

Beyond Lactate: Is There a Role for Serum Lactate Measurement in Diagnosing Acute Mesenteric Ischemia?

Ihsan Ekin Demir Güralp O. Ceyhan Helmut Friess

Department of Surgery, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany

Key Words

Lactate, serum · Acute mesenteric ischemia · Serum markers · D-lactate · L-lactate

Abstract

Background/Aims: Measurement of serum lactate remains the most frequently applied laboratory investigation to diagnose acute mesenteric (intestinal) ischemia. The present review aims at critically questioning the widespread measurement of serum lactate to diagnose acute mesenteric ischemia in clinical practice and at drawing attention to more novel markers of intestinal ischemia. **Methods:** An electronic search of multiple databases was performed with the key words 'lactate', 'marker', 'mesenteric', 'intestinal' and 'ischemia' to detect all relevant studies. Additionally, the references of published articles were also reviewed. **Results:** Serum lactate is an unspecific marker of tissue hypoperfusion and undergoes significant elevation only after advanced mesenteric damage. While L-lactate is the routinely measured stereoisomer of lactate, the other stereoisomer, D-lactate, has been shown to bear a somewhat higher specificity, which is still not comparable to the extremely specific nature of ischemia markers from other organs (e.g. cardiac

ischemia). Larger studies are currently lacking to reliably advocate the routine clinical usage of novel markers like mucosal damage markers such as intestinal fatty acid-binding protein. **Conclusion:** Based on current evidence, the level of no single serum marker, including serum lactate, is elevated early and specifically enough in the serum to diagnose acute mesenteric ischemia.

Copyright © 2012 S. Karger AG, Basel

Introduction

Diagnosing acute mesenteric ischemia is notoriously difficult. The lack of specific symptoms in its early phase and its detrimental course (i.e. bowel infarction) in the case of missed or late diagnosis necessitate a diagnostic marker of early disease stage [1, 2]. Like any other diagnostic marker in clinical medicine, such a tool should bear a high sensitivity and specificity. As diagnostic imaging, including duplex ultrasonography and computer tomographic angiography, is not sensitive enough for small (distal) vascular occlusions, clinicians have long sought to identify a serum biochemical marker fulfilling these criteria [3]. Consequently, research on identi-

fyng such a marker has been undertaken both at experimental and clinical levels and has contributed to the emergence of several markers with the potential of indicating acute mesenteric ischemia [3]. Classically, leukocytosis, increased serum amylase and metabolic acidosis as evidenced by decreased base excess are common on the biochemical profile [1, 2]. However, traditionally, the serum marker which clinicians frequently rely on is serum lactate [4]. Still, the discrepancy between the common usage of serum lactate and the certainty of diagnosing acute mesenteric ischemia is extremely wide. The ideal marker for acute mesenteric ischemia should therefore not only have a higher sensitivity and specificity, but – most importantly – also enable earlier diagnosis [3]. Despite the emergence of novel and more promising markers, their validation in larger cohorts is eagerly awaited, and there is ongoing usage of serum lactate in modern clinical practice with the intention to diagnose acute mesenteric ischemia. The present review aims at critically questioning the widespread usage of serum lactate to diagnose acute mesenteric ischemia in clinical practice and to draw attention to potentially better markers which have recently been demonstrated to be somewhat superior to serum lactate in diagnosing this lethal condition.

Questioning the Rationale behind Measuring Serum Lactate: Hyperlactatemia Is Not an Exclusive Indicator of Tissue (Gut) Hypoperfusion

Central to the pathophysiology of acute mesenteric ischemia is the reduction in mesenteric blood flow [5]. As a result of such a hypoperfusion, the necrotic cells in the gut wall are assumed to release substances that can be subjected to biochemical detection analysis. Hence, measuring serum lactate as a diagnostic tool in acute mesenteric ischemia is derived from the common assumption that increased serum lactate indicates tissue hypoperfusion [3]. At this point, it has to be critically underlined that this assumption does not take other potential causes of increased serum lactate into account.

Revision of lactate metabolism provides insight into what factors may lead to increased serum lactate beyond tissue hypoperfusion. Normally, cells derive their energy from either aerobic or anaerobic metabolism of pyruvate, which is generated during glycolysis [6]. In the case of oxygen deficiency and thus impaired oxygen-dependent (aerobic) metabolism, cells can also derive adenosine triphosphate (ATP) from the anaerobic conversion of pyru-

vate into lactate and water by lactate dehydrogenase (LDH). Lactate from peripheral tissues can then be converted (utilized) into pyruvate and glucose in the liver (to a lesser extent in the kidneys) during the Cori cycle (fig. 1) [6–8]. Looking at this normal metabolism of lactate, the two main reasons for increased serum lactate are (1) increased lactate release from cells (e.g. enhanced glycolysis) or (2) decreased lactate utilization in the liver [7–10]. It should be noted that there is no net release of H⁺ ions in this process (since LDH binds H⁺ ions during pyruvate conversion into lactate) and thus no active generation of acidosis [6, 11]. These ions are derived from hydrolysis of ATP during energy consumption of cells and are reutilized by mitochondrial ATP synthase during oxidative phosphorylation [11]. However, as anaerobic lactate generation does not utilize H⁺ ions, these are increasingly left in the cell. Hence, for an additional acidosis to occur, an increase in serum lactate is not sufficient by itself; there should be an accompanying decrease in the oxidative metabolism in the mitochondria [6, 11]. Therefore, increased serum lactate is first of all not always accompanied by a lactic ‘acidosis’ and does not equal an acidotic state [6–8]. Looking at the normal lactate metabolism, increased serum lactate may thus also be encountered in states of adequate tissue perfusion or proper tissue oxygenation (nonhypoxic conditions), e.g. during impaired liver or kidney function (as may be seen in sepsis and shock), due to agents that can uncouple oxidative phosphorylation (e.g. toxins, drugs) or some underlying disorders that may alter lactate metabolism (congenital mitochondrial disorders, diabetes, malignancies) [7, 8]. Therefore, proper understanding of lactate metabolism would easily help us understand that measurement of serum lactate alone is unlikely to be of sufficient diagnostic specificity in acute mesenteric ischemia.

Emergence of Serum Lactate Measurement in Diagnosing Acute Mesenteric Ischemia: A Historical Perspective

So why has lactate long been considered to be a serum diagnostic marker of acute mesenteric ischemia? Increased serum lactate levels were initially reported by studies on intestinal vascular occlusion during surgical interventions involving reconstruction of aortic or intestinal vessels. It is noteworthy that from the end of the 1980s to the mid-1990s, measurement of serum lactate was shown to be beneficial in diagnosing acute mesenteric ischemia in some European case series, though each

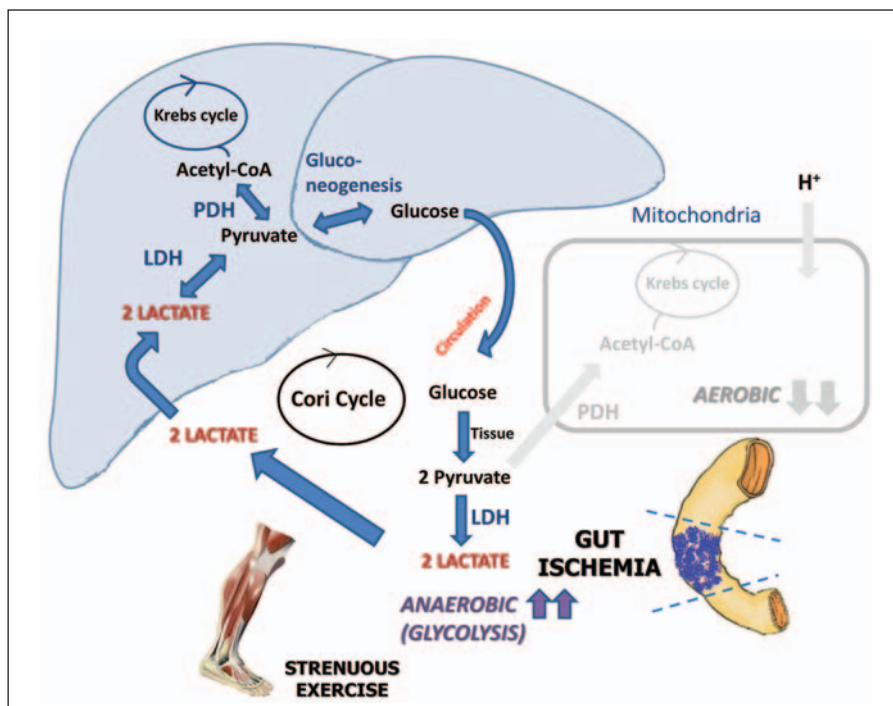


Fig. 1. Overview of lactate metabolism. Lactate is the end product of anaerobic glycolysis and is converted from pyruvate by lactate dehydrogenase (LDH). Upon its release from peripheral tissues, it arrives in the liver and undergoes LDH-mediated conversion to pyruvate, which can then be recruited for gluconeogenesis or oxidative phosphorylation in the liver, the latter being catalyzed by pyruvate dehydrogenase (PDH). Hence, in the case of strenuous exercise, it serves as a fuel during such periods of increased anaerobic metabolism. Moreover, serum lactate does not cause acidosis per se. Rather, an acidotic state results from the diminished recruitment of H^+ ions into the mitochondria during states of suppressed oxidative phosphorylation (e.g. hypoxia). An anaerobic

metabolism is also assumed to take place in the ischemic gut during acute mesenteric ischemia, which would result in increased lactate release from the gut into the portal vein. However, for the serum lactate in the general circulation to be elevated, the amount of released lactate from the ischemic gut must exceed the conversion capacity of the liver. Therefore, increased serum lactate is rather a marker of anaerobic metabolism and can undergo elevation during hepatic failure but also other nonhypoxic states which affect lactate conversion rates, such as diabetes, malignancies or congenital disorders of lactate metabolism. Acetyl-CoA = Acetyl coenzyme A.

time in very small cohorts subject to selection bias [4, 12–17]. Among the earliest case series reporting elevated serum lactate, the study by Janda et al. [18] demonstrated tenfold increased serum lactate levels among patients who developed postoperative occlusion of intestinal arteries as opposed to uncomplicated cases. Furthermore, among patients with acute abdomen and intestinal vascular occlusion, there was a 7-fold increase in serum lactate as opposed to patients without intestinal ischemia [18]. This seemingly specific increase in serum lactate in acute mesenteric ischemia was also advocated by Nutz and Sommer [19], who noted that the rationale for measuring serum lactate is the high demand of the intestine for blood and oxygen and thus its high ischemic vulnerability. They postulated that in the presence of ischemia, intestinal cells would depend on anaerobic metabolism,

resulting in acidosis and a serum lactic acid increase (lactacidemia) even before necrosis of the tissue [19]. While this idea was repeatedly supported by additional clinical studies [20, 21], these studies did not include specific remarks on the potential time delay between the onset of ischemia and time of diagnosis.

However, these initial reports which ascribed elevated serum lactate an important role in diagnosing acute mesenteric ischemia were soon followed by a US study comparing mucosal versus seromuscular enzymes of the gut wall during acute mesenteric ischemia. There, all of the studied enzymes were found to be of no value for early diagnosis of acute mesenteric ischemia regardless of their origin in the gut wall [22]. Surprisingly, seromuscular enzymes like creatine phosphokinase tended to be elevated earlier than mucosal enzymes like diamine oxidase, which

is why the authors questioned the general quest for a mucosa-specific marker of intestinal ischemia. However, the investigators also correctly noted that the value of any enzyme as a diagnostic tool depends not only on its location, but also on its quantity, mechanism of release, clearance from the serum and specificity for the intestine [22]. Even during the past 10 years, similar small-scale case series either favoring the measurement of serum lactate to diagnose acute mesenteric ischemia [23, 24] or reporting unchanged lactate levels among patients with intestinal ischemia [25, 26] continued to emerge. Overall, one can recognize that a considerable number of small case series reporting elevated serum lactate in acute mesenteric ischemia have continuously been paralleled by studies which did not confirm this observation.

Experimental Studies on Serum Lactate Levels in Acute Mesenteric Ischemia

The discrepancy of the results on the specificity and usefulness of serum lactate in diagnosing acute mesenteric ischemia can be similarly seen in several experimental studies. Nutz et al. [27] performed a study in which they cross-clamped the superior mesenteric artery in rabbits, and they noted increased serum lactate until about 40 min after revascularization of the bowel, which was absent after cross-clamping of the common femoral artery. Similar observations were made after occlusion of the superior mesenteric artery as opposed to, for example, clamping of celiac vessels [28, 29]. However, this seeming experimental specificity could not be confirmed in a study by Schlichting and Lyberg [30], who observed a similar increase in serum lactate in experimental shock and general hypoperfusion in pigs. In two similar studies on small intestinal pH and lactate production, lactate increase in the mesenteric vein was absent in sepsis-induced intestinal injury, although it was detected in ischemia-reperfusion of the bowel [31, 32]. Therefore, it became increasingly clear that serum lactate elevation may not be due to a specific ischemia of the bowel but also due to a general hypoxia or hypoperfusion.

The relevance of hepatic utilization for serum lactate levels in intestinal ischemia seems to be first considered in a decisive study by Jakob et al. [10] on the dynamics of intestinal ischemia. There, the investigators showed that intestinal hypoperfusion first results in increased lactate levels in the portal vein, which are compensated by accelerated hepatic lactate uptake and metabolization [10].

Hence, in cases of intestinal ischemia, there is an increase in the portal venous-arterial lactate gradient [10, 33]. Furthermore, several studies were able to show that a systemic lactate increase is actually a late consequence of acute mesenteric ischemia unless hypovolemia develops [10, 34, 35]. In similar studies, compromised mesenteric blood flow could not be detected by means of serum (arterial) lactate levels but rather by changes in the intramucosal carbon dioxide partial pressure [36], gastric intramucosal pH [37] and amount of intestinal luminal lactate [38–40]. Hence, numerous experimental studies also provided evidence that serum lactate is only sometimes elevated in very advanced acute mesenteric ischemia and is in general not helpful for diagnosing its early phase.

Comparison of D-Lactate and L-Lactate for Diagnosing Acute Mesenteric Ischemia

A critical observation related to the dynamics of lactate in serum goes back to the studies by Murray et al. [41, 42], who for the first time analyzed the two stereoisomers of lactate, i.e. D-lactate and L-lactate, separately to diagnose acute mesenteric ischemia. These investigators demonstrated a significant correlation between the elevation of plasma D-lactate levels and the histopathological intestinal injury scores in a rat model of acute mesenteric ischemia [41], which was confirmed by a similar model from a different group [43]. More importantly, they could additionally detect significantly higher D-lactate levels among patients with acute mesenteric ischemia when compared to controls with acute abdomen due to other causes or patients undergoing laparotomy [42].

The two lactate stereoisomers are characterized by a different biological origin. L-Lactate is produced by all cells of the human body and is a product of glycolysis, especially under compromised oxygen supply. As stated above, L-lactate is rapidly taken up and metabolized by the liver. Therefore, increased serum lactate is not necessarily of intestinal origin but may unspecifically reflect reduced tissue perfusion. Thus, L-lactate may be physiologically elevated under anaerobic glycolysis and used as a fuel for muscles, e.g. during strenuous exercise. Conversely, D-lactate solely originates from bacteria (e.g. in the gut lumen) as a normal product of bacterial fermentation. Acute mesenteric ischemia results in overgrowth of the resident bacterial flora which release D-lactate into the portal and systemic circulation. Originally, humans (and all mammals) were believed not to produce the en-

zyme for metabolizing the D-isomer, and an increase in D-lactate had been advocated as a more sensitive and specific marker of acute mesenteric ischemia [41, 42, 44], especially in cardiovascular surgery-related acute mesenteric ischemia [45–47]. However, more recently, humans have been reported to be able to metabolize D-lactate by means of a putative D-LDH [48]. Unfortunately, the medical literature does not contain sufficient examples of studies differentiating between the two stereoisomers of lactate in terms of their potential to aid in the diagnosis of acute mesenteric ischemia.

In a recent systematic review, Evennett et al. [3] performed a comparative analysis of all major serum markers of acute mesenteric ischemia. For this purpose, they screened the medical literature for all studies from which one could derive the true and false negative and positive rates of each marker for diagnosing acute mesenteric ischemia and calculated a pooled estimate of diagnostic accuracy [3]. From all investigated markers, D-lactate demonstrated the best overall performance with the highest diagnostic accuracy index. While the authors underlined the different diagnostic capacity of D-lactate versus L-lactate, the study did not show the overall performance (diagnostic odds ratio, DOR) of L-lactate versus D-lactate in a comparative manner [3]. Although the diagnostic accuracy of D-lactate was best among the studied markers, none of the DOR values of the studied markers, including D-lactate, were as high as other known serological markers of ischemia of other organs, like troponin for cardiac ischemia [3]. Looking at the calculated sensitivity, specificity and false positive and negative rates in that study, it seems that there is quite a difference between D-lactate and L-lactate in terms of diagnostic accuracy, but the reader cannot easily calculate the DOR value of L-lactate from the study on his/her own. Therefore, the medical literature still lacks comparative studies of D-lactate versus L-lactate for diagnosing acute mesenteric ischemia.

The lack of such comparative studies is paralleled by an ignorance of the specifics of lactate measurement equipment in clinical practice. Serum lactate is frequently measured by means of an arterial blood gas analyzer, e.g. in intensive care units. Normally, the lactate values provided by the measurement device do not differentiate between the two isomers, so clinicians may consider inquiring about the subtype of lactate measured by the device, i.e. L-lactate, D-lactate or total serum lactate. There is only a single study which paid attention to this detail in diagnosing potential acute mesenteric ischemia [45].

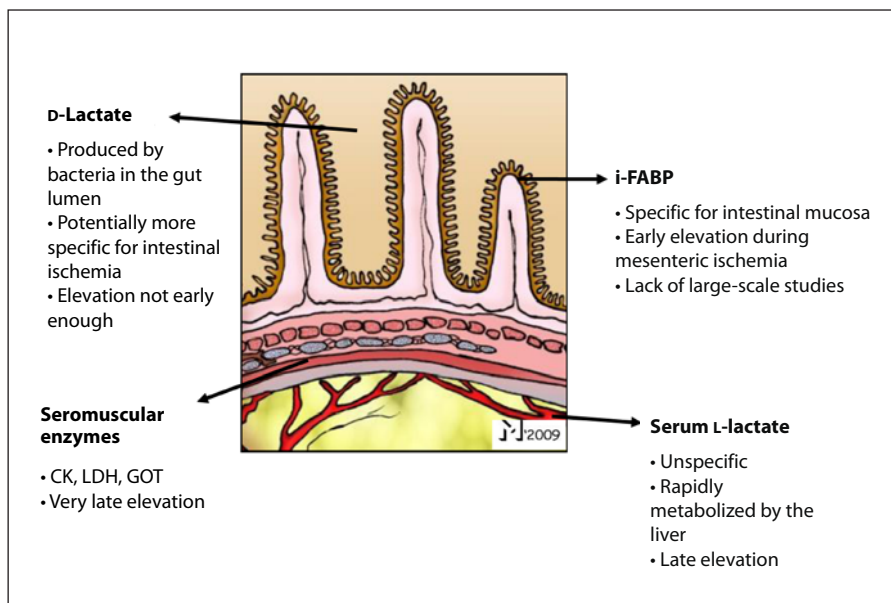
Moreover, it should be noted that, despite the potential advantages of D-lactate over L-lactate in acute mesenteric ischemia, D-lactate should also not be considered to be specific for this lethal condition. Serum D-lactate elevation has been reported to occur in patients following jejunioileal bypass operation [49, 50], in short bowel syndrome [51, 52] or in association with the intake of probiotics [53]. In a review on D-lactate-associated acidosis, Uribarri et al. [54] summarized the pathomechanistic factors involved in the development of increased serum D-lactate levels. In particular, they suggested that carbohydrate malabsorption, ingestion of large amounts of carbohydrates (glucose, starch) and the subsequent bacterial fermentation, diminished colonic motility and impaired D-lactate metabolism in humans lead to increased D-lactate levels. Therefore, current evidence does not confirm D-lactate as a specific and useful marker of acute mesenteric ischemia.

The Quest for a Better Marker of Acute Mesenteric Ischemia: Focus on Intestinal Mucosa

Due to dissatisfaction with the overall performance of serum lactate in the diagnosis of acute mesenteric ischemia, clinicians and researchers have put numerous enzymes and metabolites under the scope. Some of these markers represent classical components of the chemical serum bioprofile or blood count, including white blood cell count [55, 56], creatine kinase [57], amylase [55, 56], LDH [58, 59], alkaline phosphatase [55] and base excess [60], among others. In general, none of these markers has proven to be superior to lactate in comparative studies [3, 55, 59].

Two markers which have also been propagated as useful are glutathione-S-transferase and D-dimer. Unfortunately, neither marker is suitable for diagnosing acute mesenteric ischemia when used alone, especially due to their unspecific nature [3]. Glutathione-S-transferase can also be released from the liver under oxidative stress [56, 61], and D-dimer is elevated in any thrombotic event in the human body [62, 63]. As intestinal damage during acute mesenteric ischemia is assumed to start from the intestinal mucosa, another marker which has been favored for diagnosing acute mesenteric ischemia is intestinal fatty acid-binding protein (i-FABP), which is released into the blood stream from damaged enterocytes at the tip of intestinal villi [64]. Promisingly, numerous studies have detected significantly elevated i-FABP levels under acute mesenteric ischemia [64–73], and no major

Fig. 2. The origins and characteristics of serum markers for mesenteric ischemia. In addition to the traditional L-lactate, the currently available serological markers of mesenteric ischemia can be classified as (1) seromuscular markers, including creatine kinase (CK), LDH and glutamic oxaloacetic transaminase (GOT), (2) gut lumen-derived markers such as D-lactate or (3) mucosa-derived markers such as i-FABP. Overall, none of these markers is sufficient on its own for the diagnosis of mesenteric ischemia.



concerns have so far been pronounced in terms of its specificity for acute mesenteric ischemia. However, a denominator of studies on i-FABP is the small sample size and the absence of specific remarks on the time course of i-FABP elevation. However, this marker is currently and continuously being used to detect enterocyte damage in experimental studies [74–76], and clinical studies with larger cohorts and better temporal monitoring of i-FABP levels are likely to be very useful for the ultimate judgment of the role of i-FABP in acute mesenteric ischemia.

The origins and characteristics of the various serum markers for mesenteric ischemia are shown in figure 2.

Prospective Clinical Studies on Serum Lactate Levels and Acute Mesenteric Ischemia

Review of the current literature reveals that the number of prospective clinical studies on intestinal ischemia markers is still astonishingly quite small (for a recent systematic review, please see Evennett et al. [3]). Moreover, there is a further lack of studies which have examined serum L-lactate levels in a prospective manner in a clinical setting (table 1). In the studies by Lange and Jackel [4] and Lange and Toivola [20], in which the investigators analyzed patients with acute abdomen or abdominal complaints, serum lactate was detected to be elevated in nearly all cases of acute mesenteric ischemia,

but also in all cases of bacterial peritonitis, in half of the cases with intestinal obstruction and in around one third of the cases with acute pancreatitis. From these results, the authors concluded that despite a near-100% sensitivity, serum lactate measurement was associated with a very low specificity, often below 50%. However, the main gain in information out of the considerable number of investigated patients in these studies has been the identification of serum lactate concentration at the time of diagnosis as a predictor of mortality [21, 77]. In recent years, there has been an increase in the number of prospective studies which have simultaneously compared several serum markers for acute mesenteric ischemia (e.g. Gearhart et al. [56] and Block et al. [55]). These studies repeatedly demonstrated that none of the applied markers exhibit convincing accuracy for diagnosing acute mesenteric ischemia. Interestingly, there are no prospective studies in the literature which showed an absence of an increase in serum lactate during acute mesenteric ischemia in larger cohorts. Among the few studies in which no elevated serum lactate was measured, including the above-mentioned study by Akutsu et al. [25], Acosta et al. [26] detected normal serum lactate levels after acute superior mesenteric artery occlusion in only around half of the patients (12/27), thereby once again underlining the rather late character of the serum lactate increase in suspected acute mesenteric ischemia. Overall, considering the data from a recent systematic review and another comprehensive review [3,

Table 1. Clinical studies on the sensitivity, specificity and accuracy of L-lactate, the commonly used lactate isoform in diagnosing mesenteric ischemia

Investigators	Study design	Lactate in mesenteric ischemia	Limitations	Evaluation
Lange and Jackel 1994 [4]	prospective study patients with acute abdomen n = 85 blood sampling before operation/final diagnosis	elevated lactate in all cases of mesenteric ischemia (n = 20)	elevated lactate in: all cases of bacterial peritonitis; some cases of intestinal obstruction (10 out of 20)	very low specificity (42%) no remark on the elevation time course of lactate
Meyer et al. 1998 [17]	retrospective study patients with clinically suspected mesenteric ischemia n = 46	elevated lactate in over 90% of mesenteric ischemia cases	16 out of a total of 22 patients with mesenteric ischemia were diagnosed via clinical suspicion and angiography	elevated serum lactate does not prove mesenteric ischemia
Lange and Toivola 1997 [20]	prospective study patients with abdominal complaints n = 120	elevated lactate in 24 out of 25 patients with mesenteric ischemia	elevated lactate in: 20 out of 20 general bacterial peritonitis patients; 6 out of 20 acute pancreatitis patients	very low specificity (36%) no remark on the elevation time course of lactate
Gearhart et al. 2003 [56]	prospective study patients with clinically suspected mesenteric ischemia n = 58	elevated lactate in 24 out of 31 patients with intestinal necrosis	significant elevation not present when subanalysis performed with small bowel and colonic necrosis	78% sensitivity 53% specificity accuracy of mere 47–69% only significant in necrotic, but not ischemic bowel
Cronk et al. 2006 [65]	prospective study validation cohort of patients admitted for mechanical small bowel obstruction n = 21	comparison of serum L-lactate with i-FABP levels	elevated lactate in 1 out of 3 patients with gut necrosis false negative elevation in 5 out of 18 patients without gut necrosis	33% sensitivity 72% specificity small cohort for evaluating serum lactate in bowel necrosis
Acosta et al. 2011 [26]	retrospective study patients with acute mesenteric artery occlusion n = 55	elevated lactate and troponin I in mesenteric ischemia	elevated lactate in 12 out of 27 patients	normal lactate may not be infrequent after mesenteric artery occlusion
Akutsu et al. 2007 [25]	case report type B aortic dissection	near-normal serum lactate upon admission	single case in contradiction to another case report in which increased serum lactate was detected during type A aortic dissection	aortic dissection may not be associated with serum lactate elevation despite intraoperatively observed overt mesenteric ischemia

The common denominator of the studies listed above is the very low specificity and the late increase of serum lactate among patients with mesenteric ischemia.

78], large-scale prospective studies on the alterations of lactate during acute mesenteric ischemia are widely lacking and very much needed to conclusively determine the dynamics of serum lactate alterations in human acute mesenteric ischemia.

Conclusion

In the 21st century, acute mesenteric ischemia continues to represent a true diagnostic challenge. Despite advances in diagnostic imaging, damaged or ischemic bowel cannot be detected upon clinical imaging with high

certainty. Therefore, there is ongoing reliance upon serum markers of acute mesenteric ischemia. Since its inauguration into routine clinical practice during the 1970s, serum lactate has repeatedly been assumed to be the best marker of acute mesenteric ischemia. However, numerous clinical and experimental studies have proved that serum lactate is merely an unspecific marker of tissue hypoperfusion and does not reflect the early, deciding phase of intestinal damage.

As a result of efforts to identify better markers, D-lactate as the stereoisomer of the routinely measured L-lactate has been shown to bear a somewhat higher specificity, which is still not comparable to the extremely specific nature of ischemia markers from other organs. Therefore, currently, no single serum marker, including the traditional serum lactate, can be regarded as reliable enough to diagnose acute mesenteric ischemia. Enhanced understanding of the pathophysiology of intestinal damage has shifted the attention of researchers towards mucosal damage markers. Consequently, markers

such as i-FABP are increasingly utilized in diagnosing experimental and early clinical acute mesenteric ischemia. However, there is an urgent need to verify the efficiency and diagnostic accuracy of such novel markers in larger patient cohorts with concomitant close marker monitoring. Until the advent of sufficient evidence for these novel markers, diagnosing acute mesenteric ischemia with currently available markers like serum lactate remains a true clinical challenge. Therefore, clinicians should combine their clinical impression from patients with potential acute mesenteric ischemia together with alterations of several of the above-mentioned markers to obtain the best possible support for their suspected diagnosis.

Acknowledgement

We thank Dr. Matthias Maak for his assistance with the figures.

References

- McKinsey JF, Gewertz BL: Acute mesenteric ischemia. *Surg Clin North Am* 1997;77:307–318.
- Lock G: Acute intestinal ischaemia. *Best Pract Res Clin Gastroenterol* 2001;15:83–98.
- Evennett NJ, Petrov MS, Mittal A, Windsor JA: Systematic review and pooled estimates for the diagnostic accuracy of serological markers for intestinal ischemia. *World J Surg* 2009;33:1374–1383.
- Lange H, Jackel R: Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. *Eur J Surg* 1994;160:381–384.
- Herbert GS, Steele SR: Acute and chronic mesenteric ischemia. *Surg Clin North Am* 2007;87:1115–1134, ix.
- Mizock BA: Controversies in lactic acidosis. Implications in critically ill patients. *JAMA* 1987;258:497–501.
- Buchalter SE, Crain MR, Kreisberg R: Regulation of lactate metabolism in vivo. *Diabetes Metab Rev* 1989;5:379–391.
- Kreisberg RA: Lactate homeostasis and lactic acidosis. *Ann Intern Med* 1980;92:227–237.
- Vary TC, Drnevich D, Jurasinski C, Brennan WA Jr: Mechanisms regulating skeletal muscle glucose metabolism in sepsis. *Shock* 1995; 3:403–410.
- Jakob SM, Merasto-Minkkinen M, Tenhunen JJ, Heino A, Alhava E, Takala J: Prevention of systemic hyperlactatemia during splanchnic ischemia. *Shock* 2000;14:123–127.
- Eng C, Kiuru M, Fernandez MJ, Aaltonen LA: A role for mitochondrial enzymes in inherited neoplasia and beyond. *Nat Rev Cancer* 2003;3:193–202.
- Paes E, Vollmar JF, Hutschenreiter S, Schoenberg MH, Kubel R, Scholzel E: Mesenterial infarct. New aspects of diagnosis and therapy (in German). *Chirurg* 1988;59: 828–835.
- Lange H: Differential diagnostic significance of lactate in acute abdominal diseases (in German). *Chirurg* 1989;60:356–360.
- Chabert S, Porcheron J, Balique JG: Management of acute intestinal arterial ischemia (in French). *J Chir (Paris)* 1999;136:130–135.
- Hagmuller GW: Acute mesenteric vascular occlusion: pathophysiology, clinical stages, diagnosis (in German). *Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir* 1990:291–296.
- Bottger T, Schafer W, Weber W, Junginger T: Value of preoperative diagnosis in mesenteric vascular occlusion. A prospective study (in German). *Langenbecks Arch Chir* 1990;375: 278–282.
- Meyer T, Klein P, Schweiger H, Lang W: How can the prognosis of acute mesenteric artery ischemia be improved? Results of a retrospective analysis (in German). *Zentralbl Chir* 1998;123:230–234.
- Janda A, Hagmuller GW, Denck H: Lactate in the diagnosis of acute intestinal vascular occlusions (in German). *Chirurg* 1984;55: 469–473.
- Nutz V, Sommer HJ: Hyperlactacidemia in intestinal ischemia. I. Theoretical considerations (in German). *Langenbecks Arch Chir* 1987;370:63–68.
- Lange H, Toivola A: Warning signals in acute abdominal disorders. Lactate is the best marker of mesenteric ischemia (in Swedish). *Lakartidningen* 1997;94:1893–1896.
- Newman TS, Magnuson TH, Ahrendt SA, Smith-Meek MA, Bender JS: The changing face of mesenteric infarction. *Am Surg* 1998; 64:611–616.
- Thompson JS, Bragg LE, West WW: Serum enzyme levels during intestinal ischemia. *Ann Surg* 1990;211:369–373.
- Kurimoto Y, Morishita K, Fukada J, Kawaharada N, Komatsu K, Yama N, Asai Y, Abe T: A simple but useful method of screening for mesenteric ischemia secondary to acute aortic dissection. *Surgery* 2004;136:42–46.
- Huwer H, Winning J, Straub U, Isringhaus H, Kalweit G: Clinically diagnosed nonocclusive mesenteric ischemia after cardiopulmonary bypass: retrospective study. *Vascular* 2004;12:114–120.
- Akutsu K, Matsuda H, Sasaki H, Minatoya K, Ogino H, Kasai S, Tamori Y, Yokoyama N, Nonogi H, Takeshita S: A case of acute type B aortic dissection: limited role of laboratory testing for the diagnosis of mesenteric ischemia. *Ann Thorac Cardiovasc Surg* 2007;13: 360–364.

- 26 Acosta S, Block T, Bjornsson S, Resch T, Bjorck M, Nilsson T: Diagnostic pitfalls at admission in patients with acute superior mesenteric artery occlusion. *J Emerg Med* 2011, E-pub ahead of print.
- 27 Nutz V, Sommer JH, Schultze-Petzold J: Hyperlactacidemia in intestinal ischemia. II. Experimental principles (in German). *Langenbecks Arch Chir* 1987;370:69–78.
- 28 Murthy S, Hui-Qi Q, Sakai T, Depace DE, Fondacaro JD: Ischemia/reperfusion injury in the rat colon. *Inflammation* 1997;21:173–190.
- 29 Rendig SV, Chahal PS, Longhurst JC: Cardiovascular reflex responses to ischemia during occlusion of celiac and/or superior mesenteric arteries. *Am J Physiol* 1997; 272:H791–H796.
- 30 Schlichting E, Lyberg T: Monitoring of tissue oxygenation in shock: an experimental study in pigs. *Crit Care Med* 1995;23:1703–1710.
- 31 Ljungdahl M, Rasmussen I, Raab Y, Hillered L, Haglund U: Small intestinal mucosal pH and lactate production during experimental ischemia-reperfusion and fecal peritonitis in pigs. *Shock* 1997;7:131–138.
- 32 Rasmussen I, Haglund U: Early gut ischemia in experimental fecal peritonitis. *Circ Shock* 1992;38:22–28.
- 33 Heino A, Hartikainen J, Merasto ME, Alhava E, Takala J: Systemic and regional pCO₂ gradients as markers of intestinal ischaemia. *Intensive Care Med* 1998;24:599–604.
- 34 Acosta S, Nilsson TK, Malina J, Malina M: L-lactate after embolization of the superior mesenteric artery. *J Surg Res* 2007;143:320–328.
- 35 Kurimoto Y, Kawaharada N, Ito T, Morikawa M, Higami T, Asai Y: An experimental evaluation of the lactate concentration following mesenteric ischemia. *Surg Today* 2008;38: 926–930.
- 36 Knichwitz G, Rotker J, Mollhoff T, Richter KD, Brussel T: Continuous intramucosal PCO₂ measurement allows the early detection of intestinal malperfusion. *Crit Care Med* 1998;26:1550–1557.
- 37 Ruettimann U, Urwyler A, Von Flue M, Reinhardt D, Pargger H: Gastric intramucosal pH as a monitor of gut perfusion after thrombosis of the superior mesenteric vein. *Acta Anaesthesiol Scand* 1999;43:780–783.
- 38 Tenhunen JJ, Kosunen H, Alhava E, Tuomisto L, Takala JA: Intestinal luminal microdialysis: a new approach to assess gut mucosal ischemia. *Anesthesiology* 1999;91:1807–1815.
- 39 Tenhunen JJ, Jakob SM, Takala JA: Gut luminal lactate release during gradual intestinal ischemia. *Intensive Care Med* 2001;27:1916–1922.
- 40 Solligard E, Juel IS, Spigset O, Romundstad P, Gronbech JE, Aadahl P: Gut luminal lactate measured by microdialysis mirrors permeability of the intestinal mucosa after ischemia. *Shock* 2008;29:245–251.
- 41 Murray MJ, Barbose JJ, Cobb CF: Serum D(-)-lactate levels as a predictor of acute intestinal ischemia in a rat model. *J Surg Res* 1993;54:507–509.
- 42 Murray MJ, Gonze MD, Nowak LR, Cobb CF: Serum D(-)-lactate levels as an aid to diagnosing acute intestinal ischemia. *Am J Surg* 1994;167:575–578.
- 43 Sun XQ, Fu XB, Zhang R, Lu Y, Deng Q, Jiang XG, Sheng XY: Relationship between plasma D(-)-lactate and intestinal damage after severe injuries in rats. *World J Gastroenterol* 2001;7:555–558.
- 44 Gunel E, Caglayan O, Caglayan F: Serum D-lactate levels as a predictor of intestinal ischemia-reperfusion injury. *Pediatr Surg Int* 1998;14:59–61.
- 45 Muraki S, Fukada J, Morishita K, Kawaharada N, Abe T: Acute type A aortic dissection with intestinal ischemia predicted by serum lactate elevation. *Ann Thorac Cardiovasc Surg* 2003;9:79–80.
- 46 Poeze M, Froom AH, Greve JW, Ramsay G: D-lactate as an early marker of intestinal ischaemia after ruptured abdominal aortic aneurysm repair. *Br J Surg* 1998;85:1221–1224.
- 47 Assadian A, Assadian O, Senekowitsch C, Rotter R, Bahrami S, Furst W, Jaksch W, Hagemuller GW, Hubl W: Plasma D-lactate as a potential early marker for colon ischaemia after open aortic reconstruction. *Eur J Vasc Endovasc Surg* 2006;31:470–474.
- 48 Ewaschuk JB, Naylor JM, Zello GA: D-lactate in human and ruminant metabolism. *J Nutr* 2005;135:1619–1625.
- 49 Narula RK, El Shafei A, Ramaiah D, Schmitz PG: D-lactic acidosis 23 years after jejunoileal bypass. *Am J Kidney Dis* 2000;36:E9.
- 50 Kadakia SC: D-lactic acidosis in a patient with jejunoileal bypass. *J Clin Gastroenterol* 1995;20:154–156.
- 51 Forsyth RJ, Moulden A, Hull D: D-Lactate associated encephalopathy in short bowel syndrome: management with long-term non-absorbable oral antimicrobials. *Clin Nutr* 1991;10:352–355.
- 52 Zhang DL, Jiang ZW, Jiang J, Cao B, Li JS: D-lactic acidosis secondary to short bowel syndrome. *Postgrad Med J* 2003;79:110–112.
- 53 Mack DR: D(-)-lactic acid-producing probiotics, D(-)-lactic acidosis and infants. *Can J Gastroenterol* 2004;18:671–675.
- 54 Uribarri J, Oh MS, Carroll HJ: D-lactic acidosis. A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. *Medicine (Baltimore)* 1998;77: 73–82.
- 55 Block T, Nilsson TK, Bjorck M, Acosta S: Diagnostic accuracy of plasma biomarkers for intestinal ischaemia. *Scand J Clin Lab Invest* 2008;68:242–248.
- 56 Gearhart SL, Delaney CP, Senagore AJ, Banbury MK, Remzi FH, Kiran RP, Fazio VW: Prospective assessment of the predictive value of alpha-glutathione S-transferase for intestinal ischemia. *Am Surg* 2003;69:324–329, discussion 329.
- 57 Fried MW, Murthy UK, Hassig SR, Woo J, Oates RP: Creatine kinase isoenzymes in the diagnosis of intestinal infarction. *Dig Dis Sci* 1991;36:1589–1593.
- 58 Graeber GM, Clagett GP, Wolf RE, Cafferty PJ, Harmon JW, Rich NM: Alterations in serum creatine kinase and lactate dehydrogenase. Association with abdominal aortic surgery, myocardial infarction and bowel necrosis. *Chest* 1990;97:521–527.
- 59 Roth M, Jaquet PY, Rohner A: Increase of creatine kinase and lactate dehydrogenase in the serum of rats submitted to experimental intestinal infarction. *Clin Chim Acta* 1989; 183:65–69.
- 60 Delaney CP, O'Neill S, Manning F, Fitzpatrick JM, Gorey TF: Plasma concentrations of glutathione S-transferase isoenzyme are raised in patients with intestinal ischaemia. *Br J Surg* 1999;86:1349–1353.
- 61 Khurana S, Corbally MT, Manning F, Armeise T, Kierce B, Kilty C: Glutathione S-transferase: a potential new marker of intestinal ischemia. *J Pediatr Surg* 2002;37:1543–1548.
- 62 Kulacoglu H, Kocaerkek Z, Moran M, Kulah B, Atay C, Kulacoglu S, Ozmen M, Coskun F: Diagnostic value of blood D-dimer level in acute mesenteric ischaemia in the rat: an experimental study. *Asian J Surg* 2005;28:131–135.
- 63 Acosta S, Nilsson TK, Bjorck M: Preliminary study of D-dimer as a possible marker of acute bowel ischaemia. *Br J Surg* 2001;88: 385–388.
- 64 Kanda T, Nakatomi Y, Ishikawa H, Hitomi M, Matsubara Y, Ono T, Muto T: Intestinal fatty acid-binding protein as a sensitive marker of intestinal ischemia. *Dig Dis Sci* 1992;37:1362–1367.
- 65 Cronk DR, Houseworth TP, Cuadrado DG, Herbert GS, McNutt PM, Azarow KS: Intestinal fatty acid binding protein (I-FABP) for the detection of strangulated mechanical small bowel obstruction. *Curr Surg* 2006;63: 322–325.
- 66 Niewold TA, Meinen M, van der Meulen J: Plasma intestinal fatty acid binding protein (I-FABP) concentrations increase following intestinal ischemia in pigs. *Res Vet Sci* 2004; 77:89–91.
- 67 Holmes JHt, Lieberman JM, Probert CB, Marks WH, Hill ME, Paull DL, Guyton SW, Sacchetti J, Hall RA: Elevated intestinal fatty acid binding protein and gastrointestinal complications following cardiopulmonary bypass: a preliminary analysis. *J Surg Res* 2001;100:192–196.

- 68 Sonnino R, Ereso G, Arcuni J, Franson R: Human intestinal fatty acid binding protein in peritoneal fluid is a marker of intestinal ischemia. *Transplant Proc* 2000;32:1280.
- 69 Lieberman JM, Sacchetti J, Marks C, Marks WH: Human intestinal fatty acid binding protein: report of an assay with studies in normal volunteers and intestinal ischemia. *Surgery* 1997;121:335–342.
- 70 Kanda T, Fujii H, Tani T, Murakami H, Suda T, Sakai Y, Ono T, Hatakeyama K: Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. *Gastroenterology* 1996;110:339–343.
- 71 Kanda T, Fujii H, Fujita M, Sakai Y, Ono T, Hatakeyama K: Intestinal fatty acid binding protein is available for diagnosis of intestinal ischaemia: immunochemical analysis of two patients with ischaemic intestinal diseases. *Gut* 1995;36:788–791.
- 72 Gollin G, Marks C, Marks WH: Intestinal fatty acid binding protein in serum and urine reflects early ischemic injury to the small bowel. *Surgery* 1993;113:545–551.
- 73 Gollin G, Marks WH: Elevation of circulating intestinal fatty acid binding protein in a luminal contents-initiated model of NEC. *J Pediatr Surg* 1993;28:367–370, discussion 370–371.
- 74 Derikx JP, Matthijsen RA, de Bruine AP, van Bijnen AA, Heineman E, van Dam RM, Dejong CJ, Buurman WA: Rapid reversal of human intestinal ischemia-reperfusion induced damage by shedding of injured enterocytes and reepithelialisation. *PLoS One* 2008;3:e3428.
- 75 Hietbrink F, Besselink MG, Renooij W, de Smet MB, Draisma A, van der Hoeven H, Pickkers P: Systemic inflammation increases intestinal permeability during experimental human endotoxemia. *Shock* 2009;32:374–378.
- 76 Mensink PB, Hol L, Borghuis-Koertshuis N, Geelkerken RH, Huisman AB, Doelman CJ, van Vuuren AJ, Kuipers EJ, Kolkman JJ: Transient postprandial ischemia is associated with increased intestinal fatty acid binding protein in patients with chronic gastrointestinal ischemia. *Eur J Gastroenterol Hepatol* 2009;21:278–282.
- 77 Ritz JP, Germer CT, Buhr HJ: Prognostic factors for mesenteric infarction: multivariate analysis of 187 patients with regard to patient age. *Ann Vasc Surg* 2005;19:328–334.
- 78 Acosta S, Nilsson T: Current status on plasma biomarkers for acute mesenteric ischemia. *J Thromb Thrombolysis* 2011;33:355–361.