

Research

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Lactate concentration gradient from right atrium to pulmonary artery

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Received: 26 Apr 2005 Revisions requested: 9 May 2005 Revisions received: 16 May 2005 Accepted: 20 May 2005 Published: 10 Jun 2005

Critical Care 2005, **9**:R425-R429 (DOI 10.1186/cc3741)This article is online at: <http://ccforum.com/content/9/4/R425>© 2005 Gutierrez *et al.*, licensee BioMed Central Ltd.This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is cited.

Abstract

Introduction We compared simultaneous measurements of blood lactate concentration ([Lac]) in the right atrium (RA) and in the pulmonary artery (PA). Our aim was to determine if the mixing of right atrial with coronary venous blood, having substantially lower [Lac], results in detectable decreases in [Lac] from the RA to the PA.

Methods A prospective, sequential, observational study was conducted in a medical-surgical intensive care unit. We enrolled 45 critically ill adult individuals of either sex requiring pulmonary artery catheters (PACs) to guide fluid therapy. Immediately following the insertion of the PAC, one paired set of blood samples per patient was drawn in random order from the PAC's proximal and distal ports for measurement of hemoglobin concentration, O₂ saturation (SO₂) and [Lac]. We defined Δ [Lac] as ([Lac]_{ra} - [Lac]_{pa}), Δ SO₂ as (S_{ra}O₂ - S_{pa}O₂) and the change in O₂ consumption (Δ VO₂) as the difference in systemic VO₂ calculated using Fick's equation with either S_{ra}O₂ or S_{pa}O₂

in place of mixed venous SO₂. Data were compared by paired Student's t-test, Spearman's correlation analysis and by the method of Bland and Altman.

Results We found S_{ra}O₂ > S_{pa}O₂ (74.2 ± 9.1 versus 69.0 ± 10.4%; p < 0.001) and [Lac]_{ra} > [Lac]_{pa} (3.9 ± 3.0 versus 3.7 ± 3.0 mmol.l⁻¹; p < 0.001). Δ [Lac] correlated with Δ VO₂ (r² = 0.34; p < 0.001).

Conclusion We found decreases in [Lac] from the RA to PA in this sample of critically ill individuals. We conclude that parallel decreases in SO₂ and [Lac] from the RA to PA support the hypothesis that these gradients are produced by mixing RA with coronary venous blood of lower SO₂ and [Lac]. The present study is a preliminary observation of this phenomenon and further work is needed to define the physiological and clinical significance of Δ [Lac].

Introduction

Pulmonary artery (PA) blood comprises the mixed venous effluent from all organs, with the notable exception of the lungs. PA O₂ saturation (S_{pa}O₂) has been promoted as an

index of tissue oxygenation [1,2] because it is thought to be related to the average end capillary blood PO₂ [3].

In a prior study [4], we measured the O₂ saturation (SO₂) of right atrial blood (S_{ra}O₂) and S_{pa}O₂ in samples drawn from the

CV = coronary venous; CVP = central venous pressure; DO₂ = systemic O₂ delivery; DP = double product; ERO₂ = oxygen extraction ratio; [Hb] = hemoglobin concentration; HR = heart rate; IVC = inferior vena cava; Δ [Lac] = lactate concentration gradient from right atrium to pulmonary artery; [Lac] = blood lactate concentration; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure; MPP = mean pulmonary pressure; MVO₂ = myocardial O₂ consumption; PA = pulmonary artery; PAC = pulmonary artery catheter; PAOP = pulmonary artery occlusion pressure; RA = right atrium; SO₂ = O₂ saturation; Δ SO₂ = O₂ saturation gradient from right atrium to pulmonary artery; SVRI = systemic vascular resistance index; VO₂ = O₂ consumption.

proximal and distal ports of PA catheters (PACs) placed in critically ill patients. We noted that $S_{pa}O_2$ was consistently lower than $S_{ra}O_2$ by approximately 5%. Others have noted a similar step-down in O_2 saturation from the right atrium (RA) to the PA [5,6], and continuous measurements in critically ill patients have shown a similar difference between $S_{pa}O_2$ and central venous (CV) O_2 saturation ($S_{cv}O_2$) of approximately 7% [7].

The RA to PA O_2 saturation gradient (defined as $\Delta SO_2 = S_{ra}O_2 - S_{pa}O_2$) is likely the result of mixing atrial blood with highly desaturated blood entering the right heart chambers from the coronary veins. This includes blood flowing from the coronary sinus, the great cardiac vein and other major epicardial veins.

As a result of myocardial lactate extraction from the coronary circulation, the CV lactate concentration ($[Lac]_{cv}$) is the lowest of any venous blood [8,9]. In the present study we compare blood lactate concentration ($[Lac]$) in paired samples drawn from the proximal and distal ports of PACs placed in critically ill patients ($[Lac]_{ra}$ and $[Lac]_{pa}$) to establish whether we could also detect a decreasing lactate concentration gradient from right atrium to pulmonary artery ($\Delta[Lac] = [Lac]_{ra} - [Lac]_{pa}$).

Methods

This was a prospective, sequential study performed in the George Washington University Hospital intensive care unit. The George Washington University Institutional Review Board approved the study and informed consent was obtained from the patient or from the next of kin.

The data presented were culled from a subset of patients enrolled in a previous study [4]. We enrolled individuals older than 18 years of age of either sex in whom their physicians determined that a PAC was required to guide fluid therapy. Enrollment in the study occurred at the time the patient or the nearest relative consented to the introduction of the PAC. On the basis of their medical history, we excluded patients with uncorrected valvular incompetence, intra-cardiac shunting or those who required insertion of the pulmonary artery catheter through the femoral vein.

A 7.5 French, 5 lumen, 110 cm length, PAC with the right atrial lumen positioned 30 cm from the tip (Edwards Lifesciences, Irvine, CA, USA) was inserted through the internal jugular vein or the subclavian vein using a percutaneous sheath introducer (8.5 French; Edwards Lifesciences). The insertion technique is described elsewhere [4]. Care was taken to place the distal port catheter in the PA and the proximal port in the RA.

Immediately after the insertion of the PA catheter, each patient had one set of paired blood samples drawn in rapid succession, and in random order, from the proximal and distal port. We took proximal port blood to be representative of RA blood, whereas distal port blood was considered to be PA blood. The

first 2 ml of blood drawn for each sample were discarded to prevent contamination with flushing fluid. Blood samples were drawn with the catheter balloon deflated to avoid contamination of the distal port sample with pulmonary capillary blood. Arterial O_2 saturation was determined from a previously *in vivo* calibrated pulse oximeter.

Blood samples were placed on ice and taken to a central laboratory for measurement of $[Lac]$ (Ektachem 950 IRC Chemistry Analyzer with a Vitros Products lactate slide, Ortho-Clinical Diagnostic, Inc., Rochester, NY, USA), hemoglobin concentration ($[Hb]$) and O_2 saturation (ABL700 Radiometer America Inc., Westlake, OH, USA). We measured cardiac output (CO) by the thermodilution method as the average of three sequential determinations.

Systemic O_2 delivery (DO_2), O_2 consumption (VO_2), O_2 extraction ratio (ERO_2), double product (DP; heart rate (HR) \times mean arterial pressure (MAP)) and left ventricular stroke work index (LVSWI) were computed using standard formulae. We defined ΔVO_2 as the difference in systemic VO_2 calculated with Fick's equation with either $S_{pa}O_2$ or $S_{ra}O_2$ in place of the mixed venous SO_2 (S_vO_2); $\Delta VO_2 = Q_{pa} \times 13.4 \times [Hb] \times (S_{ra}O_2 - S_{pa}O_2)$ ml.min⁻¹.

Paired Student's t-test was used to compare atrial to PA measurements. $[Lac]_{ra}$ and $[Lac]_{pa}$ were compared by Spearman's correlation analysis [10]. The method of Bland and Altman [11] was used to investigate the effect of lactate concentration on the differences between paired observations. The relationships between $\Delta[Lac]$ and ΔSO_2 , ΔVO_2 and other hemodynamic parameters were analyzed by Spearman's correlation analysis. Data are shown as mean \pm SD with $p < 0.05$ denoting a significant difference.

Results

We enrolled 45 patients in the study, including 18 women. The study group was composed of 31 post-operative patients (26 post-cardiac surgery), 11 patients in septic shock from various medical conditions, 2 patients with severe gastrointestinal bleeding and 1 patient in congestive heart failure. Demographic and hemodynamic parameters for the group are listed in Table 1.

The mean SO_2 and lactate concentrations for RA and PA blood samples are shown in Table 2. $S_{ra}O_2$ was greater than $S_{pa}O_2$ ($p < 0.001$), with $\Delta SO_2 = 5.2 \pm 4.8\%$. $[Lac]_{ra}$ was greater than $[Lac]_{pa}$ ($p < 0.001$), with $\Delta[Lac] = 0.2 \pm 0.2$ mmol.l⁻¹.

Shown in Fig. 1 is a Bland-Altman plot comparing $[Lac]_{ra}$ and $[Lac]_{pa}$. There was a bias towards greater $[Lac]_{ra}$ of 0.2 mmol.l⁻¹ ($p < 0.001$) with a 95% confidence interval for the population of -0.15 to 0.56 mmol.l⁻¹. There was no discernable relationship between $[Lac]_{ra}$ and $\Delta[Lac]$ ($r^2 = 0.03$; $p = 0.33$),

Table 1**Study population demographic and hemodynamic parameters**

Patient parameters (n = 45)	Mean ± SD
Age (years)	57.6 ± 13.2
APACHE II score	13.8 ± 6.0
HR (bpm)	92.1 ± 16.5
MAP (mmHg)	81.8 ± 13.0
MPP (mmHg)	27.6 ± 9.9
PAOP (mmHg)	18.6 ± 7.0
CVP (mmHg)	15.0 ± 6.1
Cardiac output (ml.min ⁻¹)	6.1 ± 2.6
Cardiac Index (ml.min ⁻¹ .m ⁻²)	3.3 ± 1.5
LVSWI (g.m.m ⁻² .beat)	39.7 ± 12.6
DP (mmHg.beat.min ⁻¹)	7694 ± 1944
SVRI (dynes.sec.m ⁻⁵)	2002 ± 1316
Hemoglobin (g.dl ⁻¹)	10.8 ± 2.0

CVP, central venous pressure; DP, double product (HR × MAP); HR, heart rate; LVSWI, left ventricular stroke work index; MAP, mean arterial pressure; MPP, mean pulmonary pressure; PAOP, pulmonary artery occlusion pressure; SVRI, systemic vascular resistance index.

Table 2**O₂ saturation and lactate concentration of paired RA and PA blood samples**

	RA blood	PA blood	Gradient (Δ)
O ₂ saturation (%)	74.2 ± 9.1 (53.1, 94.3)	69.0 ± 10.4 ^a (47.3, 90.5)	5.2 ± 4.8 (-8.1, 14.9)
Lactate concentration (mmol.l ⁻¹)	3.9 ± 3.0 (0.6, 11.7)	3.7 ± 3.0 ^a (0.3, 11.9)	0.2 ± 0.2 (-0.3, 0.7)

^aP < 0.001 when comparing atrial to mixed venous blood by paired t-test. Mean ± SD; range shown in parenthesis; n = 45. RA, right atrium; PA, pulmonary artery.

indicating that Δ[Lac] was not a concentration dependent phenomenon. Moreover, we found no significant relationships between [Lac]_{ra} and S_{ra}O₂ or between [Lac]_{pa} and S_{pa}O₂.

There was a significant relationship between Δ[Lac] and ΔVO₂ (Δ[Lac] mmol.l⁻¹ = 0.0026 ΔVO₂ ml.min⁻¹ + 0.0975; r² = 0.34; p < 0.0001) with a standard error of the estimate of 0.15 mmol.l⁻¹ (Fig. 2). There were no significant correlations between Δ[Lac] and cardiac index, DP, LVSWI, DO₂, VO₂ or ERO₂.

Discussion

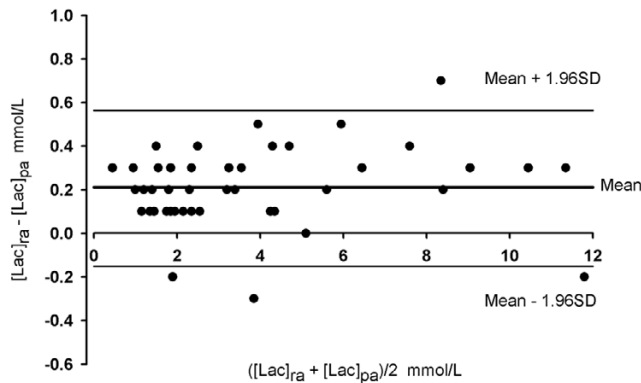
We detected a decreasing Δ[Lac] when comparing paired blood samples drawn from the proximal and distal ports of PACs. We also noted Δ[Lac] correlated with ΔVO₂. To our knowledge, these novel findings have not been reported elsewhere.

Only one other study in the literature has compared central venous [Lac] to [Lac]_{pa}. This study found no differences in [Lac], although it was biased by the use of multiple blood samples (n = 50) drawn from 12 critically ill patients [12]. Our study used only one comparison per subject, which perhaps may explain the difference in results.

We used a standard clinical laboratory instrument to measure [Lac] having a 95% precision of ± 0.1 mmol.l⁻¹. Even assuming a worst case scenario of a systematic instrument bias of -0.1 mmol.l⁻¹, the difference in [Lac] between RA and PA would have remained statistically significant.

The declining [Lac] gradient from RA to PA is likely the result of mixing RA blood with blood of lower [Lac] emanating from the coronary venous system. Lactate oxidation accounts for 10% to 20% of total myocardial aerobic energy production

Figure 1



Bland-Altman plot comparing [Lac]_{ra} and [Lac]_{pa}. Bias 0.21 mmol.L⁻¹ with a 95% confidence interval for the population of -0.15 to 0.56 mmol.L⁻¹.

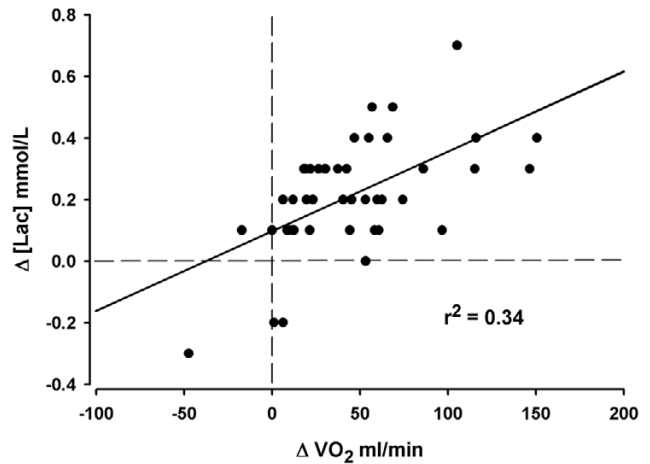
[13], a proportion that increases substantially in sepsis [14]. As a result of myocardial lactate extraction, coronary venous [Lac] is substantially lower than arterial [Lac] and is the lowest of all venous effluents [15]. The dilution of RA blood by coronary venous blood of lower [Lac] is a plausible explanation for the small but detectable difference in [Lac] from RA to PA.

Since RA blood is the mixture of superior vena cava and inferior vena cava (IVC) blood, the possibility exists that these blood streams had not thoroughly mixed at the proximal PAC sampling port. In this case, one could expect further mixing to occur between IVC and RA blood while flowing into the pulmonary artery. Our results do not support this hypothesis. Direct measurements in humans show that IVC blood has the highest [Lac] of any major vein [9] and further mixing of RA with IVC blood would have produced higher, not lower, [Lac]_{pa}. A factual resolution of this question can only be achieved by direct measurement of [Lac] from IVC to PA.

Only three individuals in our group had [Lac]_{ra} < [Lac]_{pa}. These patients had no distinguishing features to help us differentiate them from others in the group. It is possible that accidental mislabeling of the samples may have accounted for a negative Δ[Lac] but we think it unlikely, given the care taken with the labeling and measuring of the samples. Another possibility is that these individuals experienced myocardial ischemia, a condition associated with an upsurge in glucose metabolism and net lactate release by the heart [17-19]. Myocardial lactate release, as opposed to the normal state of myocardial uptake, would have resulted in [Lac]_{ra} < [Lac]_{pa}.

Others have noted a linear relationship between myocardial O₂ consumption (MVO₂) and myocardial lactate uptake, reflecting the O₂ cost of lactate utilization by the heart [14]. We did not measure MVO₂ directly but calculated ΔVO₂, a parameter denoting the difference in systemic VO₂ prior to and immediately after entry of myocardial effluent blood into the

Figure 2



Linear correlation of Δ[Lac] to ΔVO₂. The latter represents the difference in VO₂ calculated using either SraO₂ or SpaO₂ in place of mixed venous SO₂ in the Fick's Equation (Δ[Lac] mmol.L⁻¹ = 0.0026 ΔVO₂ ml.min⁻¹ + 0.0975; r² = 0.34; p < 0.0001). Standard error of the estimate 0.15 mmol.L⁻¹.

venous circulation. As such, ΔVO₂ bears a direct relationship to MVO₂. We noted a linear relationship between ΔVO₂ and Δ[Lac] (Fig. 2) similar to that described between MVO₂ and myocardial lactate uptake. This finding suggests that Δ[Lac] also may be related, in a yet to be established fashion, to MVO₂.

Conclusion

We found decreases in [Lac] from RA to PA in this sample of critically ill individuals. We conclude that parallel decreases in SO₂ and [Lac] from RA to PA support the hypothesis that these gradients are produced by mixing RA with coronary venous blood of lower SO₂ and [Lac]. The present study is a preliminary observation of this phenomenon and further work is needed to define the physiological and clinical significance of Δ[Lac].

Key messages

- Oxygen and lactate concentrations are lower in PA blood than in RA blood.
- The oxygen and lactate concentration gradients from RA to PA are likely the result of mixing atrial with coronary venous blood.
- The possibility exists that these concentration gradients may reflect changes in myocardial energy requirements.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

GG conceived the study, participated in its design, performed statistical analysis and drafted the manuscript. LSC and HZ participated in the design of the study, collected data and helped to draft the manuscript. MGS and NMK conducted the study, collected data and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The George Washington University Medical Center Department of Anesthesiology Research Fund financed the study in its entirety. Preliminary results of the study were presented in abstract form at the 2003 American Thoracic Society International Conference, Seattle, WA, USA.

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Commentary

Lactate concentration gradient from right atrium to pulmonary artery: a commentary

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Published online: 1 July 2005

This article is online at <http://ccforum.com/content/9/4/337>

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Critical Care 2005, **9**:337-338 (DOI 10.1186/cc3769)

See related research by Gutierrez *et al.* in this issue [<http://ccforum.com/content/9/4/R425>]

Abstract

Inadequate myocardial performance is a common complication of severe sepsis. Studies in humans strongly argue against a decrease in coronary blood flow in the pathogenesis of this sepsis-induced cardiac injury. Moreover, regional myocardial ischemia may well be present in sepsis patients with coexistent coronary artery disease. Nevertheless, the diagnosis of myocardial ischemia remains difficult in patients with sepsis, since elevation of troponin in these patients can be the result of a variety of conditions other than acute myocardial ischemia. The use of the right atrium to pulmonary artery lactate gradient could perhaps help the clinician in detecting myocardial ischemia in patients with sepsis.

In this issue, Gutierrez *et al.* [1] compared simultaneous measurements of blood lactate concentrations in the right atrium and pulmonary artery in critically ill patients. They found decreases in both blood lactate concentrations and venous blood oxygen saturation in gradients from the right atrium to the pulmonary artery. These gradients are presumably produced by mixing right atrial blood with coronary venous blood, which has lower lactate concentrations and blood oxygen saturation. More interestingly, in this study, the lactate gradient was inverted in three patients, suggesting myocardial ischemia, a condition associated with lactate release by the heart.

Blood lactate levels are typically elevated in hypoperfusion states when pyruvate cannot enter the Krebs cycle as the cellular oxygen supply becomes insufficient. The pyruvate is shunted to lactate through the enzyme lactate dehydrogenase, producing only two molecules of energy-rich ATP for every two molecules of pyruvate (from one molecule of glucose), compared with 38 molecules of ATP for each glucose molecule through the aerobic mitochondrial process when sufficient oxygen is present. This causes the lactate to pyruvate ratio to increase (the normal value is around 10:1). Once molecular oxygen is again available, assuming that mitochondrial function is preserved, the excess lactate is

rapidly metabolized back through pyruvate into carbon dioxide and water via the Krebs cycle. Lactate in the blood is metabolized mainly by the liver (50%) and kidney (20%). Liver function and liver blood flow can influence hepatic lactate clearance. Striated muscles, the heart and the brain can also metabolize lactate and, in some conditions, this clearance can be significant.

Traditionally, elevated blood lactate levels in hemodynamically unstable patients have been interpreted as reflecting acute circulatory shock. Elevated blood lactate levels have been correlated with mortality in all types of shock [2,3]. The speed at which lactate is cleared from the blood through vigorous resuscitation strongly correlates with ultimate outcome, including mortality and organ failure. The best chances of survival occur when resuscitation efforts result in lactate clearance to normal values within 12 to 24 h [4-6].

Blood lactate concentration represents a global marker of tissue oxygenation but does not reflect loco-regional tissue oxygenation. The venoarterial lactate gradient on both sides of an organ can be used to detect regional hypoxia. De Backer *et al.* [7] demonstrated that lung lactate production occurs in subjects with acute lung injury states but not in patients with normal lungs, cardiogenic pulmonary edema or pneumonia. Thus, lung lactate production requires a diffuse inflammatory process. Other organs can also produce lactate and experimental studies suggest that the gut can produce lactate in sepsis, which is probably from anaerobic metabolism as the portal lactate to pyruvate ratio is increased. The investigation of splanchnic lactate turnover in humans is much more complicated as access to the portal vein is not possible outside the operating room. Since the liver is usually able to clear this small amount of gut-produced lactate, splanchnic ischemia may go unsuspected. De Backer *et al.* [8] reported that hepatosplanchnic lactate release is uncommon in patients with severe sepsis and is not related to

arterial lactate concentrations, abdominal infection or signs of gut or liver dysoxia.

Inadequate myocardial performance, characterized by left ventricular systolic depression and diastolic dilatation, is a common and early complication of septic shock [9,10]. Several factors may contribute to the occurrence of myocardial damage during septic shock. A possible direct cardiac myocytotoxic effect of bacterial endotoxins or mediators (e.g. cytokines or reactive oxygen species) induced by the infectious process and produced by activated leukocytes, macrophages and endothelial cells [10] should be considered. Studies in humans [11,12] strongly argue against a decrease in coronary blood flow in the pathogenesis of this sepsis-induced cardiac injury. However, a dysfunctional microcirculation that produces regional flow disturbances and abnormal tissue oxygenation is a hallmark of septic shock, and may cause relative ischemia in various organs, including the heart [13,14]. Moreover, regional myocardial ischemia may well be present in sepsis patients with identifiable coronary risk factors or coexistent coronary artery disease. In this context, the diagnosis of myocardial ischemia remains difficult in sedated and mechanically ventilated patients with sepsis. Indeed, elevation of troponin can be detected in a variety of conditions other than acute myocardial ischemia, especially in critically ill patients with severe sepsis. The use of the right atrium to pulmonary artery lactate gradient reported by Gutierrez *et al.* in this issue [1] could perhaps help the clinician to detect myocardial ischemia in septic patients. However, the amplitude of the lactate gradients reported in this study [1] is close to the measurement error of blood lactate concentrations provided by many blood gas analyzers.

The present study is a preliminary observation. Further studies are needed to confirm these results and to study the usefulness of this lactate gradient in the detection of myocardial ischemia in critically ill patients.

Competing interests

The author(s) declare that they have no competing interests.

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