

The Effect of a Single Dose of Thiamine on Oxygen Consumption in Patients Requiring Mechanical Ventilation for Acute Illness: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial

IMPORTANCE: Lower oxygen consumption is associated with worse survival in septic shock and in other forms of critical illness. No treatment that increases oxygen extraction, a key determinant of oxygen consumption, has been found. Thiamine is required for aerobic metabolism, and deficiency is common in the critically ill.

OBJECTIVES: We evaluated the effect of thiamine on oxygen consumption in patients requiring mechanical ventilation for an acute illness.

DESIGN: Phase II, randomized, double-blind, and placebo-controlled trial.

SETTING AND PARTICIPANTS: ICUs in a tertiary care hospital in the United States. Patients admitted to the ICU and requiring mechanical ventilation were screened for enrollment.

INTERVENTIONS: After enrollment, baseline measurement of oxygen consumption and baseline laboratories including lactate, central venous oxygen saturation, and pyruvate dehydrogenase, a single dose of 200 mg IV thiamine or placebo was administered. Oxygen consumption was then monitored for 6 additional hours and repeat laboratories were drawn at the end of the protocol.

MAIN OUTCOMES AND MEASURES: The primary outcome was the change in oxygen consumption. Analysis was done using linear regression with a first-order autoregressive variance-covariance structure to account for repeated measures within subjects. Secondary outcomes included change in lactate, central venous oxygen saturation, and pyruvate dehydrogenase quantity and activity.

RESULTS: Sixty-seven patients were enrolled. After excluding 11 patients due to inadequate quantity or quality of oxygen consumption data, 56 patients were included. There was no difference in change in oxygen consumption in the 6 hours after study drug. Results for secondary outcomes were similarly negative. In the prespecified subgroup of 18 thiamine deficient patients, there was a difference in the two oxygen consumption curves ($p = 0.006$), although no difference in median oxygen consumption or area under the curve.

CONCLUSIONS AND RELEVANCE: A single dose of IV thiamine did not alter oxygen consumption in patients requiring mechanical ventilation for acute illness.

KEY WORDS: calorimetry; metabolic resuscitation; oxygen consumption; thiamine

Katherine M. Berg, MD^{1,2}

Anne V. Grossestreuer, PhD²

Lars W. Andersen, MD, PhD^{2,3}

Xiaowen Liu, PhD²

Michael W. Donnino, MD^{1,2}

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Oxygen consumption (Vo_2) is determined by oxygen delivery (DO_2), a product of cardiac output and the oxygen content of arterial blood, and oxygen extraction. DO_2 usually far exceeds the body's needs. Vo_2

is not dependent on DO_2 until delivery is so low that everything delivered is used, a point referred to as the critical DO_2 .

In the critically ill, lower VO_2 is associated with higher mortality (1, 2). Previous investigators have sought to increase VO_2 in the critically ill with the goal of improving tissue oxygenation and outcome (2, 3). Prior efforts focused on increasing DO_2 , but this ultimately failed to show efficacy (3, 4). Although patients in whom an increase in DO_2 led to an increase in VO_2 did well, those patients whose VO_2 did not increase when DO_2 was increased had exceedingly high mortality, highlighting the importance of oxygen extraction (4). Cytopathic hypoxia, or the failure of aerobic metabolism in the presence of adequate DO_2 , is now known to be an important prognostic factor (5). While the association of impaired oxygen extraction with mortality appears clear, it is not known if modifying this is beneficial. No intervention that effectively increases oxygen extraction has been described.

Thiamine is a co-factor for pyruvate dehydrogenase (PDH), an essential enzyme for aerobic metabolism. In thiamine deficiency, pyruvate cannot enter the Krebs cycle and anaerobic metabolism predominates. Decreased adenosine triphosphate production, vasodilatory shock, and lactic acidosis ensue. Administration of thiamine rapidly reverses these effects in patients with thiamine deficiency (6, 7). Thiamine deficiency is common in the critically ill (8, 9). Thiamine administration also increased VO_2 and decreased lactate in an animal model of sepsis and in healthy human athletes regardless of initial thiamine level (10, 11). In our previous single-arm pilot study of patients on mechanical ventilation, administration of a single dose of thiamine was associated with an increase in VO_2 in the subgroup with preserved cardiac index, whether or not thiamine deficiency was present (12). In a randomized, placebo-controlled trial of thiamine for septic shock, thiamine led to decreased lactate, and a trend toward lower mortality in the 35% with thiamine deficiency, although there were no significant differences overall (13). Recent trials of the combination of thiamine, ascorbic acid, and corticosteroids for septic shock have not found benefit, although one trial reported a benefit in the subgroup with higher severity of illness and those deemed to have “uncertain” likelihood of survival at enrollment (14–16). These somewhat conflicting data leave open the possibility that

thiamine may decrease lactate and severity of illness in some patients, but whether and to whom thiamine is beneficial remains unclear. The mechanism of any effect has not been directly tested and a better understanding of mechanism may be useful in determining who thiamine might benefit. We hypothesized that IV thiamine would increase oxygen extraction in critically ill patients regardless of baseline thiamine deficiency. To test this hypothesis, we conducted the following randomized, double-blind, placebo-controlled trial to evaluate the effect of IV thiamine on VO_2 and lactate in patients requiring mechanical ventilation for an acute illness.

METHODS

Study Design

This was a single-center, phase II, randomized, double-blind placebo-controlled trial of the effect of IV thiamine on VO_2 and lactate in patients requiring mechanical ventilation for acute illness. The study was conducted at Beth Israel Deaconess Medical Center, a tertiary care academic center in Boston, Massachusetts, and was approved by the Beth Israel Deaconess Committee on Clinical Investigations (Protocol Number 2013P-000240). This study was registered on ClinicalTrials.gov (NCT01985685) and was supported by grants from the American Heart Association (13CRP16930000) and the National Heart, Lung, and Blood Institute (5K23HL128814-03, K24HL127101).

Patients and Screening/Enrollment

All patients in our ICUs who were on mechanical ventilation were screened for enrollment. Inclusion criteria were: 1) age greater than 18, 2) requiring mechanical ventilation for an acute illness, with stable ventilator settings for at least 3 hours, 3) upper central venous catheter in place, and 4) cardiac index (CI) greater than $2.4\text{L}/\text{min}/\text{m}^2$ as measured by the Cheetah Noninvasive Cardiac Output Monitor. We used a requirement for mechanical ventilation both to identify patients with critical illness and because the VO_2 monitor used is designed for patients on mechanical ventilation. The cardiac index criterion was due to our pilot data showing that only patients with preserved cardiac index had a response in VO_2 when given thiamine. Patients were excluded if they had 1)

fever greater than 100.5°F, 2) positive end-expiratory pressure greater than 12 cm H₂O or F_{IO}₂ greater than 0.6, 3) evidence of air leak in the ventilatory system (e.g., endotracheal tube cuff leak or chest tube with air leak), or 4) supplementation with thiamine greater than the amount found in a multivitamin in the prior 2 weeks. These exclusion criteria were either factors that can alter Vo₂ significantly or that could lead to abnormally high thiamine levels at baseline. Members of protected populations (pregnant women, prisoners, and the intellectually disabled) were also excluded. Written, informed consent was obtained from the legally authorized surrogate for all patients prior to enrollment.

Randomization, Blinding, and Protocol

Patients were randomized in a 1:1 ratio, in blocks of four, to receive either thiamine 200 mg IV in 50 mL D5W or placebo (50 mL D5W) as a single dose. Randomization was done by an independent statistician and only the research pharmacy possessed the randomization list. Study personnel were not aware of the randomization sequence. Upon enrollment, the research pharmacy was notified and prepared and delivered the blinded study drug. All investigators, patients, and clinical staff were blinded to the study drug. Thiamine is odorless and colorless, and thus, there is no detectable difference between IV thiamine and the placebo (D5W). All consented patients had cardiac index measured with the NICOM and were enrolled in the study if cardiac index was greater than or equal to 2.4 L/min/m². After enrollment, the NICOM was left in place. The Vo₂ monitor was connected in-line with the ventilator tubing by a respiratory therapist and baseline Vo₂ was collected continuously for 3 hours. The Vo₂ monitor used was a General Electric Anesthesia monitor with gas exchange module, connected to the ventilator tubing via an adapter with an attached gas sampling line. This device has been validated against the metabolic cart and measures Vo₂ continuously using an incorporated pneumotachograph to measure the volume of gas being exchanged and a paramagnetic analyzer to detect differences in inspired and expired oxygen (17). The patient's ventilator settings were not changed by our team and a certified respiratory therapist connected and disconnected the monitor for all patients. After 3 hours, blood was drawn for thiamine level,

central venous oxygen saturation (CVO₂), and lactate. Study drug was then administered as a single dose over 15 minutes. Vo₂ and cardiac index data were then collected for an additional 6 hours, at which time a lactate and CVO₂ were drawn again. All patients were followed to hospital discharge for mortality, although this was not a primary outcome of the study.

Sample size calculation and statistical analysis

Prior to our earlier pilot study, there were no data on the effect of thiamine on Vo₂ in hospitalized patients. We therefore relied on data from our pilot study for the sample size calculation. In patients with mean baseline CI greater than or equal to 2.5 L/m², the average increase in Vo₂ after thiamine administration was 35 mL/min. Using the average change in Vo₂ of 35 mL/min and a SD of 45 mL/min, we calculated the need for 28 patients in each arm (56 total) to achieve a power of 0.8 with a type I error of 0.05. We targeted a total enrollment of 60 in anticipation of some patients dropping out due to unanticipated interruptions in Vo₂ data collection due to acute illness.

Changes in F_{IO}₂, patient movement, suctioning, or other such changes can lead to brief artifactual changes in recorded Vo₂. To address this, while still blinded to study drug and outcomes, the principal investigator and a co-investigator (K.M.B., L.W.A.) visually inspected graphical read outs of minute-by-minute Vo₂ values and excluded clear outliers that were not physiologically feasible.

Descriptive statistics were used to characterize the study population. Continuous variables are presented as means with SD or medians with first and third quartiles depending on the normality of the data. Categorical variables are presented as counts with relative frequencies. The primary outcome was the change in Vo₂ after study drug. We used a linear regression model with a first-order autoregressive variance-covariance structure to account for repeated measures within subjects. Our primary analysis was unadjusted. A post hoc decision was made to retrospectively calculate Sequential Organ Failure Assessment (SOFA) scores and conduct a secondary analysis adjusting for SOFA score. For patients with missing values for components of the SOFA score (missing Pao₂ and missing total bilirubin were the only missing values), the most favorable value was imputed. Due to the potential

contribution of cardiac index to changes in VO_2 , we conducted an additional a priori analysis adjusting for changes in cardiac index.

As the temporal relationship between thiamine administration and changes in VO_2 is unknown, we created a flexible model including polynomial terms of time (linear, quadratic, and cubic) to allow for nonlinear effects. Interactions between the study group and each of the terms of time were added to the model to assess the effect of thiamine. This model was compared with a model without the group interactions with the likelihood ratio test with 3 degrees of freedom. The model also included adjustment for baseline VO_2 values (average value from the 3 hr before study drug administration). As a secondary analysis, median VO_2 and the area under the curve for VO_2 after study drug administration were compared between groups.

Secondary outcomes included change in PDH quantity, activity, and specificity and change in lactate and CVO_2 . Lactate and CVO_2 were measured in the Beth Israel Deaconess Medical Center clinical laboratory. The methods used to measure PDH activity and quantity have been described previously (18). They are calibrated to the total amount of protein in the sample and reported as optical density per minute per milligram protein. PDH-specific activity is calculated as $(\text{PDH activity}/\ln[\text{PDH quantity}])$. Plasma samples for baseline thiamine levels were collected and stored in light-blocked tubes and sent to Quest Diagnostics (Nichols Institute, Chantilly, VA) for analysis using Liquid Chromatography/Tandem Mass Spectrometry. Thiamine deficiency was determined using a previously established laboratory reference range of less than or equal to 7 nmol/L. To compare all secondary outcomes at 6 hours, we calculated the relative change from baseline (i.e., $[\text{6-hr value} - \text{baseline value}]/\text{baseline value}$) and compared the groups with

the Wilcoxon rank-sum test given non-normality of the data. Mortality was compared between groups using Fisher exact test. Planned subgroup analyses included patients with a baseline lactate greater than 2 and those found to be thiamine deficient at time of enrollment.

The analyses were performed based on a modified intention to treat population including those receiving the study drug and who had complete data on the primary outcome. All hypothesis tests were two-sided, with a significance level of p value of less than 0.05. Given the pilot nature of the current study, no adjustments were made for multiple testing and all secondary outcomes should therefore be considered exploratory. Statistical analyses were conducted in SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Of 1,747 patients screened, 67 were enrolled from November 2013 to May 2016 (Fig. 1). The number enrolled was extended beyond the planned 60 as several patients were excluded due to insufficient usable VO_2 data. Eleven out of 67 patients were excluded prior

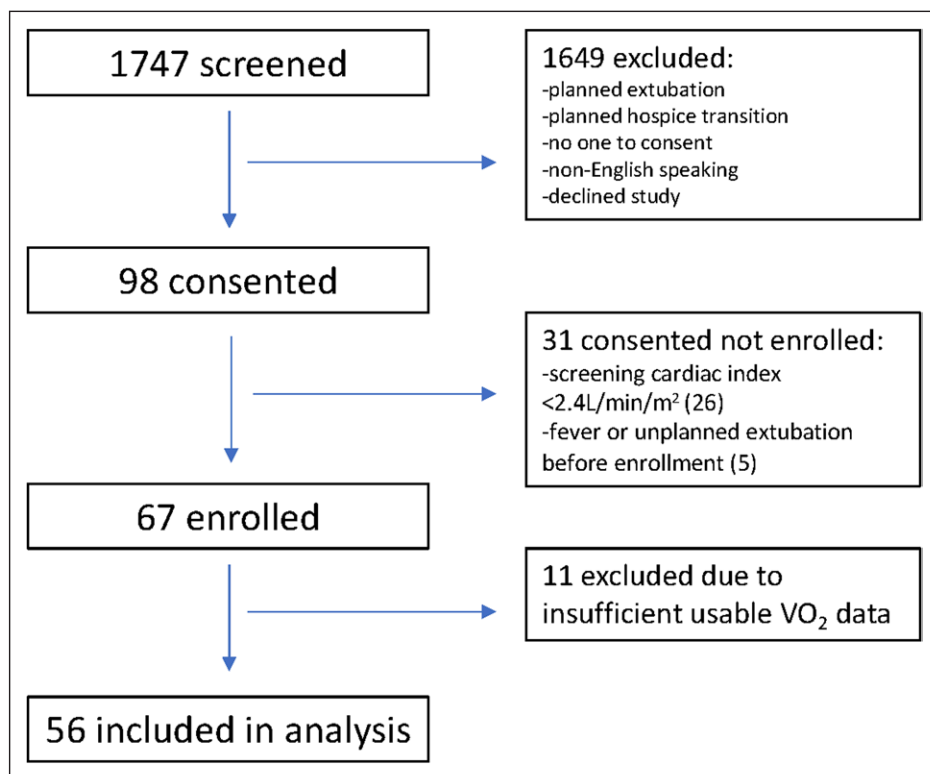


Figure 1. Flow diagram of patient screening and enrollment. VO_2 = oxygen consumption.

TABLE 1.
Baseline Characteristics of the Patients
Prior to Study Dug

Patient Characteristics	Placebo (n = 27)	Thiamine (n = 29)
Demographics		
Age (yr)	66 (49–75)	70 (61–75)
Sex (female)	12 (44)	14 (48)
Weight (kg)	89 (73–106)	85 (74–97)
Race		
White	20 (74)	25 (86)
Black	3 (11)	1 (3)
Other	4 (15)	3 (10)
Past medical history		
Chronic obstructive pulmonary disease	7 (26)	4 (14)
Coronary artery disease	5 (15)	8 (28)
Chronic heart failure	5 (19)	3 (10)
Diabetes	7 (26)	7 (24)
Liver disease	1 (4)	3 (10)
Admission diagnosis		
Sepsis	9 (33)	11 (38)
Pneumonia	10 (37)	9 (31)
Congestive heart failure	1 (4)	2 (7)
Acute renal failure	8 (30)	4 (14)
Myocardial infarction	1 (4)	2 (7)
Other	21 (78)	22 (76)
Ventilatory setting		
Positive end-expiratory pressure (cm H ₂ O)	5 (5–8)	8 (5–10)
FiO ₂ (%)	40 (40–50)	40 (40–50)
Ventilatory mode		
Controlled mechanical ventilation	9 (33)	12 (41)
Pressure support ventilation	13 (48)	13 (45)
Other	5 (19)	4 (14)
Medication		
Vasopressors	8 (30)	11 (38)
Sedation	16 (59)	22 (76)
Laboratory values		
Lactate (mmol/L)	1.3 (1.0–1.6)	1.3 (1.0–1.6)
Lactate > 2 mmol/L	2 (7)	6 (21)
Central venous oxygen (%) ^a	78 (68–80)	76 (67–81)
Thiamine level (nmol/L) ^b	12 (7–22)	10 (7–16)
Thiamine deficient (i.e., ≤ 7 nmol/L) ^b	8 (30)	10 (34)

(Continued)

TABLE 1. (Continued).
Baseline Characteristics of the Patients
Prior to Study Dug

Patient Characteristics	Placebo (n = 27)	Thiamine (n = 29)
Vital signs		
Temperature (°C)	99.1 (98.6–99.8)	98.5 (98.0–99.4)
Systolic blood pressure (mm Hg)	126 (104–141)	113 (108–133)
Heart rate (beats/min)	90 (77–101)	85 (75–97)
Baseline cardiac index (L/min/m ²) ^c	2.8 (2.6–3.7)	3.0 (2.7–3.8)
SOFA score ^d	8 (6.5–10.5)	8.5 (6.5–12)
SOFA score imputed ^e	7 (5–10)	8 (6–11)

SOFA = Sequential Organ Failure Assessment.

^aMissing on three patients in the placebo group and one patient in the thiamine group.^bMissing on one patient in the thiamine group.^cMissing on seven patients in the placebo group and four patient in the thiamine group.^dValues calculated for all patients with available values for SOFA components within 1 d of enrollment. Missing on five patients in thiamine group and 12 patients in placebo group due to absence of Po₂ or total bilirubin values within a day of enrollment.^eThis row includes imputed SOFA for those patients with missing Po₂ or total bilirubin. To calculate an imputed SOFA score for those patients, the most favorable category for the missing value was chosen, and the score was calculated based on those values. Continuous variables are presented as median (quartiles) and categorical variables as count (percentage).

to data analysis or unblinding for this reason. This left 56 patients for analysis; 27 in the placebo group and 29 in the thiamine group. Baseline characteristics are presented in **Table 1**. Age, severity of illness score, baseline lactate, and thiamine levels were similar between groups. Fourteen patients died (25%) before hospital discharge.

Oxygen Consumption

The median of the individual median baseline Vo₂ in the 3 hours prior to study drug administration was 4.0 mL/min/kg (quartiles: 3.5–5.3 mL/min/kg; range: 2.7–8.0 mL/min/kg) in the placebo group and 4.1 mL/min/kg (quartiles: 3.6–5.4 mL/min/kg; range: 2.4–10.1 mL/min/kg) in the thiamine group. In the main analysis using a cubic repeated measures model, there

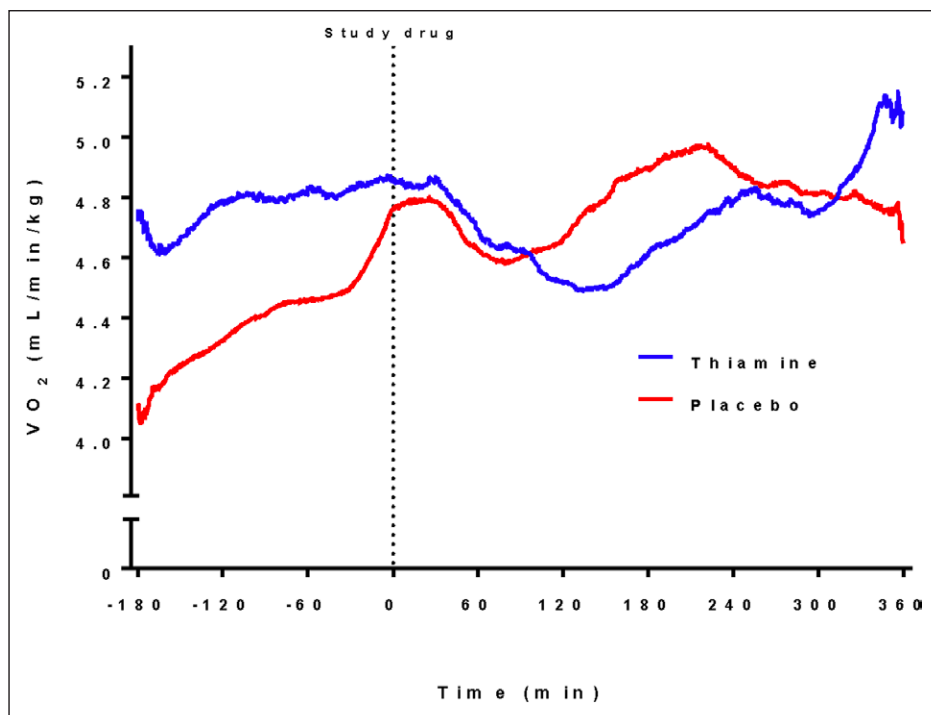


Figure 2. Smoothed curves of oxygen consumption (VO_2) values for all patients, according to study group. Logically weighted scatterplot smoothing curves for VO_2 values in the thiamine (blue) and placebo (red) group created using all available data points (i.e., not accounting for repeated measures within the same subject). Using a cubic polynomial model and adjusting for baseline values, there was no difference in VO_2 after study drug administration between the two groups ($p = 0.99$).

was no significant difference between the two groups in VO_2 values from study drug administration until 6 hours after study drug administration ($p = 0.99$; **Fig. 2**). The results did not change when adjusting for cardiac index or severity of illness (as represented by a baseline SOFA score). These results were also unchanged when including only linear or quadratic

terms of time, or no time variable at all.

The median of the individual median VO_2 values from study drug until 6 hours after study drug was 4.3 mL/min/kg (quartiles: 3.5–5.3 mL/min/kg; range: 2.9–10.9 mL/min/kg) in the placebo group and 4.2 mL/min/kg (quartiles: 3.7–5.7 mL/min/kg; range: 2.5–10.0 mL/min/kg) in the thiamine group. There was no difference between the groups in this value ($p = 0.87$).

The area under the VO_2 curve from administration of study drug until 6 hours after was similar between the groups (1,544 mL/kg [quartiles: 1,336–2,033 mL/kg; range: 1,039–3,812 mL/kg] in the placebo group and 1,539 mL/kg [quartiles: 1,309–2,006 mL/kg; range: 901–4,597 mL/kg] in the thiamine group; $p = 0.96$).

Secondary Outcomes

There was no difference in change in median lactate from time of study drug administration to 6 hours after study drug (median change of -0.1 mmol/L [-0.3 to 0.1 mmol/L] in the placebo group and -0.1 mmol/L [-0.4 to 0.1 mmol/L] in the thiamine group; $p = 0.77$).

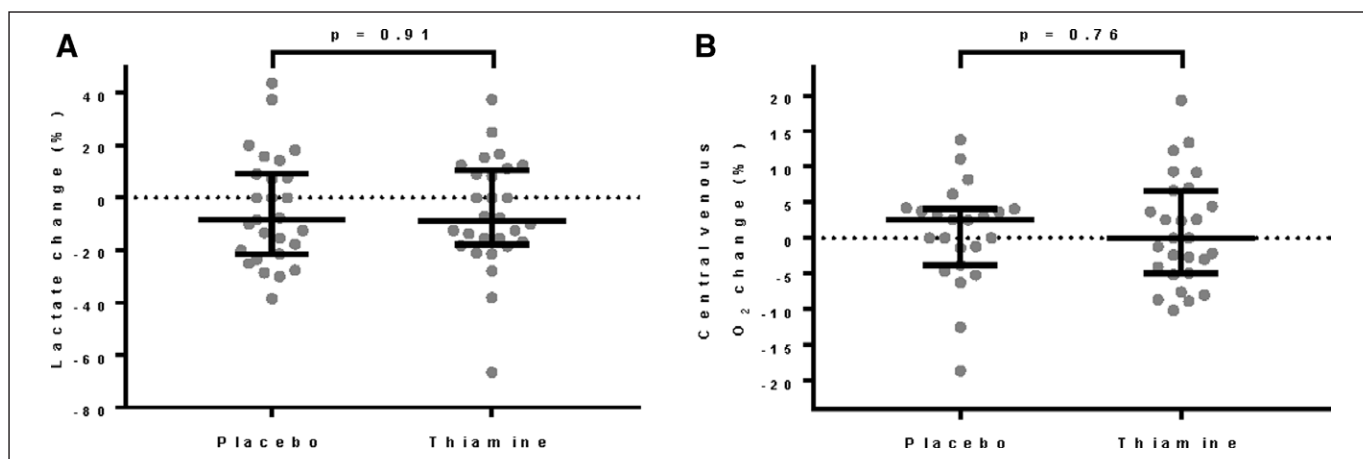


Figure 3. Secondary outcomes. Relative lactate (A) and central venous oxygen (B) change according to group for all patients. The relative change from baseline was calculated as $([6\text{-hr value} - \text{baseline value}] / \text{baseline value}) \times 100\%$. There was no difference between the groups.

Median percentage lactate change in both groups is presented in **Figure 3A**. Data were missing on one patient in the thiamine group.

The median relative central venous oxygen change was 3% (quartiles: -4% to 4%) in the placebo group and 0% (quartiles: -5% to 7%) in the thiamine group ($p = 0.76$; **Fig. 3B**). Data were missing on four patients in the placebo group and two patients in the thiamine group.

There was no difference in PDH activity (1% [quartiles: -9% to 50%] vs 12% [quartiles: -11% to 44%]; $p = 0.90$), PDH quantity (-3% [quartiles: -9% to 9%] vs 0% [quartiles: -14% to 46%]; $p = 0.38$), or PDH-specific activity (6% [quartiles: -12% to 44%] vs 4% [quartiles: -10% to 42%]; $p = 0.86$) between the placebo and thiamine group (**Fig. 4**). Data for PDH values were missing on two patients in the thiamine group. Mortality was similar between the groups; five patients died (19%) in the placebo group and nine patients died (31%) in the thiamine group ($p = 0.36$).

Subgroup Analysis

Eighteen patients were thiamine deficient; eight (30%) in the placebo group and 10 (34%) in the thiamine group. The median of the individual median baseline VO_2 prior to study drug administration was 4.0 mL/min/kg (quartiles: 3.6–5.1 mL/min/kg; range: 2.4–8.0 mL/min/kg) in the nonthiamine deficient group and 4.4 mL/min/kg (quartiles: 3.3–5.5 mL/min/kg; range: 2.7–10.1 mL/min/kg) in the thiamine deficient group ($p = 0.99$ for comparison). In the thiamine deficient group only, the median of the individual median VO_2 in the 3 hours prior to study drug administration was 4.1 (interquartile range [IQR], 3.4–5.0) in the placebo group and 4.9 (IQR, 3.3–5.6) in the thiamine group ($p = 0.762$). In the prespecified

subgroup analysis of thiamine deficient patients, a cubic repeated measures model, adjusted for baseline VO_2 values, indicated a difference in the two VO_2 curves after study drug administration ($p = 0.006$) (**Fig. 5**). There was no significant difference in the median of the individual median VO_2 values from study drug until 6 hours after study drug (4.0 mL/min/kg [quartiles: 3.4–5.2 mL/min/kg; range: 3.1–6.5 mL/min/kg] in the placebo group and 5.5 mL/min/kg [quartiles: 3.2–5.7 mL/min/kg; range: 3.0–10.0 mL/min/kg] in the thiamine group; $p = 0.76$). The median area under the VO_2 curve from administration of study drug until 6 hours after was also not significantly different between the groups (1,371 mL/kg [quartiles: 1,234–1,854 mL/kg; range: 1,115–2,370 mL/kg] in the placebo group and 1,990 mL/kg [quartiles: 1,200–2,045 mL/kg; range: 1,071–4,597 mL/kg] in the thiamine group; $p = 0.76$).

We were unable to perform a meaningful subgroup analysis of the patients with high lactate as only eight patients had baseline lactate greater than 2 mmol/L.

DISCUSSION

In a mixed cohort of intensive care patients requiring mechanical ventilation for an acute illness, most of whom did not have an elevated lactate, a single dose of IV thiamine did not increase VO_2 or decrease lactate. This relationship was not affected by severity of illness as measured by the SOFA score. In the subgroup of 18 thiamine deficient patients, there was a statistically significant difference in the VO_2 curves after study drug administration, but no difference in area under the curve or median VO_2 . Visual inspection of the logically weighted scatterplot smoothing (LOWESS) curves (**Fig. 5**) suggests more variability after study drug in

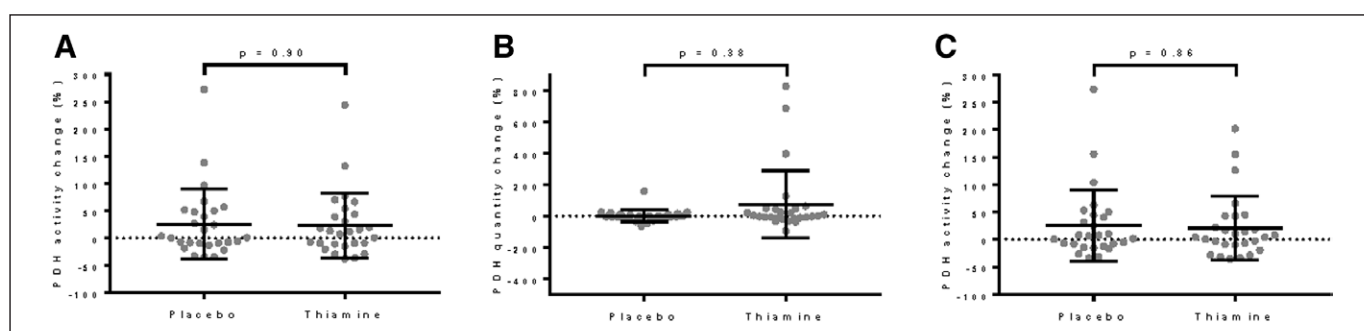


Figure 4. Pyruvate dehydrogenase (PDH) values. Change in PDH activity (**A**), quantity (**B**), and specific activity (**C**) according to group for all patients. The relative change from baseline was calculated as $[(6\text{-hr value} - \text{baseline value}) / \text{baseline value}] \times 100\%$. There was no difference between the groups.

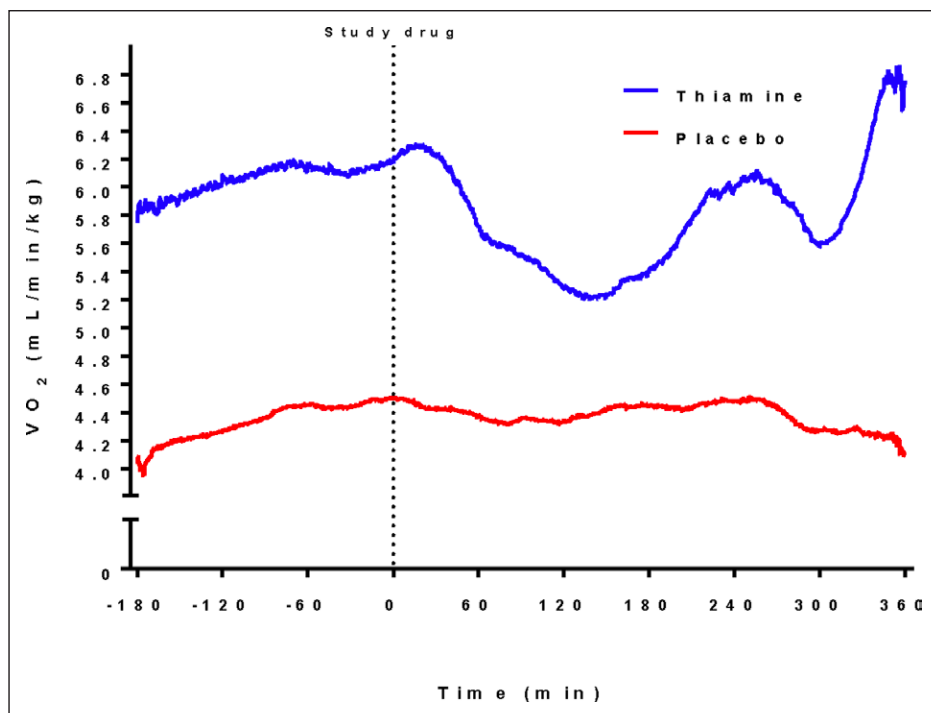


Figure 5. Smoothed curves of oxygen consumption (VO_2) values according to group for the subgroup of 18 patients with baseline thiamine deficiency. Logically weighted scatterplot smoothing curves for VO_2 values in the thiamine (*blue*) and placebo (*red*) group created using all available data points (i.e., not accounting for repeated measures within the same subject) in the 18 patients (eight in the placebo group and 10 in the thiamine group) who were thiamine deficient at baseline. Using a cubic polynomial model and adjusting for baseline values, there was a significant difference between the curves ($p = 0.006$).

the group, given thiamine is the main difference besides the difference in baseline values. LOWESS curves include all values and can thus be influenced by variability and outliers more than medians are, which may account for this difference. Based on the lack of significant difference in the medians or area under the curve, it is unlikely that the increased variability in values in the thiamine group is clinically meaningful.

Elevated lactate has repeatedly been shown to be a powerful predictor of mortality in many disease states, including septic shock and cardiac arrest (19, 20). This association is thought due to lactate being a marker of poor perfusion and impaired aerobic metabolism, not because lactate is itself harmful. Low VO_2 has also been associated with mortality in these patient populations (2–4, 21). The importance of lactate and VO_2 is thought to be as indicators of both impaired tissue perfusion related to hypotension and alterations in oxygen extraction. Poor perfusion is generally addressed by volume resuscitation, plus vasopressor, or inotropic support as indicated, but as of yet no therapy has been

found to specifically target impaired oxygen extraction.

A prior randomized trial found that thiamine decreases lactate and may improve survival in septic shock patients with thiamine deficiency, although there was no difference in the overall cohort (13). Retrospective work using matched controls found improved lactate clearance and survival at 28 days in patients who received thiamine within 24 hours of ICU admission for septic shock (22). It is hypothesized that thiamine improves lactate clearance by increasing PDH function and thus supporting aerobic metabolism. An increase in aerobic metabolism should lead to an increase in VO_2 , and our pilot single-arm study supported this hypothesis in showing an increase in VO_2 after thiamine administration in patients with preserved cardiac index (12). That pilot study, as well as one previous ran-

domized trial in healthy adults, suggested that thiamine can augment VO_2 even in the absence of thiamine deficiency or frank impairment in oxygen extraction (10). The lack of a detectable effect in the present study, however, together with the results of the previously described randomized trial in septic shock (13) and three more recent trials of thiamine, ascorbic acid, and corticosteroids (14–16), suggest that thiamine may not function as a universal “metabolic resuscitator” unless there is clear dysfunction of aerobic metabolism and/or clinically significant thiamine deficiency.

Although we had 18 patients whose thiamine levels at baseline were low, it is not clear that serum levels are the best measure of thiamine stores. Only eight of our patients had a lactate greater than 2 at baseline, suggesting that few patients had clinically important thiamine deficiency. One of the recent trials of thiamine together with ascorbic acid and steroids found that those with higher severity of illness showed more of a response (14). We did not find that SOFA score altered the relationship between thiamine and VO_2 , but

we had several missing values in this post hoc analysis. A future study with more careful selection of patients at risk for deficiency and with higher severity of illness plus evidence of dependence on anaerobic metabolism (e.g., elevated lactate) may be warranted.

The small number of patients with a lactate above normal or thiamine deficiency may have limited our ability to detect any benefit from thiamine administration. Our inclusion criteria, focusing on need for mechanical ventilation rather than lactate elevation or other markers of shock, may have inadvertently selected for a patient population less likely to benefit from thiamine, although the mortality of our cohort was relatively high. Multiple factors, including medications, temperature, and sedation level, can affect VO_2 and lead to artifactual differences. Due to the randomized nature of this trial and the lack of major differences in these variables between groups, adjustment for such factors was not done. We administered thiamine as a bolus dose over 15 minutes, and prior work has suggested thiamine uptake may be better with slower infusions over several hours (23). Finally, this trial was not designed for clinical outcomes, and thus, we did not evaluate whether thiamine had an effect on clinical outcomes in spite of the lack of effect on VO_2 .

CONCLUSIONS

A single dose of thiamine did not alter VO_2 , lactate, or CVO_2 in a mixed critically ill cohort without elevated lactate at baseline. Future research in more select patient populations, particularly those with clear evidence of thiamine deficiency or a breakdown in aerobic metabolism, may be warranted.

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- 1 Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA.
- 2 Center for Resuscitation Science, Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA.

3 Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark.

Dr. Berg conceived of the study, obtained funding, led the execution of the trial, oversaw data collection, contributed to the analysis plan, and drafted the article. Drs. Grossestreuer and Andersen curated the data, participated in data collection, conducted all analyses, and critically revised the article. Dr. Liu participated in study conception and design, carried out key laboratory analyses, and critically revised the article. Dr. Donnino conceived of the study, provided supervision of all aspects of the data collection and trial execution, obtained funding, and critically revised the article.

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This study was approved by the Beth Israel Deaconess Committee on Clinical Investigations (Protocol Number 2013P-000240).

Written, informed consent was obtained from the legally authorized surrogate for all patients prior to enrollment. All authors have given their approval and consent for publication.

Deidentified data generated and used for the current study are available from the corresponding author on reasonable request. Data have not been made publicly available in order to protect patient confidentiality and due to size of oxygen consumption files and complexity of cleaning and analyzing continuous metabolic data.

This study was registered on ClinicalTrials.gov (NCT01985685).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: kberg@bidmc.harvard.edu

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