can mainly explain why ΔPCO_2 remained unchanged or even slightly increased between 10 and 15 μg/kg/min of dobutamine. This hypothesis is further supported by the absence of significant changes in $ScvO_2$ and EO_2 observed at 15 μg/kg/min of dobutamine. Indeed, the increase of VO_2 between 10 and 15 μg/kg/min of dobutamine counterbalances the increase of CI and explains the absence of any additional improvement in $ScvO_2$ and EO_2. Similar results were found in previous studies [7, 26].

Several mechanisms can be suggested to explain the increases of VO_2 and VCO_2 observed in our study. A first possibility is that, under anaerobic tissue metabolism conditions, VO_2 becomes dependent on DO_2, so that when DO_2 is acutely increased, VO_2 increases until the critical level of DO_2 has been surpassed. This increase of VO_2 is therefore due to the beneficial recovery of an oxygen debt situation. This mechanism is, however, unlikely to have occurred in our patients because of the normal blood lactate levels observed at baseline, the small slope in the VO_2/DO_2 relationship (Fig. 2b), and the increase of $ScvO_2$, all of which rule out an oxygen supply dependency phenomenon. A second potential explanation is that the increase of VO_2 and, therefore, VCO_2 could be attributed to an increase of blood supply to organs such as the liver and the kidney whose needs are proportional to the blood flow. Indeed, increased blood flow to the kidneys is associated with an increase of renal metabolism [27]. We believe that such a mechanism may have contributed to the increase of VO_2 between 0 and 10 μg/kg/min of dobutamine in our study. Indeed, we noted a substantial increase of DO_2 (59 %) between 0 and 10 μg/kg/min of dobutamine whereas the increase of VO_2 was only of 6 % suggesting that the increase in blood flow may largely explain the increase of VO_2. A third possibility is that the increase of VO_2 and VCO_2 is due to an increase in cellular oxygen demand primarily under the influence of β-adrenergic stimulation by dobutamine. The thermogenic effects of catecholamines are well known [28]. Dobutamine, like other catecholamines, increases cellular metabolism in healthy volunteers even at low doses [3, 4]. However, the metabolic effects of dobutamine can differ between healthy subjects and critically ill patients who are under stress, probably because of some differences in basal catecholamine levels and a downregulation of β-adrenergic receptors in the latter group [29]. Interestingly, Uusaro et al. [30] demonstrated that the thermogenic effects of low doses of dobutamine were significantly reduced after a metabolic stress situation (that imitates the conditions of critically ill patients) has been induced in healthy subjects. Therefore, it is unlikely that the calorigenic effects of dobutamine might have played a considerable role in the increase of VO_2 observed at low doses (<10 μg/kg/min) in our study. However, the thermogenic effects may be more pronounced at high doses of dobutamine in critically ill patients. In our study, VO_2 increased markedly (8.6 %) between 10 and 15 μg/kg/min of dobutamine while DO_2 increased by only 6 % (Table 2). Therefore, the proportionally higher increase of VO_2 compared to DO_2 associated with the absence of an oxygen supply dependency phenomenon suggests that the thermogenic effects of dobutamine were responsible for the increase of VO_2 at the dose of 15 μg/kg/min. Our results are in agreement with the observations by Teboul et al. [7, 26] who reported calorigenic effects of dobutamine only at high doses (15 μg/kg/min) of the drug when infused in stable CHF patients.

Our results are of clinical importance. Since all patients in septic shock are usually equipped with central venous and arterial catheters, ΔPCO_2 is easily obtained at the bedside. ΔPCO_2 can assist the clinician in distinguishing between the hemodynamic and the metabolic effects of dobutamine. Indeed, dobutamine infusion at high doses may unfavorably alter the balance between tissue oxygen delivery and consumption through its thermogenic effects and thereby reduce tissue oxygenation. However, further clinical trials are required to assess the accuracy and utility of ΔPCO_2 measurement in the choice of the dose of dobutamine to be administered to septic shock patients.

We acknowledge some limitations to our study. First, the number of patients studied was small. Second, the

study was performed in a sample of septic shock patients from a single center with internal practices as reference. Third, our results do not pertain to septic shock patients with evidence of a supply dependency phenomenon.

Conclusion

Our study demonstrates that, in stable septic shock patients, dobutamine administration leads to an increase of DO_2, which is associated with an increase of VO_2 especially at high doses (calorigenic effects). ΔPCO_2 appears to provide a good indication of the changes of VO_2 induced by dobutamine. Monitoring ΔPCO_2, along with $ScvO_2$ and EO_2, could be a useful tool to assess the adequacy of oxygen supply versus oxygen demand and, therefore, may help to guide therapy with dobutamine in stable septic shock patients.

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Conflicts of interest The authors declare that they have no competing interests.

References

1. Ruffolo RR Jr (1987) The pharmacology of dobutamine. Am J Med Sci 294:244–248
2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Intensive Care Med 39:165–228
3. Bhatt SB, Hutchinson RC, Tomlinson B, Oh TE, Mak M (1992) Effect of dobutamine on oxygen supply and uptake in healthy volunteers. Br J Anaesth 69:298–303
4. Green CJ, Frazer RS, Underhill S, Maycock P, Fairhurst JA, Campbell IT (1992) Metabolic effects of dobutamine in normal man. Clin Sci 82:77–83
5. McHardy GJ (1967) The relationship between the differences in pressure and content of carbon dioxide in arterial and venous blood. Clin Sci 32:299–309
6. Dres M, Monnet X, Teboul JL (2012) Hemodynamic management of cardiovascular failure by using PCO(2) venous-arterial difference. J Clin Monit Comput 26:367–374
7. Teboul JL, Mercat A, Lenique F, Berton C, Richard C (1998) Value of the venous-arterial PCO_2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. Crit Care Med 26:1007–1010
8. Cuschieri J, Rivers EP, Donnino MW, Katilius M, Jacobsen G, Nguyen HB, Pamukov N, Horst HM (2005) Central venous-arterial carbon dioxide difference as an indicator of cardiac index. Intensive Care Med 31:818–822
9. van Beest PA, Lont MC, Holman ND, Loef B, Kuiper MA, Boerma EC (2013) Central venous-arterial PCO_2 difference as a tool in resuscitation of septic patients. Intensive Care Med 39:1034–1039
10. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definition conference. Crit Care Med 31:1250–1256
11. Ait-Oufella H, Lemoinne S, Boelle PY, Galbois A, Baudel JL, Lemant J, Joffre J, Margetis D, Guidet B, Maury E, Offenstadt G (2011) Mottling score predicts survival in septic shock. Intensive Care Med 37:801–807
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
13. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG, On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 22:707–710
14. Vincent JL, Van der Linden P, Domb M, Blecic S, Azimi G, Bernard A (1987) Dopamine compared with dobutamine in experimental septic shock: relevance to fluid administration. Anaesth Analg 66:565–571
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18:1440–1463
16. McLellan S, Walsh T, Burdess A, Lee A (2002) Comparison between the Datex-Ohmeda M-COVX metabolic monitor and the Deltatrac II in mechanically ventilated patients. Intensive Care Med 28:870–876
17. Mallat J, Pepy F, Lemyze M, Barrailler S, Gasan G, Tronchon L, Thevenin D (2012) Extravascular lung water indexed or not to predicted body weight is a predictor of mortality in septic shock patients. J Crit Care 27:376–383
18. Roy A (2006) Estimating correlation coefficient between two variables with repeated observations using mixed effects model. Biom J 48:286–301
19. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F (2008) Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 36:1701–1706
20. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717–1722

21. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R, SvO2 Collaborative Group (1995) A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025–1032
22. De Backer D, Moraine JJ, Berre J, Kahn RJ, Vincent JL (1994) Effects of dobutamine on oxygen consumption in septic patients. Direct versus indirect determinations. Am J Respir Crit Care Med 150:95–100
23. Vincent JL, Roman A, De Backer D, Kahn RJ (1990) Oxygen uptake/supply dependency. Effects of short-term dobutamine infusion. Am Rev Respir Dis 142:2–7
24. Schaffartzik W, Sanft C, Schaefer JH, Spies C (2000) Different dosages of dobutamine in septic shock patients: determining oxygen consumption with a metabolic monitor integrated in a ventilator. Intensive Care Med 26:1740–1746
25. De Backer D (2000) VO_2/DO_2 relationship: how to get rid of methodological pitfalls? Intensive Care Med 26:1719–1722
26. Teboul JL, Graini L, Boujdaria R, Berton C, Richard C (1993) Cardiac index versus oxygen-derived parameters for rational use of dobutamine in patients with congestive heart failure. Chest 103:81–85
27. Levy MN (1959) Influence of variations in blood flow and of dinitrophenol on renal oxygen consumption. Am J Physiol 196:937–942
28. Chioléro R, Flatt JP, Revelly JP, Jéquier E (1991) Effects of catecholamines on oxygen consumption and oxygen delivery in critically ill patients. Chest 100:1676–1684
29. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T (1984) Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 311:819–823
30. Uusaro A, Hartikainen J, Parviainen M, Takala J (1995) Metabolic stress modifies the thermogenic effect of dobutamine in man. Crit Care Med 23:674–680