Lactate measurement: arterial versus venous blood sampling

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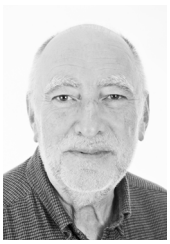

Chris Higgins
Little Acre, Main Road
Shurdington
Nr Cheltenham
Gloucester
GL51 4XF, UK
E-mail: cjhiggins@hotmail.co.uk

Lactate is the end product of the metabolic process of glucose utilization, known as anaerobic glycolysis, which occurs in the cytoplasm of all cells. In well-oxygenated tissues this lactate is metabolized further, but if tissues are inadequately oxygenated, lactate accumulates locally and blood concentration increases.

As a blood marker of tissue hypoxia, lactate measurement has long-established clinical utility, most notably in the assessment and monitoring of acutely/critically ill patients and major trauma victims in emergency room and intensive care units.

Arterial blood is the gold standard sample for lactate measurement, but a reading of the literature and current practice suggests that venous blood is considered an acceptable alternative.

The purpose of this article is to review the evidence base for the notion that venous blood lactate concentration approximates to that in arterial blood, and thereby, that venous blood is an acceptable alternative sample.

Until fairly recently the evidence base was sparse and somewhat conflicting, but eight relevant studies have been published since 2011, and these will be a focus of this article.

The article begins with a general discussion of the distinction between arterial blood and three types of venous blood that could be used for lactate measurement: peripheral venous blood, central venous blood and mixed venous blood.

Blood sampling from different sites – some general considerations

Arterial blood is constant in its lactate concentration irrespective of the site of sampling. It is considered the ”gold standard” sample for

assessment of lactate measurement because it is derived from mixed venous blood and thus provides a representative sum of all sources of tissue lactate production.

By contrast, the concentration of lactate in venous blood could, theoretically at least, vary depending on the site of sampling because of variation, both physiological and pathological, in local tissue lactate production.

Early studies [1, 2] that established the link between reduced blood perfusion and increased lactate – and thereby the clinical utility of lactate measurement – were conducted on arterial blood; and lactate reference range was first established using arterial blood.

Arterial blood remains the gold standard sample for assessment of patient acid-base and oxygenation status. The blood gas analyzers used for these assessments now commonly have the capacity for simultaneous measurement of lactate in the same arterial sample.

Arterial blood is usually sampled by needle puncture of a peripheral artery, most commonly the radial artery in the wrist, the brachial artery in the arm or femoral artery in the groin. Compared with venipuncture (the procedure used to obtain peripheral venous blood), arterial puncture is technically more demanding and certainly more painful and hazardous for the patient [3, 4].

Specialist training in arterial blood collection is essential for patient safety and comfort, so that in some countries medically qualified staff have sole responsibility for the procedure. By contrast, venipuncture is a very commonplace procedure that can be easily and safely performed, after minimal training, by ancillary staff with no medical or nursing education.

In intensive care and operating room settings catheterization of radial or femoral artery, principally for continuous arterial blood pressure monitoring, offers an alternative means of safely and conveniently sampling arterial blood for a small minority of patients.

However, insertion of an arterial catheter is itself a technically difficult procedure [5] associated with risk of serious complications [6, 7]. Novel, non-invasive technology for continuous monitoring of arterial blood pressure [8] is set to reduce the necessity for arterial catheterization in the future, so that this mode of sampling arterial blood could well become even less common.

Given the difficulties and limitations associated with sampling arterial blood, it would be logistically attractive for clinical staff, as well as safer and more comfortable for patients, if venous blood could be used for lactate measurement.

By far the most common venous blood sample is that obtained by needle puncture of a peripheral (superficial) vein in the forearm (at the antecubital fossa) or back of the hand; this is peripheral venous blood and must be distinguished from central venous blood and mixed venous blood.

Central venous blood is sampled via a central venous catheter (CVC). CVCs are commonly inserted to intensive care patients and less commonly to emergency room patients; they provide vascular access for delivery of drugs, blood transfusion and fluid therapy.

In addition, they allow monitoring of central venous pressure, central venous oxygen saturation and, importantly for this article, the means for easy sampling of venous blood for routine laboratory testing, including measurement of lactate concentration.

CVCs are usually inserted cutaneously via the jugular vein in the neck or subclavian vein in the upper chest to one of the two largest central veins, called the superior vena cava. This vessel drains all

venous blood from the upper half of the body to the right atrium of the heart.

The tip of the CVC, from which blood is sampled, is ideally sited in the superior vena cava close to its junction with the right atrium. Central venous blood is thus the mixed venous blood from the upper half of the body. Since it does not include venous blood from the lower half of the body, which is drained to the right atrium via the inferior vena cava, central venous blood cannot be considered truly mixed venous blood.

Mixing of venous blood drained from the lower and upper halves of the body occurs in the right atrium and right ventricle. Only blood flowing from the right ventricle to the lungs via the pulmonary artery is truly mixed venous blood. Mixed venous blood can only be sampled by catheterization of the pulmonary artery, a procedure used in critical care for hemodynamic monitoring of selected patients.

The value of pulmonary artery catheterization has been challenged and is now less frequently used than was once the case [9], but for those critically ill patients with a pulmonary artery catheter there remains the option of conveniently sampling venous blood, specifically mixed venous blood, for lactate measurement.

To summarize, for the vast majority of patients including most in the emergency room, the only available venous sample for lactate measurement is peripheral venous blood. But for critically ill and trauma patients being cared for in intensive care units and occasionally in the emergency room, who have either a central venous line or pulmonary artery catheter fitted, it is more convenient to sample central venous blood or mixed venous blood than to sample peripheral venous blood.

Comparing arterial and venous lactate concentration – study design

A number of studies [11-24] that test the validity of using venous blood in lieu of arterial blood for lactate measurement have been conducted since the first was published in 1987 [10]. More than half of these studies [17-24] are recently published (in the past 5 years), signifying that the issue remains relevant and to some extent, unresolved.

In essence, all these studies have a common and simple design based on the assumption that arterial blood is the gold standard sample. Lactate concentration of venous blood is compared with lactate concentration of arterial blood collected from the same patient at the same time, among a defined cohort of intensive care or emergency room patients. (One study [17] includes a small cohort of healthy controls.)

Some of the important differences in detail of the studies are highlighted in Table I, which reveals, for example, that the type of venous blood used to compare with arterial blood differs. Whilst most studies [11, 13-15, 17, 19-24] compare arterial and peripheral venous lactate, four studies [10, 16-18] examine the relationship between arterial and central venous lactate, and just two, the relationship between arterial and mixed venous lactate [10, 12].

Three studies [18, 20, 23] are retrospective in nature (lactate results being retrieved from laboratory records); all others are prospective in design. The studies vary greatly in terms of the size of study cohort; the smallest is seven pediatric intensive care patients [12] and the largest is 232 adult emergency room patients retrospectively selected on the basis of increased lactate. [20].

The number of paired lactate results (arterial and venous) available for statistical analysis in each study also varies greatly, ranging from 20 [12] to 673 [18]. The studies vary somewhat in the method

Study date (Ref) Retrospective (R) or Prospective (P)	Number of Patients studied (ICU or ED)	Venous sample Peripheral (PV) Central (CV) or Mixed (MV)	Number of pairs	Time between sampling arterial and venous blood	Method of lactate measurement
1987 [10] P	35 adults ICU	CV & MV	50 for CV 104 for MV	"Simultaneous"	Enzymatic central laboratory
1988 [11] P	20 adults ICU	PV	20	"Simultaneous"	Enzymatic central laboratory
1994 [12] P	7 children ICU	MV	21	"Simultaneously as possible"	Enzymatic central laboratory
1996 [13] P	48 adults ED	PV	48	Mean time 6 ±5.5 mins	"Lactimeter"
1997 [14] P	69 adults ED	PV	69	<5 mins	Clin Chem analyzer
2000 [15] P	221 adult trauma victims ED	PV	221	<2 mins	Blood Gas analyzer
2006 [16] P	110 adult ICU	CV	167	"Simultaneously as possible"	Blood Gas analyzer
2011 [17] P	32 adult ICU patients 10 healthy controls	PV & CV	77 for PV 80 for CV	"Simultaneous"	Enzymatic central laboratory
2012 [18] R	188 adults ICU	CV	673	All <30 mins Median time 2 mins	Blood Gas analyzer
2013 [19] P	72 adults ED	PV	72	<5 mins	Blood Gas analyzer
2014 [20] R	232 adults ED All with raised lactate (≥2.0 mmol/L)	PV	232	Median 22 mins (IQR 13-36 mins)	Blood Gas analyzer
2015 [21] P	103 adults ED	PV	103	Mean time 8 ±2 mins	Point-of-care lactate analyzer
2015 [22] P	26 adults ICU	PV	102	"Simultaneous"	Blood Gas analyzer
2016 [23] R	60 children with sepsis PICU	PV but not made absolutely clear	60	<60 mins	Blood Gas analyzer
2016 [24] P	68 adults with sepsis ICU	PV	68	Not recorded	Blood Gas analyzer

TABLE I: Study design and characteristics

Study Date [Ref] No. of pairs	Arterial lactate range and mean (mmol/L)	Mean difference Venous – Arterial (mmol/L)	95% limits of agreement (mmol/L)	Correlation r, r^2 (p-value)
1988 [11] 20 pairs	1.0-10.5 Mean not recorded	Not recorded	Not recorded	r = 0.99 (p<0.001)
1996 [13] 48 pairs	0.3-7.6 only 13 pairs abnormal (>1.6 mmol/L)	0.18	−0.012 to 0.372 Agreement less good at higher concentration	r = 0.71 (p<0.001)
1997 [14] 69 pairs	0.5-11.5 Mean 2.8	0.22	−1.3 to 1.7	r = 0.94 r^2 = 0.89
2000 [15] 221 pairs	0.5-18.0 Mean 3.11	0.32	Not recorded	r = 0.94 (p <0.0001) Regression eqtn allows prediction of arterial lactate (AL) from venous lactate (VL) AL = 0.076 + 0.889 × VL)
2011[17] 77 pairs	0.8-4.8 Mean 1.55	0.35	−0.7 to 1.4	r = 0.79 (p<0.0001)
2013 [19] 72 pairs	0.4-15.0 Mean 2.15 (Only 37 of 72 pairs abnormal lactate i.e. >1.6 mmol/L)	0.268	−0.4 to1.1	r^2 = 0.94 Regression eqtn allows prediction of arterial lactate (AL) from venous lactate (VL) AL = −0.259 + 0.997 × VL
2014 [20] 232 pairs	1.0-13.2 Mean 2.45 All abnormal (venous lactate > 2.0 mmol/L)	1.06	−1.53 to 3.66 mmol/L	Not recorded
2015 [21] 103 pairs	0.6-10.0 Mean 2.03	0.48	Not recorded	r = 0.96 (p<0.0001)
2015 [22] 102 pairs	1.5-4.3 Mean 2.3	0.3	−1.8 to 2.4	r =0.972 (p<0.001)
2016 [23] 55 pairs	Not recorded Approx. range 0.5-13.5	0.8	−1.9 to 1.9	Not recorded
2016 [24] 68 pairs	0.5-17.0 (Interquartile range 1.2-4.1) Mean 2.1	0.66	−2.3 to 3.66	r = 0.934 (p<0.001) Regression eqtn allows prediction of arterial lactate (AL) from venous lactate (VL) AL = −0.236 + 0.934 × VL

TABLE II: Study results – arterial versus peripheral venous

Study Date [Ref] No. of pairs	Arterial lactate range and mean (mmol/L)	Mean difference Venous – Arterial (mmol/L)	95% limits of agreement (mmol/L)	Correlation r, r^2 (p-value)
1987 [10] 50 pairs	0.39-9.71 Mean 2.32	0.029 Maximum difference 0.5 mmol/L	Not recorded	r = 0.995 (p <0.001)
2006 [16] 167 pairs	0.38-6.51 Mean 1.13	0.08	–0.27 to 0.42	Not recorded
2011 [17] 80 Pairs	0.8-4.8 Mean 1.55	0.08	–1.4 to 1.2	r = 0.84 (p<0.0001)
2012 [18] 673 pairs	0.6-26.6 Mean 3.2	0.04	–1.2 to 1.2	r2 = 0.97 (p<0.0001)

TABLE III: Study results – arterial versus central venous

Study Date [Ref] No. of pairs	Arterial lactate range and mean (mmol/L)	Mean difference Venous – Arterial (mmol/L)	95% limits of agreement (mmol/L)	Correlation r, r^2 (p-value)
1987 [10] 104 pairs	0.46-12.99 Mean 2.63	0.03	Not recorded Max absolute difference 0.82	r = 0.998 (p <0.0001)
1994 [12] 21 pairs	0.92-11.1 Mean 2.97	0.02	–0.2 to 0.24	r = 0.995

TABLE IV: Study results arterial versus mixed venous

used to determine arterial and venous lactate concentration, but in eight of ten studies published since 2000, blood gas analyzers, often sited at the point of care (ICU or ED), were used.

Comparing arterial and venous lactate concentration – study results

There is in general a commonality among these studies in the way the primary data (paired arterial and venous lactate concentrations) are statistically manipulated and presented. In all but three studies, overall correlation between arterial and venous values is determined with generation of Pearson's correlation coefficient (r or r^2) for the data set.

The authors of three studies [15, 19, 24] provide a derived regression equation that allows calculation of arterial lactate concentration from measured venous lactate concentration.

In common with correlation analysis, nearly all studies employ Bland-Altman analysis to determine agreement between arterial and venous values. This allows generation of mean difference (bias) between venous and arterial values and 95% limits of agreement (LOA), which defines the precision of the bias.

Results of studies comparing arterial and peripheral venous lactate are provided in Table II. Results of studies comparing arterial and central venous lactate are provided in Table III; and finally results of studies comparing arterial and mixed venous lactate are provided in Table IV.

It is apparent from these tables that venous blood lactate concentration correlates very strongly with arterial lactate concentration. The results of three early studies [10-12] suggest near-perfect correlation (r ≥0.99) with almost all other studies reporting correlation coefficients in the range of 0.84-0.98.

All studies reveal a bias, with venous blood lactate tending to be higher than arterial blood lactate. The magnitude of this bias, however, varies significantly between studies, with mean difference (venous lactate – arterial lactate) ranging from 0.02 mmol/L in one study [12] to 1.06 mmol/L in another [20]. Likewise, the 95% limits of agreement (LOA) vary across studies.

The best agreement in terms of 95% LOA is –0.22 to 0.24 [12] and the worst, –2.33 to 3.66 [24]. The results of this last study [24] imply that in 95% of cases arterial lactate could be anywhere between 2.33 mmol/L less than venous lactate value and 3.66 mmol/L greater than that venous value; clearly very poor agreement.

Comparing the bias and 95% LOA results for all studies suggest that agreement between arterial lactate and venous depends crucially on the site of venous blood sampling. Peripheral venous lactate agreement appears not as good as that for central venous lactate or mixed venous lactate.

And there is limited evidence from two early, relatively small studies [10, 12] that mixed venous blood lactate reflects arterial blood lactate better than either peripheral or central venous blood lactate. This empirical evidence of very close agreement between mixed venous lactate and arterial lactate is not surprising since arterial blood is derived directly from mixed venous blood.

Indeed, one of the studies [12] that confirms the closeness of this agreement was conceived and designed over 20 years ago in order to justify the use of arterial blood for lactate measurement in lieu of what the authors considered to be the ideal reference sample, mixed venous blood.

Variable agreement between peripheral venous and arterial lactate

There is evidence from a number of studies [13, 17, 20, 23, 24] that agreement between peripheral venous and arterial lactate is satisfactory at normal lactate concentration, but declines as lactate concentration increases.

Nascente *et al* [17] investigated the relationship between peripheral venous lactate and arterial lactate in a cohort of 10 healthy individuals with normal lactate and found excellent correlation (r = 0.90) and very close agreement (mean bias 0.07 mmol/L, 95% LOA –0.3 to +0.2).

This close agreement between peripheral venous and arterial lactate is not evident in study patients, particularly if the study cohort includes a high proportion of patients with abnormal lactate. The study [20] returning the largest bias and the second broadest LOA is unique in that the patient population studied all had a raised lactate (venous lactate >2.0 mmol/L).

Younger *et al* [13] acknowledge that results of their study of 48 patients of whom only 16 had a raised lactate show "greater spread (less agreement) at higher lactate concentration".

Samaraweera *et al* [23] found close agreement between venous (presumed peripheral) and arterial for those samples with lactate <2.0 mmol/L, but poor agreement above this concentration.

Theerawith *et al* [24] found that excluding data for 20 patients with highest lactate (>4.0 mmol/L) had the effect of reducing mean bias from 0.66 to 0.38, and reducing 95% LOA from (–2.33 to 3.66) to (–1.19 to 1.95).

Central venous lactate superior to peripheral venous lactate

The poor agreement between peripheral venous lactate and arterial lactate at higher lactate concentration has prompted the authors of a number of recent studies [14, 17, 20, 23, 24] to advise caution in the routine substitution of peripheral venous blood lactate for arterial blood lactate.

To summarize this cautionary view: peripheral venous blood lactate concentration cannot be assumed to be clinically indistinguishable from arterial blood lactate concentration, unless it is normal or only marginally increased (<2.0 mmol/L).

By contrast authors of all studies comparing central venous lactate and arterial lactate [10, 16, 17, 18] have no reservations in stating that central venous lactate and arterial lactate agree sufficiently well, irrespective of lactate concentration, for them to be considered interchangeable for all practical purposes.

The study by Nascente *et al* [17] of 32 ICU patients with severe sepsis/septic shock is unique in comparing agreement of arterial lactate with venous blood from both a peripheral and central venous site in the same patient. Their data, derived from 238 samples, reveals better correlation, smaller bias, and narrower 95% LOA for central venous compared with that for peripheral venous site samples.

They demonstrate that in terms of clinical management central venous lactate is more concordant with arterial lactate than peripheral venous lactate. They conclude that *"in septic patients central venous lactate may replace arterial lactate [...] the same cannot be said of peripheral venous lactate because despite reasonable correlation with arterial lactate, it tends to overestimate arterial lactate, which may lead to unnecessary therapeutic interventions for such patients"*.

Samaraweera *et al* [23] suggest that if peripheral venous blood lactate is >2.0 mmol/L, then arterial blood should be sampled to confirm the result.

Although retrospective in design, the study by Reminiac *et al* [19] provides the most compelling evidence of the notion that central venous lactate and arterial lactate are interchangeable. Their study is one of the largest in terms of patients studied and by far the largest in terms of the number of paired (venous and arterial) samples for lactate measurement.

The studied population comprises a very high proportion with abnormal lactate, across a wide concentration range. Their analysis clearly indicates that irrespective of the lactate concentration, central venous lactate is sufficiently close to arterial lactate for the two values to be considered clinically interchangeable.

Summary

Arterial blood is considered the "gold standard" sample for lactate measurement. For a number of reasons venous blood is a more attractive sample. Justification for current routine use of venous blood at some institutions is based on a few studies conducted over 20 years ago that revealed excellent correlation between arterial and venous lactate concentration.

Recent study conducted in the past 5 years has confirmed this good correlation, but revealed that the site of venous blood sampling is an important factor in the extent to which venous lactate and arterial lactate concentration agree. If venous blood is sampled from a central vein or pulmonary artery, venous lactate concentration can be considered a clinically acceptable approximation of arterial lactate concentration.

A more nuanced view is indicated if venous blood is sampled from a peripheral vein. Under these circumstances, evidence suggests that venous blood lactate concentration is probably a clinically acceptable approximation of arterial blood lactate concentration if lactate is normal or marginally increased (<2.0 mmol/L), but may not be if lactate concentration is increased above this level.

Caution is advised in making the assumption that peripheral venous lactate concentration is the same as arterial lactate concentration, particularly among patients with markedly increased lactate.

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