Dig Dis Sci (2006) 51:2400–2403
DOI 10.1007/s10620-006-9334-7

ORIGINAL PAPER

The Relationship Between Intestinal Hypoperfusion and Serum D-Lactate Levels During Experimental Intra-Abdominal Hypertension

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Received: 29 January 2006 / Accepted: 22 March 2006 / Published online: 1 November 2006

Abstract Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) may result from several clinic situations and carries high morbidity and mortality risk, particularly in intensive care unit patients. The clinical spectrum changes from splanchnic hypoperfusion and intestinal ischemia to multiple organ failure. Previous studies demonstrated that serum D-lactate levels may be an early indicator in intestinal ischemia. This study aimed to investigate the relationship between intestinal ischemia and serum D-lactate levels during experimental IAH. Thirty-two male Wistar Albino rats weighing 250 ± 50 g were divided into four groups. Three different intra-abdominal pressure (IAP) levels supplied by placement of an intraperitoneal Peritofix catheter and iso-osmotic polyethylene glycol infusion. Each of the IAP levels (15, 20, and 25 mm Hg groups) was checked with the monitor system and fixed for an hour. Control-group animals were not subjected to increased IAP. One hour later, 5-ml blood samples were taken for measurement of serum D-lactate levels and 2-cm intestinal tissue samples were taken 5 cm proximal to the ileocecal valve for histopathologic examination. Elevated serum D-lactate levels were recorded in animals with higher IAP levels.There was a positive correlation between serum D-lactate levels and IAP levels. Histological examinations of the intestinal tissue samples showed no significant pathologic changes in concordance with intestinal ischemia. Serum D-lactate levels may be an early indicator for increased IAP pressure before intestinal ischemic changes occur.

Keywords D-Lactate · Intestinal hypoperfusion · Intra-abdominal pressure · Abdominal compartment syndrome

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Introduction

The abdominal cavity has a limited capacity for enlargement. Many clinical situations may cause acute elevations in intra-abdominal pressure (IAP), termed intra-abdominal hypertenion (IAH). Sustained and uncontrolled IAH adversely affects organ functions. Organ dysfunction due to IAH has been defined as abdominal compartment syndrome (ACS). ACS is a late and serious complication of sustained IAH [1, 2].

IAH and ACS are frequently encountered entities in intensive care patients, more than expected [1–3]. Untreated IAH converts to ACS and results in multiorgan failure with high risk of morbidity and mortality [1, 2, 4]. Thus early diagnosis of IAH, before ACS occurs, is extremely important. Experimental and clinical reports indicate that splanchnic hypoperfusion and reduced intestinal mucosal blood flow are early physiopathologic alterations due to IAH [3–8]. It has also been shown that serum D-lactate levels may be an early indicator for detection of intestinal ischemia [9–12].

The purpose of this study was to investigate the relationship between serum D-lactate levels and increased IAP levels.

Materials and methods

Experimental design

The local ethics committee of Ankara Numune Teaching and Research Hospital approved the study protocol. Thirty-two male Wistar albino rats weighing 250 ± 50 g were randomly divided into four groups. The rats were allowed free access to normal food and water before experimentation. The animals were anesthetized with an intramuscular injection of ketamine hydrochloride (50 mg/kg; Ketalar) and xylazine hydrochloride (5 mg/kg; Rompun). Abdominal skin was shaved. It was cleaned with povidone iodine solution.

A 1-cm midline incision was performed and a Peritofix catheter (B/Braun, Melsungen AG, Germany) was placed intraperitoneally for infusion of a polyethylene glycol (PEG) solution in all animals except those in the control group. Iso-osmotic PEG solution was infused into the abdominal cavity via a three-way stopcock. The intra-abdominal pressure (IAP) was measured continuously with this catheter connected to a pressure transducer from a monitor system (Petaş, KMA 275, Turkey).

Group 1 served as the controls; animals were not subjected to increased IAP. The IAP was recorded continuously until it reached a level of 15 mm Hg in Group II ($n = 8$), 20 mm Hg in Group III ($n = 8$), and 25 mm Hg in Group IV ($n = 8$) animals. The IAP was maintained for 60 min using monitoring, and additional PEG infusion was applied when needed. One hour later, relaparotomy was done in all groups and 2-cm intestinal tissue specimens were taken 5 cm proximal to the ileocecal valve for histological examinations. Then 5-ml blood samples were taken in heparinized syringes for serum D-lactate levels.

Measurement of serum D-Lactate levels

Sera were separated from 5 ml of heparinized blood (20 IU/ml) by centrifugation at 3200 rpm for 10 min and stored at –70°C before measurements. We used a UV-spectrophotometric method for measurement of D-lactate levels. All reagents were purchased from Roche (R-Biopharm Catalog No. 11 112 821 035; Mannheim, Germany). We used a Shimadzu 1201 UV-visible spectrophotometer (Shimadzu, Kyoto, Japan). Results are presented as millimolar concentration [13].

Histological evaluation

Small bowel segments were placed in 10% formaldehyde and stained with hematoxylin-eosin. They were evaluated according to Park-Chiu classification [14].

Statistical analyses

All data were recorded using SPSS 11.00 for Windows for statistical analyses. Statistical comparisons were performed using the Tukey post hoc test. P values <0.05 were considered significant.

Results

Mean serum D-lactate levels and ranges in all groups are detailed in Table 1 (see also Fig. 1). Serum D-lactate levels were significantly elevated in groups with 25 mm Hg IAP compared with the other groups. Mean serum D-lactate levels were also relatively high in groups with 15 mm Hg IAP and in groups with 20 mm Hg IAP (0.43 and 0.46 mM, respectively) compared with the control group. These elevations were not statistically significant. The degrees of statistical significance of the elevated serum D-lactate levels according to group are shown in Table 2.

Histopathologic evaluation of the intestinal tissue samples revealed no ischemic changes in elevated-IAP groups. Decreased intestinal wall thickness was a unique histopathologic alteration, noted only in groups with 25 mm Hg IAP.

Discussion

Elevated IAP or IAH is a frequently encountered problem in critically ill patients and carries a high risk of morbidity and mortality [15]. There has been an exponential increase in investigations focused on increased IAP and subsequent adverse effects such as ACS [16]. There is still controversy about the exact level of IAP at which ACS occurs [1, 17]. Increased IAP and ACS are not synonymous. Although ACS is a late and highly lethal complication of increased IAP but not an inevitable result of IAH [12, 18]. Thus a clinician should be aware of the physiopathological implications of IAH and ACS in patients at risk for increased IAP. Acute ACS is increasingly recognized as a cause for multiorgan dysfunction. Early detection and timely prevention of IAH are extremely important and require suspicion. Of course

Table 1 Serum D-lactate levels of the groups

Group	Mean D-lactate level (mM)	D-Lactate (min–max mM)
Control	0.25	0.21–0.29
15 mm Hg IAP	0.43	0.40–0.46
20 mm Hg IAP	0.46	0.35–0.56
25 mm Hg IAP	0.81	0.52–1.10

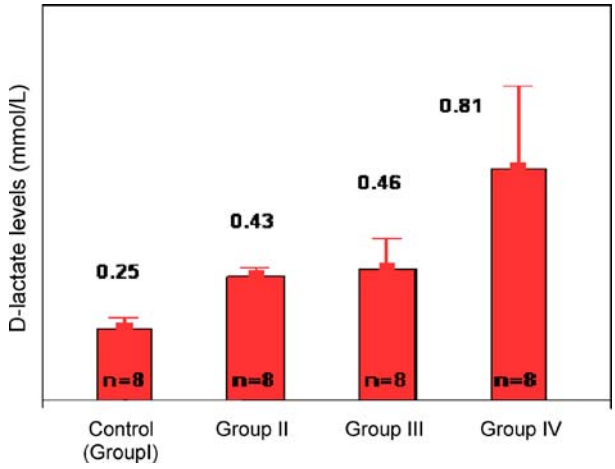

Fig. 1 Serum D-lactate levels of the study groups

the aphorism "Prevention is better than treatment" is always valid for this challenging problem [4, 19].

Physical abdominal examination is not reliable for detecting increased IAP. However, routine IAP monitoring is not acceptable for practice. A variety of ACS models and IAP measurement methods has been suggested in animal models and clinical investigations [6, 17, 18, 20–25]. The main goal of all these studies is to clarify the pathophysiologic alterations related to IAH and ACS.

PEG, Ringer's lactate, saline infusions, and carbon dioxide insufflation have been applied to increase IAP in different experimental abdominal compartment syndrome models [6, 21–23, 25]. In this study, PEG was used to increase the IAP, as it is an economical and easily applicable agent.

Various pressure levels and durations have been used in various experimental models. Bloomfield *et al*. maintained an IAP level of 25 mm Hg for 0, 30, 60, 90, and 120 min in their study [22]. Rezende-Neto *et al*. examined the physiopathologic changes related to IAH at an IAP level of 20 mm Hg for 60 and 90 min [16]. Doty *et al*. observed the effects of a 30 mm Hg IAP level for 60 min [26]. All experimental studies showed that IAP levels of $\geq$25 mm Hg resulted in decreased urine output and mesenteric blood flow, elevated interleukin-1b cytokine levels, and derangement of cardiopulmonary functions in a 1-hr period. We examined the adverse effects of IAP levels of 15, 20, and 25 mm Hg for a 1-hr period in rats. Elevated serum D-lactate levels recorded were significantly higher than those of the control group only at the 25 mm Hg IAP level in the current study.

There is no consensus about the exact IAP level that is associated with clinically significant impairment of organ function [2, 19, 27]. Although an IAP >20 mm Hg is clinically significant in most patients, even at the relatively low pressure of 10–15 mm Hg significant impairments of organ function may occur. Hunter *et al*. demonstrated a significant decrease in mesenteric arterial and mucosal blood flow at an IAP level of 20 mm Hg despite minimal changes in cardiac output [27]. It has also been shown that hepatic arterial blood flow and portal venous blood flow significantly decrease when the IAP is as low as 10 mm Hg. Barnes *et al*. showed that there was a 61% reduction in superior mesenteric blood flow at an IAP level of 40 mm Hg [6]. Diebel *et al*. demonstrated that significant reductions in intestinal mucosal blood flow and mesenteric, hepatic, and portal blood flows occurred even when cardiac output and systemic blood pressure were maintained at normal levels in a porcine model of increased IAP [6].

These studies also showed that splanchnic hypoperfusion and reduced intestinal mucosal blood flow without histopathological findings of intestinal ischemia are early adverse effects of raised IAP. Intestinal and hepatic ischemia possibly lead to multiorgan dysfunction syndrome secondary to bacterial translocation and cytokine release. Thus early determination of intestinal ischemia is very important for prevention of multiorgan dysfunction syndrome [6, 26, 28, 29]. Poeze *et al*. reported that D-lactate is a better marker of splanchnic hypoperfusion than its isomer L-lactate [12]. Murray *et al*. showed that serum D-lactate level measurements may be a useful marker of acute intestinal ischemia [12, 13]. In our study, significantly increased serum D-lactate levels were attributed to decreased intestinal mucosal blood flow. However, we found no distinct histopathologic changes except decreased intestinal wall thickness in animals with an IAP of 25 mm Hg. We believe that serum D-lactate levels may be an early marker of intestinal hypoperfusion in the presence of IAH.

Conclusion

In conclusion, there is a positive correlation between serum D-lactate levels and increased IAP levels. An IAP of 25 mm

Table 2 Statistical significance of increased serum D-lactate levels according to study group

	Controls	15 mm Hg IAP	20 mm Hg IAP	25 mm Hg IAP
Controls	—	NS[a]	NS	$P < 0.001$
15 mm Hg IAP	NS	—	NS	$P = 0.002$
20 mm Hg IAP	NS	NS	—	$P = 0.004$
25 mm Hg IAP	$P < 0.001$	$P = 0.002$	$P = 0.004$	—

[a]Nonsignificant.

Hg has significant adverse effects on splanchnic and intestinal mucosal blood flow in our experimental IAH model. We believe that significantly increased serum D-lactate levels are likely to be a useful determinant of intestinal hypoxia due to increased IAP.

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