Intravenous Thiamine Is Associated with Increased Oxygen Consumption in Critically Ill Patients with Preserved Cardiac Index

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Abstract

Rationale: Oxygen consumption may be impaired in critically ill patients.

Objectives: To evaluate the effect of intravenous thiamine on oxygen consumption ($\dot{V}O_2$) in critically ill patients.

Methods: This was a small, exploratory open-label pilot study conducted in the intensive care units at a tertiary care medical center. Critically ill adults requiring mechanical ventilation were screened for enrollment. Oxygen consumption ($\dot{V}O_2$) and cardiac index (CI) were recorded continuously for 9 hours. After 3 hours of baseline data collection, 200 mg of intravenous thiamine was administered. The outcome was change in $\dot{V}O_2$ after thiamine administration.

Measurements and Main Results: Twenty patients were enrolled and 3 were excluded because of incomplete $\dot{V}O_2$ data, leaving 17 patients for analysis. There was a trend toward increase in $\dot{V}O_2$ after thiamine administration (16.3 ml/min, SE 8.5; $P = 0.052$). After preplanned adjustment for changes in CI in case of a delivery-dependent state in some patients (with exclusion of one additional patient because of missing CI data), this became statistically significant (16.9 ml/min, SE 8.6; $P = 0.047$). In patients with average CI greater than our cohort's mean value of 3 L/min/m^2, $\dot{V}O_2$ increased by 70.9 ml/min (± 16; $P < 0.0001$) after thiamine. Thiamine had no effect in patients with reduced CI (< 2.4 L/min/m^2). There was no association between initial thiamine level and change in $\dot{V}O_2$ after thiamine administration.

Conclusions: The administration of a single dose of thiamine was associated with a trend toward increase in $\dot{V}O_2$ in critically ill patients. There was a significant increase in $\dot{V}O_2$ in those patients with preserved or elevated CI. Further study is needed to better characterize the role of thiamine in oxygen extraction. Clinical trial registered with www.clinicaltrials.gov (NCT01462279).

Keywords: oxygen consumption; $\dot{V}O_2$; thiamine; $\dot{D}O_2$; oxygen extraction

(Received in original form June 16, 2014; accepted in final form September 2, 2014)

Supported, in part, by grant UL1 RR025758-Harvard Clinical and Translational Science Center, from the National Center for Research Resources. M.W.D. is supported by the NHLBI (1K02HL107447-01A1) and NIH (R21AT005119-01). This study was additionally funded in part by a SEED grant from the American Medical Association, and K.M.B. is supported by American Heart Association grant 13CRP16930000. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources, the National Institutes of Health, or the American Heart Association.

Author Contributions: K.M.B. helped conceive of and design the study, oversaw patient enrollment and data collection, was involved in data analysis, and was the primary writer of the manuscript. S.G. helped with study design and statistical analysis and critically reviewed and edited the manuscript. J.D.S. contributed to data collection and patient enrollment, as well as data analysis and manuscript writing. T.G. was involved in trial design, data analysis, and manuscript writing and revision. B.S. assisted with data analysis and contributed to the writing of the manuscript. M.W.D. oversaw the design of the study, patient enrollments, data analysis, and writing of the manuscript. All authors have approved the final content of this manuscript.

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Ann Am Thorac Soc Vol 11, No 10, pp 1597–1601, Dec 2014

DOI: 10.1513/AnnalsATS.201406-259BC
Internet address: www.atsjournals.org

Oxygen consumption ($\dot{V}O_2$) is determined by oxygen delivery ($\dot{D}O_2$), a product of cardiac output and the oxygen content in the blood, and oxygen extraction. Normally, $\dot{D}O_2$ far exceeds the body's needs. $\dot{V}O_2$ is not dependent on $\dot{D}O_2$ until delivery is so low that everything delivered is being used, a point referred to as the critical $\dot{D}O_2$.

In the critically ill, lower $\dot{V}O_2$ is associated with higher mortality (1). Previous investigators have sought to increase $\dot{V}O_2$ in the critically ill with the

goal of improving outcome (2, 3). Prior efforts focused on increasing $\dot{D}O_2$, based on the theory that in the critically ill $\dot{V}O_2$ is pathologically dependent on $\dot{D}O_2$, but this ultimately failed to show efficacy (2, 4). In fact, those patients whose $\dot{V}O_2$ did not increase when $\dot{D}O_2$ was increased were found to have exceedingly high mortality, suggesting the importance of impaired oxygen extraction (4). Cytopathic hypoxia, or the pathologic breakdown of aerobic metabolism and oxygen extraction, is now known to be an important factor in critical illness (5). In spite of the wide acceptance of this concept, however, no effective intervention for increasing the extraction component of $\dot{V}O_2$ has been described.

Thiamine is a cofactor for pyruvate dehydrogenase, an essential enzyme for aerobic metabolism. In thiamine deficiency, pyruvate cannot enter the Krebs cycle, and anaerobic metabolism takes over. Decreased ATP production, vasodilatory shock, and lactic acidosis ensue. Thiamine administration rapidly reverses these effects in patients with thiamine deficiency. Investigators have shown previously that thiamine deficiency is more common in the critically ill (6, 7). Thiamine administration has also been shown to improve $\dot{V}O_2$ and lower lactate in an animal model of sepsis and in healthy humans, regardless of initial thiamine level (8, 9). This suggests that thiamine may augment aerobic metabolism in the critically ill, even in the absence of absolute deficiency. We hypothesized that the administration of intravenous thiamine to critically ill patients would cause an increase in oxygen extraction and $\dot{V}O_2$. As there are no prior data in critically ill patients, we conducted the following pilot, open label study investigating the effect of a single dose of intravenous thiamine on $\dot{V}O_2$ in critically ill adults.

Methods

Study Design

This was a pilot, open label, prospective study of critically ill adults presenting to an urban tertiary care center. All adult patients admitted to an intensive care unit at our institution and requiring mechanical ventilation were screened for enrollment. This study was approved by the institutional review board, and written informed consent was obtained from each patient or their legally authorized surrogate before enrollment. This trial was registered on ClinicalTrials.gov (study ID: NCT01462279).

Patient Selection

Inclusion criteria were age at least 18 years, admission to an intensive care unit (ICU), and need for mechanical ventilation. We included only patients requiring mechanical ventilation because of our method of measuring $\dot{V}O_2$. Regardless of the method used, $\dot{V}O_2$ measurement is less accurate at a high fraction of inspired oxygen (FI_{O_2}) or in the presence of an air leak, and changes in body temperature are known to alter $\dot{V}O_2$ (10, 11). Exclusion criteria therefore included the following: rapidly escalating ventilator settings, FI_{O_2} greater than 60%, evidence of significant air leak, or temperature greater than 100°F. We excluded protected populations (pregnant patients and incarcerated patients), and patients taking more than 6 mg daily of thiamine before presentation or being given thiamine for a clinical indication in the hospital.

Data Collection

Baseline data collected included demographics, admission diagnosis, comorbidities, routine laboratory values, ventilator settings, vasopressors or sedatives being used, and vital signs. An initial venous blood sample was collected to determine thiamine level, lactate, and central venous oxygen saturation, if a central venous line was in place. Each patient was connected to both the Cheetah noninvasive cardiac output monitor (NICOM; Cheetah Medical, Newton Center, MA) and to the GE compact anesthesia monitor (General Electric, Fairfield, CT) for the duration of the study. The NICOM uses bioreactance to estimate cardiac index by interpreting signal from adhesive sensors attached to the patient's torso, and has been validated in prior studies (12). The GE compact anesthesia monitor measures $\dot{V}O_2$ using a pneumotachograph and a rapid paramagnetic analyzer attached in-line with the ventilator tubing, and has been validated in critically ill, mechanically ventilated patients (10, 11, 13). $\dot{V}O_2$ and CI were recorded every 5 minutes for the duration of the 9-hour protocol. CI was measured due to the potential partial dependence of $\dot{V}O_2$ on $\dot{D}O_2$ in lower cardiac output states. We planned to measure

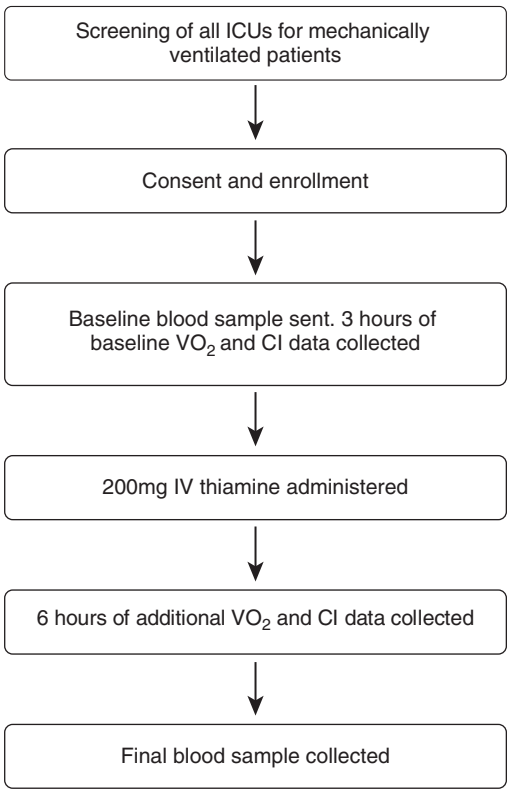

Figure 1. Flow chart of study protocol. CI = cardiac index; IV = intravenous; $\dot{V}O_2$ = oxygen consumption.

Table 1. Baseline characteristics

Characteristic	Value
Age, yr, mean (±SD)	66.1 (±17.4)
Male, %	64.71
Race, %	
White	88.24
Black	5.88
Asian	5.88
Past medical history, %	
None	17.60
CAD	5.90
Stroke	5.90
COPD	11.80
DM	11.80
IVDA	11.80
Liver disease	11.80
Hyperlipidemia	29.41
Alcohol dependence	11.76
Obesity	23.53
Admitting diagnosis, %	
Pneumonia	17.65
Sepsis	29.41
Acute renal failure	5.88
Aortic aneurysm	23.53
Other (including pancreatitis, endocarditis, pleural effusion, cardiac arrest)	41.18
Heart rate, mean (±SD)	84.4 (±13.9)
SBP, mm Hg, mean (±SD)	112.2 (±19.7)
F_{IO_2}, %, mean (±SD)	48.6 (±8.8)
PEEP, cm H_2O, mean (±SD)	7.2 (±3.1)
Lactate, mmol/L, median (IQR)	2.9 (1–3.1)
Lactate > 2 mmol/L, %	23.53
Initial thiamine, nmol/L, median (IQR)	31.9 (16–53)
Vasopressor use, %	47.06
Norepinephrine, n	5
Phenylephrine, n	2
Vasopressin, n	3
Sedation use, %	82.35
SOFA score, median (IQR)	5 (4–9)
Mortality, n (%)	6 (35)

Definition of abbreviations: CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; F_{IO_2} = fraction of inspired oxygen; IQR = interquartile range; IVDA = intravenous drug abuse; PEEP = positive end expiratory pressure; SBP = systolic blood pressure; SOFA = Sequential Organ Failure Assessment.
n = 17.

change in $\dot{V}O_2$ both in unadjusted analysis and adjusted for changes in CI based on this possibility.

After 3 hours, a single dose of 200 mg of intravenous thiamine was administered to each patient. Six hours of additional data were then collected, and a blood sample was then collected to determine thiamine level, lactate, and, if a central venous line was in place, central venous oxygen saturation. *See* Figure 1 for a flow diagram of the study protocol.

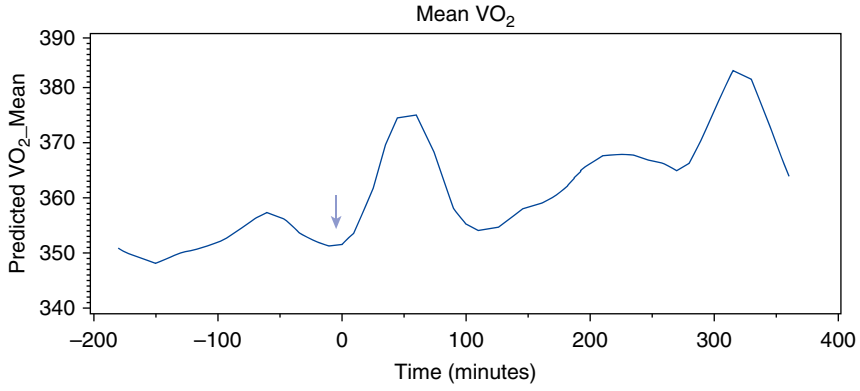

Figure 2. Smoothed curve of oxygen consumption ($\dot{V}O_2$) over time in all patients. *Arrow* at time zero indicates time of thiamine administration.

Data Analysis

Baseline characteristics were delineated using descriptive statistics. Continuous data were summarized with means and standard deviations or medians and interquartile ranges depending on the distribution of the data, discrete data with frequencies and percentages. We used linear mixed modeling for repeated measurements to assess the effect over time of the primary exposure of thiamine on $\dot{V}O_2$. We reported this result both in a univariate analysis, and adjusted for changes in CI. Missing data for CI were imputed, using the last-observation-carried-forward method. For linear mixed-effect models we assessed the following variance–covariance structures: independent, compound symmetry, first-order autoregressive [AR(1)], and unstructured. We used the Akaike information criterion (AIC) for final model selection (14). All tests of the data were two-sided and statistical analyses were performed in SAS version 9.2 (SAS, Cary, NC).

We then stratified patients by CI. We first separated patients into groups of those with preserved or depressed cardiac function (mean CI, >2.4 or ⩽ 2.4 L/m^2/min). We then analyzed the distribution of CI in our patient group, and stratified patients into those with mean CI greater than or less than the mean. A Pearson correlation was used to analyze the relationship between CI and $\dot{V}O_2$ to evaluate for any dependency of $\dot{V}O_2$ on CI.

Results

Twenty patients were enrolled in the study. Three were excluded for incomplete data (due to emergency procedures requiring interruption of study protocol or equipment malfunction leading to large blocks of missing $\dot{V}O_2$ data), leaving 17 for analysis. For one additional patient the NICOM malfunctioned, so that patient was excluded from the analysis in which we adjusted for changes in CI, and from the analysis stratified by mean CI. Baseline

Table 2. Change in oxygen consumption after thiamine administration, stratified by cardiac index group

	Average $\dot{V}O_2$ Change (*ml/min*) after Thiamine	*P* Value
All patients (n = 16)	16.3	0.052
Mean CI ⩽ 3* (n = 9)	−1.2	0.89
Mean CI > 2.4* (n = 10)	21.4	0.027
Mean CI > 3* (n = 7)	70.9	<0.0001

Definition of abbreviations: CI = cardiac index; $\dot{V}O_2$ = oxygen consumption.
*Units of CI, L/min/m^2.

characteristics are described in Table 1. The average age was 66 (±17) years, and 65% of the patients were men. Overall in-hospital mortality was 35%. Baseline thiamine levels ranged from below the detectable limit to 73 nmol/L (reference range, 9–44 nmol/L). Two patients (11.7%) had levels below the reference range. Baseline $\dot{V}O_2$ ranged from 175 to 450 ml/min.

There was a trend toward increase in $\dot{V}O_2$ after thiamine administration in all patients (16.3 ml/min, SE 8.5; $P = 0.052$), graphically represented in Figure 2. There was a very weak correlation between CI and $\dot{V}O_2$ ($r = 0.12$; $P < 0.0001$), and the increase in $\dot{V}O_2$ reached statistical significance after the planned adjustment for changes in CI (16.9 ml/min, SE 8.6; $P = 0.047$). In patients with preserved CI (>2.4 L/min/m^2) there was an increase of 21.4 ml/min ($P = 0.027$) (Table 2). There was no increase in $\dot{V}O_2$ in patients with mean CI below the group mean. In contrast, patients with a mean CI above the group mean of 3 L/min/m^2 showed an average increase of 70.9 ml/min in $\dot{V}O_2$ ($P < 0.0001$). There was a nonsignificant trend toward higher mortality in the group with CI less than or equal to 3, although median Sequential Organ Failure Assessment (SOFA) scores were largely similar (Table 3). There was no association between initial thiamine level and change in $\dot{V}O_2$. There was no change in CI after thiamine administration.

Discussion

We found a trend toward an increase in $\dot{V}O_2$ after the administration of a single dose of intravenous thiamine in critically ill patients, which achieved statistical significance after preplanned adjustment for CI. The increase in $\dot{V}O_2$ was considerably greater in patients with preserved CI, and the change was independent of baseline thiamine level.

$\dot{V}O_2$ depends on $\dot{D}O_2$ and the body's ability to extract oxygen effectively from the blood. In low CI states, $\dot{V}O_2$ is delivery dependent, but above a certain threshold, $\dot{V}O_2$ is more dependent on extraction. Cytopathic hypoxia refers to the defect in oxygen extraction that appears to develop later in sepsis and perhaps other forms of critical illness (5). If cellular metabolism is working correctly, as oxygen delivery decreases the extraction will continue at the normal rate. A greater fraction of the available oxygen will therefore be extracted by the cells, leading to a decrease in tissue P_{O_2}. If delivery is not impaired and there is a breakdown in cellular metabolism, less oxygen will be extracted and tissue P_{O_2} may actually increase. This finding has been reported in multiple animal and human studies, with skeletal muscle, bladder, and bowel mucosa P_{O_2} found to be higher than normal in septic shock, and lower in cardiogenic shock (15–17). This research, which suggests that oxygen extraction is deficient in sepsis, but not in cardiogenic shock, could explain why we saw a rise in $\dot{V}O_2$ after thiamine in patients with preserved CI (septic physiology), but not in those with low CI (cardiogenic shock physiology). Lower $\dot{V}O_2$ in spite of adequate delivery has been associated with higher lactate levels and poorer outcomes in the critically ill (4), and our data raise the possibility that thiamine could increase $\dot{V}O_2$ in these patients. The degree of rise in $\dot{V}O_2$ that would be clinically significant is unknown. In a study by Hayes and colleagues, in which they found that patients who were unable to mount an increase in $\dot{V}O_2$ when $\dot{D}O_2$ was increased had much higher mortality, the increase in $\dot{V}O_2$ in the group that did well averaged about 30%, but further study is needed (2).

Of the patients in our study, 11.7% were thiamine deficient, but thiamine level was not predictive of the change in $\dot{V}O_2$. This suggests that thiamine may be useful for the augmentation of oxygen extraction even in the absence of absolute deficiency, a response that we hypothesize is due to stimulation of pyruvate dehydrogenase and consequent augmentation of aerobic metabolism. There is scant prior literature on the effect of thiamine on $\dot{V}O_2$, but in

Table 3. Age, admitting diagnoses, time of enrollment, and mortality stratified by cardiac index group

	CI (n)	
	>3 L/min/m^2 (7)	⩽3 L/min/m^2 (9)
Age, yr, median (IQR)	61 (41–71)	69 (62–82)
Admitting diagnosis, n (%)		
Pneumonia	2 (28.57)	0
Pleural effusion	1 (14.29)	0
Valve surgery	0	1 (11.11)
Sepsis	2 (28.57)	3 (33.33)
Acute renal failure	1 (14.29)	0
Aortic aneurysm	2 (28.57)	2 (22.22)
Endocarditis	1 (14.29)	0
Pancreatitis	0	1 (11.11)
Bowel ischemia	0	2 (22.22)
Spinal hematoma	0	1 (11.11)
Days from ICU admission-enrollment, median (IQR)	4 (2–5)	2 (1–14.5)
SOFA score	5 (2.5–8)	5 (5–10)
Mortality, n (%)	1 (14)	5 (55)

Definition of abbreviations: CI = cardiac index; ICU = intensive care unit; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment.

a dog model of septic shock, Lindenbaum and colleagues demonstrated that thiamine improved lactate clearance, mean arterial pressure, and $\dot{V}O_2$, regardless of whether thiamine deficiency was present (9). Although there have been no prior studies in critically ill patients, an increase in maximal $\dot{V}O_2$ after administration of thiamine to healthy male athletes has been described (8). Our study is the first to our knowledge to investigate this effect in critically ill patients.

Our study was limited by its small size and pilot nature. The lack of a control arm prevents any conclusions about causality. Because of the small number of patients we were unable to control for other factors such as level of sedation, which could affect $\dot{V}O_2$. The patients enrolled had widely variable CIs, and patients with low CI did not mount an increase in $\dot{V}O_2$ after thiamine. Thus we might have seen a stronger effect if enrolling only patients with preserved CI. We were unable to evaluate the effect of thiamine on lactate clearance as has been done in prior studies because 75% of our patients had normal lactate levels at enrollment. With the preliminary data supplied by this pilot study, we are now enrolling patients in a randomized controlled trial (NCT01985685) comparing the effect of thiamine versus placebo on $\dot{V}O_2$ in critically ill patients to investigate this question further. Because of the differences we found in response between patients with preserved versus low CI, we are enrolling only patients with preserved CI in this follow-up study.

Conclusions

In this small, preliminary study, the administration of a single dose of thiamine was associated with a trend toward increase in $\dot{V}O_2$ in critically ill patients, which reached significance after planned adjustment for changes in CI. There was a larger and significant increase in $\dot{V}O_2$ in those patients with preserved or elevated CI. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors acknowledge the assistance of Francesca Montillo in preparation of the manuscript.

References

1 Wilson RF, Christensen C, LeBlanc LP. Oxygen consumption in critically-ill surgical patients. *Ann Surg* 1972;176:801–804.
2 Hayes MA, Yau EH, Timmins AC, Hinds CJ, Watson D. Response of critically ill patients to treatment aimed at achieving supranormal oxygen delivery and consumption: relationship to outcome. *Chest* 1993;103:886–895.
3 Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988;94:1176–1186.
4 Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994;330:1717–1722.
5 Fink MP. Bench-to-bedside review: cytopathic hypoxia. *Crit Care* 2002; 6:491–499.
6 Donnino MW, Cocchi MN, Smithline H, Carney E, Chou PP, Salciccioli J. Coronary artery bypass graft surgery depletes plasma thiamine levels. *Nutrition* 2010;26:133–136.
7 Donnino MW, Carney E, Cocchi MN, Barbash I, Chase M, Joyce N, Chou PP, Ngo L. Thiamine deficiency in critically ill patients with sepsis. *J Crit Care* 2010;25:576–581.
8 Bautista-Hernández VM, López-Ascencio R, Del Toro-Equihua M, Vásquez C. Effect of thiamine pyrophosphate on levels of serum lactate, maximum oxygen consumption and heart rate in athletes performing aerobic activity. *J Int Med Res* 2008;36: 1220–1226.
9 Lindenbaum GA, Larrieu AJ, Carroll SF, Kapusnick RA. Effect of cocarboxylase in dogs subjected to experimental septic shock. *Crit Care Med* 1989;17:1036–1040.
10 Walsh TS. Recent advances in gas exchange measurement in intensive care patients. *Br J Anaesth* 2003;91:120–131.
11 McLellan S, Walsh T, Burdess A, Lee A. Comparison between the Datex-Ohmeda M-COVX metabolic monitor and the Deltatrac II in mechanically ventilated patients. *Intensive Care Med* 2002;28: 870–876.
12 Marqué S, Cariou A, Chiche JD, Squara P. Comparison between Flotrac-Vigileo and Bioreactance, a totally noninvasive method for cardiac output monitoring. *Crit Care* 2009;13:R73.
13 Donaldson L, Dodds S, Walsh TS. Clinical evaluation of a continuous oxygen consumption monitor in mechanically ventilated patients. *Anaesthesia* 2003;58:455–460.
14 Vrieze SI. Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). *Psychol Methods* 2012;17: 228–243.
15 Boekstegers P, Weidenhöfer S, Pilz G, Werdan K. Peripheral oxygen availability within skeletal muscle in sepsis and septic shock: comparison to limited infection and cardiogenic shock. *Infection* 1991;19:317–323.
16 VanderMeer TJ, Wang H, Fink MP. Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. *Crit Care Med* 1995;23:1217–1226.
17 Rosser DM, Stidwill RP, Jacobson D, Singer M. Oxygen tension in the bladder epithelium rises in both high and low cardiac output endotoxemic sepsis. *J Appl Physiol (1985)* 1995;79:1878–1882.