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Effects of fluid challenge on gastric mucosal PCO_2 in septic patients

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Abstract *Objective:* To determine the effects of fluid challenge on systemic hemodynamic variables and gastric intramucosal partial pressure of carbon dioxide (PCO_2) in septic patients. *Design:* Short-term interventional study. *Setting:* Medical-surgical intensive care unit in a university hospital. *Patients:* Twenty-four adult patients with severe sepsis or septic shock requiring volume replacement. All patients were studied within 24 h of onset of severe sepsis or septic shock. *Interventions:* Five hundred milliliters of a 6% hydroxyethyl starch (HES) solution were administered in 30 min. *Measurements and results:* Complete hemodynamic data, blood samples, and gastric mucosal PCO_2 (automatic gas capnometry) determinations were obtained at baseline and 15 min after the end of fluid infusion. After fluid challenge, cardiac index (CI) increased from 3.8 (range 2.9–4.2) to 4.2 (range 3.1–4.9) l/min m^{-2} ($p<0.05$). The PCO_2 gap decreased from 9.8 (range 6.9–26.0) to 8.5 (range 6.6–17.4) mm Hg ($p<0.05$), but important individual variations were observed. We failed to observe significant relationships between changes in CI and in PCO_2 gap, or between indices of preload (pulmonary artery occluded pressure, right atrial pressure, and pulse pressure variations) and changes in PCO_2 gap. In addition, changes in PCO_2 gap and in (v-a) CO_2 were not related; however, changes in PCO_2 gap were related to baseline PCO_2 gap ($p=0.003$), PEEP ($p=0.02$), and cumulative doses of vasopressors ($p=0.02$). *Conclusions:* The effects of fluid challenge on gastric mucosal PCO_2 are variable and related to baseline PCO_2 gap rather than to systemic variables. In general, rapid volume infusion decreases PCO_2 gap, but this effect is more pronounced in patients with presumably impaired mucosal perfusion.

Keywords Septic shock · Fluid replacement · Gastric intramucosal PCO_2 · Multivariate analysis

Introduction

Although splanchnic blood flow is usually preserved [1] or even increased in sepsis [2], tissue oxygenation of the gut may be jeopardized due to maldistribution of blood flow and an increase in oxygen demand [1], maybe in conjunction with mitochondrial impairment [3]. Altered gut perfusion may induce or perpetuate a worsening of the septic syndrome. Gastric tonometry can be used to assess the balance between oxygen blood flow and demand. Gastric mucosal acidosis may develop in septic patients despite the normalization of conventional resuscitation endpoints, independent of changes in systemic acid–base status, or whole-body hemodynamics [4, 5]. Tonometry derived measurements have a strong prognostic value [5, 6]. Monitoring of gastric intramucosal pH (pHi) was initially proposed, but the partial pressure of carbon dioxide (PCO_2) gap, defined as the difference between

gastric mucosal PCO_2 ($PgCO_2$) and arterial PCO_2 ($PaCO_2$), may more specifically reflect the adequacy of gastric mucosal blood flow [7], as it is not influenced by systemic acid–base status. The PCO_2 gap also has a strong prognostic value [8].

Hypovolemia frequently contributes to the impairment in gut perfusion [9, 10]. In isolated hypovolemia, correction of fluid deficits is associated with an increase in pHi [9, 11]. In sepsis, fluid resuscitation is well recognized as a central component of therapy not only to correct hypovolemia but also to restore cardiac output and increase blood availability to the tissues [12]; however, the relationship between fluid resuscitation and gastric mucosal blood flow remains incompletely characterized. In several models of endotoxic shock, fluid administration failed to improve gastric or ileal mucosal PCO_2, even though mesenteric perfusion increased [13, 14]. In patients with sepsis, studies have yielded divergent results, showing a decreased [15], stable [16, 17], or even increased [18] gastric mucosal PCO_2. Several factors could explain these divergent effects including concomitant changes in vasopressor therapy [18] and technical limitations, in particular related to the use of saline tonometry [16, 17]. Interestingly, a wide interindividual variability has been recognized, both in baseline PCO_2 gap [16, 17] and in the response to fluid loading [17], but the factors determining this inter-individual variation are largely undefined. As both whole-body hemodynamics and basal PCO_2 gap, reflecting the severity of gut hypoperfusion, may influence the response to fluid loading, we studied the changes in PCO_2 gap during rapid volume infusion (fluid challenge) and investigated whether changes in systemic hemodynamic variables or basal PCO_2 gap could predict the evolution of the PCO_2 gap in patients with severe sepsis or septic shock.

Patients and methods

After approval by the Hospital Ethics Committee of the institution, 24 adult patients with severe sepsis and septic shock were included in this prospective, interventional study. As these interventions and monitoring tools are part of the routine care of these patients and cannot be delayed, informed consent was not necessary.

All patients met four sets of criteria:

1. They were infected with a presumed source of infection for which they were receiving antibiotic therapy.
2. They had signs of severe sepsis or septic shock [19].
3. They had signs of tissue hypoperfusion such as oliguria, altered skin perfusion or altered mental status, systolic blood pressure lower than 90 mm Hg, or high lactate concentrations (>2.0 mEq/l).
4. They had clinical signs of hypovolemia, such as oliguria, tachycardia or hypotension in the presence of relatively low cardiac filling pressure with a central venous pressure (CVP) or a pulmonary artery balloon occluded pressure (PAOP) <12 mm Hg.

The study was performed within 24 h after the onset of severe sepsis. Patients with recent acute coronary syndromes, mesenteric ischemia, or acute liver failure were not included.

All patients were mechanically ventilated with a positive end-expiratory pressure (PEEP) level between 0 and 18 cmH_2O and sedated with a midazolam and morphine infusion. Each patient had been treated with a H_2 receptor blocker, ranitidine, and had received no enteral feeding for at least 6 h.

Measurements

Each patient was monitored with an arterial catheter and a pulmonary artery catheter (Swan-Ganz, Baxter Edwards Critical Care, Irvine, Calif.). All pressures were measured at end-expiration. Pulse pressure variation (DeltaPP) was calculated in patients in sinus rhythm and regular heart rate [20]. Cardiac output was determined by the thermodilution technique, using 10-ml injections of cold D5 W via a closed system (CO-set, Baxter), and a cardiac output computer (COM 2, Baxter). Cardiac output was averaged from six injections cycled with the respirator (starting at end-inspiration) whose values were within 10% of each other. Cardiac index (CI), oxygen delivery index (DO_2I), and oxygen consumption index (VO_2I) were calculated using standard formulae. Immediately after cardiac output determination, arterial and mixed venous blood samples were simultaneously anaerobically collected for immediate determination of blood gases (ABL3 analyzer, Radiometer, Copenhagen, Denmark). The arterial O_2 saturation (SaO_2), and mixed venous O_2 saturation (SvO_2) were measured by a co-oximeter (Hemoximeter OSM3, Radiometer). At baseline an arterial blood sample was also obtained to determine lactate concentration in triplicate (2300 STAT plus, Yellow Spring Instruments, Ohio).

A nasogastric tonometry catheter (TRIP, NGS-Catheter, Tonometrics Division; Helsinki, Finland) was positioned in the stomach. The correct position of the tube was confirmed radiographically. Gastric mucosal PCO_2 ($PgCO_2$) was determined by automatic gas capnometry (Tonocap, Datex, Finland). Briefly, the tonometer balloon was automatically filled with approximately 6 ml air and PCO_2 was measured every 10 min in a recirculating mode [21]. Three consecutive values were averaged. The PCO_2 gap was calculated as the difference between $PgCO_2$ and $PaCO_2$.

We a priori defined responders as patients who increased their CI by more than 10% (CI responders) or decreased their PCO_2 gap by more than 3 mmHg (PCO_2-gap responders). These thresholds were used since the coefficient of variability for six CI measurements by the thermodilution technique is <5% [22] and the errors in $PaCO_2$ and $PgCO_2$ measurements are around 1 mmHg [21]. An abnormal PCO_2 gap was defined as a value higher than 8 mm Hg [23].

The APACHE II score [24] and the sequential organ failure assessment (SOFA) score [25] were calculated in all patients. The cumulative doses of vasopressors (dopamine and norepinephrine) were calculated using an equivalence factor of dopamine 20 μg/kg min^{-1}=0.3 μ/kg min^{-1} norepinephrine [26].

Complete hemodynamic data, blood samples, and gastric mucosal PCO_2 determinations were obtained at baseline. After baseline measurements, a solution of 500 ml of 6% hydroxyethyl starch (Elohaes, Fresenius, Germany) was administered over 30 min. Fifteen minutes after this infusion, a second set of measurements was obtained. No changes in vasoactive agents or respirator parameters were allowed during the entire protocol.

After exclusion of normal distribution by a Kolmogorov-Smirnov test, data were analyzed using a nonparametric test. Changes over time were analyzed using a Wilcoxon rank test for repeated measurements. Correlation between the PCO_2 gap and the other variables were assessed by a Spearman test. A multiple regression was then performed introducing all variables with an

individual p value <0.20. Data were expressed as median values and percentiles 25 and 75. A p value <0.05 was considered significant.

Results

Demographic data and the etiology of sepsis of the 24 patients are shown in Table 1. Twenty patients (80%) had septic shock. The PEEP level was 8 cmH_2O (range 5–12).

The rapid infusion of 500 ml hydroxyethyl starch (HES) resulted in significant increases in pulmonary artery occlusion pressure (PAOP) and central venous pressure (CVP). Cardiac index (CI) increased from 3.8 (range 2.9–4.2) to 4.2 (range 3.1–4.9) l/min m^{-2} (p<0.01). Oxygen delivery (DO_2) also increased significantly but oxygen consumption (VO_2) remained unchanged (Table 2). Important individual variations were observed and cardiac index increased in 15 patients (63%). Changes in CI were related to baseline DeltaPP (R2=0.33, p<0.05) but not to the other measured variables.

The PCO_2 gap decreased from 9.8 (range 6.9–26.0) to 8.5 (range 6.6–17.4) mmHg (p<0.05), but important individual variations were observed. The PCO_2 gap decreased in 10 patients, remained unaltered in 13 patients, and increased in 1 patient (Fig. 1). Similarly, pHi significantly increased after fluid challenge from 7.21 (range 7.14–7.31) to 7.25 (range 7.15–7.32; p<0.05), with large individual variations.

Table 1 Descriptive patient data. *DP* dopamine, *NE* norepinephrine, *DB* dobutamine, *PCO_2* partial pressure of carbon dioxide, *SOFA* sequential organ failure assessment, *APACHE* acute physiology and chronic health evaluation

Patient no.	Gender	Age (years)	Source of sepsis	APACHE II score	SOFA score	Vasoactive agent (dose mcg/kg per min)	Blood lactate (mEq/l)	Initial PCO_2 gap	ICU survival
1	F	60	Catheter line infection	17	10	NE 0.3	0.9	11.1	Survived
2	F	85	Hepatic abscess	20	8	–	1.7	11.3	Survived
3	M	57	Bacteremia	15	7	DP 10	1.6	8.4	Survived
4	M	32	Candidemia+peritonitis	18	9	–	0.7	6.3	Survived
5	M	40	Pancreatitis+cellulitis	10	4	–	1.1	7.1	Survived
6	M	56	Pancreatitis+peritonitis	21	16	DP 20	1.4	8.5	Survived
7	M	69	Urosepsis	18	10	DP 20	2.7	19	Survived
8	F	69	Urosepsis	10	16	DP 20	1.6	5.7	Survived
9	F	63	Peritonitis	15	13	DP 7	1.2	22.4	Survived
10	M	73	Peritonitis	25	13	DB 5, DP 20	1.6	2	Survived
11	M	46	Peritonitis	32	15	DB 6, DP 20, NE 0.6	3.2	30	Survived
12	M	82	Peritonitis	28	12	DP 15	6.5	50	Survived
13	F	61	Pneumonia	15	8	DB 5, NE 0.2	1.6	5	Survived
14	M	78	Pancreatitis+abscess	18	11	DP 8	1.9	3.9	Died
15	M	77	Osteodiscitis	19	8	DB 10, NE 0.4	1.9	0.1	Died
16	M	63	Pneumonia	12	5	DB 5	1.3	12.6	Died
17	M	76	Renal abscess	17	10	DB 17, DP 20, NE 0.3	5.3	8.2	Died
18	M	70	Pneumonia	15	8	DB 5, DP 20	1.5	32.7	Died
19	M	91	Fecal peritonitis	23	10	DP 6	2	6.7	Died
20	M	65	Cholangitis	12	7	DP 20	0.8	7.5	Died
21	M	52	Pneumonia	27	9	DP 20, NE 0.3	4.5	76.9	Died
22	M	60	Pneumonia	20	9	DP 2	4.2	43.7	Died
23	F	65	Pneumonia	19	14	DB 7, DP 20, NE 0.1	3.1	11.5	Died
24	M	67	Meningitis/pneumonia	17	12	DP 11	2.9	65.1	Died

Table 2 Evolution of global hemodynamic parameters during fluid administration (median and 25th and 75th percentiles). *NS* not significant

Parameter	Baseline	Fluid challenge	p value
Mean arterial pressure (mm Hg)	70 (66–78)	76 (69–80)	NS
Heart rate (bpm)	109 (95–121)	102 (92–113)	<0.05
Pulmonary artery occlusion pressure (mm Hg)	12 (11–15)	15 (13–17)	<0.01
Central venous pressure (mm Hg)	11 (9–13)	12 (11–14)	<0.01
Cardiac index (l/min m^{-2})	3.8 (2.9–4.2)	4.2 (3.1–4.9)	<0.01
SaO_2 (%)	96 (94–98)	97 (96–98)	NS
SvO_2 (%)	69 (64–72)	69 (67–75)	NS
Oxygen delivery (ml/min m^{-2})	443 (389–525)	476 (414–575)	<0.05
Oxygen consumption (ml/min/m^2)	122 (96–139)	125 (91–140)	NS
Oxygen extraction (%)	28 (25–33)	28 (21–31)	NS
$PvCO_2$-$PaCO_2$ gradient (mm Hg)	3.7 (1.8–4.8)	2.6 (1.6–3.8)	NS
$PgCO_2$-$PaCO_2$ gradient (mm Hg)	9.8 (6.9–26.0)	8.5 (6.6–17.4)	<0.05
pHi	7.21 (7.14–7.13)	7.25 (7.15–7.32)	<0.05

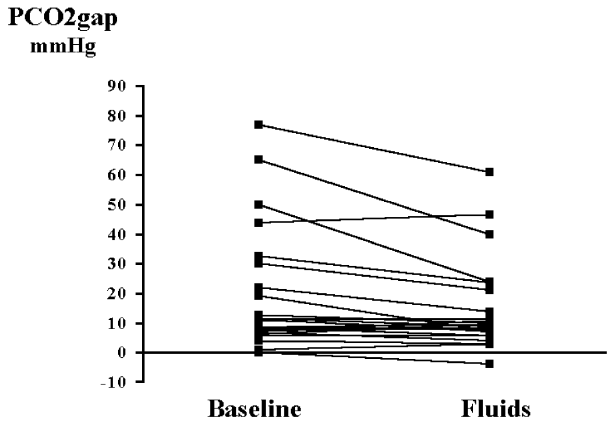

Fig. 1 Individual changes in partial pressure of carbon dioxide gap (*PCO2gap*) during fluid challenge

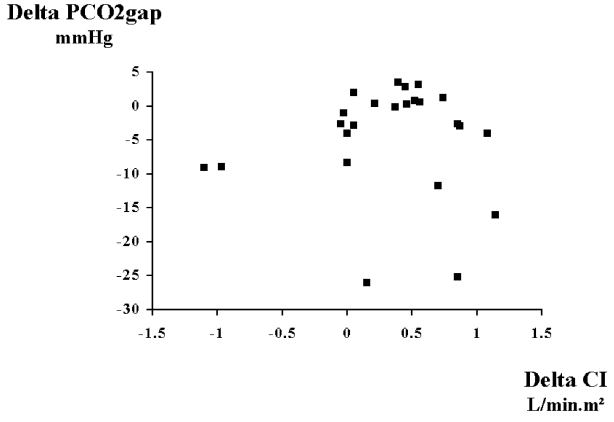

Fig. 2 Correlation between changes in cardiac index (*Delta CI*) and changes in PCO_2 gap (*Delta PCO2gap*)

There were no significant relationships between changes in CI and in PCO_2 gap (R^2=0.06 and p=0.24; Fig. 2), or between changes in PCO_2 gap and in (v-a) CO_2 gradient (R^2=0.04 and p=0.13; Table 3). In addition, the changes in PCO_2 gap were not related to baseline DeltaPP (R^2=0.03, p=0.5). On the contrary, changes in PCO_2 gap were related to baseline PCO_2 gap (R^2=0.61, p<0.0001; Fig. 3), baseline lactate levels (R^2=0.24, p<0.05), levels of PEEP (R^2=0.58, p<0.001), SaO_2 (R^2=0.41, p<0.001), cumulative dosages of dopamine and norepinephrine (R^2=0.39, p<0.01), APACHE II score (R^2=0.22, p<0.05), and hemoglobin levels (R^2=0.18, p<0.05). Multiple regression (R^2=0.81, p<0.0001) identified baseline PCO_2 gap (p=0.003) and PEEP (p=0.02) and cumulative dosages of dopamine and norepinephrine (p=0.03) as independent factors related to changes in PCO_2 gap.

If anything, the PCO_2 gap decreased more consistently in the CI non-responder group [from 7.5 (range 4.8–17) to 7.0 (range 3.4–11.5) mmHg, p<0.05] than in the CI responder group (from 11.2 (range 7.9–31.4) to 9.5 (7.2–25.7) mmHg, p=0.09]. Likewise, if anything, CI increased less consistently [from 4.1 (range 3.4–4.6) to 4.5 (range 3.4–4.7) l/min m^{-2}, p=0.12) in the PCO_2-gap responders than in PCO_2-gap nonresponders (from 3.7 (range 3.0–4.2) to 4.0 (range 3.5–4.4) l/min m^{-2}, p<0.05).

When we analyzed separately the 13 patients with elevated PCO_2 gap at baseline (>8 mmHg), the results were grossly similar (Table 1). The PCO_2 gap markedly decreased in these patients. Interestingly, CI increased in 9 (69%) of these patients, but this proportion was not

Table 3 Relationship between changes in gastric to arterial PCO_2 gradient (PCO_2 gap) and hemodynamic, biologic, therapeutic, and physiologic variables. *PEEP* positive end-expiratory pressure

Variable	R2	*p* value
Mean arterial pressure	0.05	0.3
Cardiac index	0.06	0.24
Pulse pressure variation	0.03	0.5
Pulmonary artery occluded pressure	0.1	0.13
Right atrial pressure	0.08	0.19
Hemoglobin level	0.18	0.04[a]
Lactate concentration	0.24	0.02[a]
pH	0.03	0.86
$PaCO_2$	0.03	0.86
PaO_2	0.21	0.02[a]
SaO_2	0.41	0.0008[a]
$PvCO_2$	0.16	0.44
SvO_2	0.12	0.09
Oxygen delivery	0.19	0.38
Oxygen consumption	0.02	0.4
Oxygen extraction	0.06	0.24
Baseline PCO_2 gap	0.61	0.0001[a,b]
Arteriovenous PCO_2 gradient	0.04	0.13
PEEP level	0.59	0.001[a,b]
Tidal volume	0.06	0.17
Dobutamine dose	0.09	0.51
Dopamine and norepinephrine doses	0.30	0.006[a,b]
APACHE II score	0.22	0.02[a]
SOFA score	0.11	0.1

[a] Variables identified as significant using linear regression
[b] Variables identified as significant using multiple regression

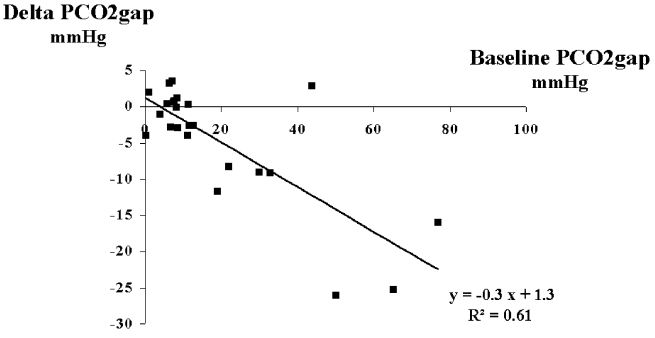

Fig. 3 Relationship between baseline PCO_2 gap and changes in PCO_2 gap (*Delta PCO2gap*)

different than in the patients with a normal PCO_2 gap (46%, p=0.75).

Discussion

Although volume infusion is considered an essential step in the initial resuscitation of septic patients [27], the ideal end points remain controversial. An important question is whether gastric tonometry could help to guide fluid administration in severe sepsis. We observed that fluid challenge decreased PCO_2 gap in some but not in all patients. These changes could not be predicted from systemic variables including cardiac filling pressures, baseline CI, or variations in pulse pressure. Importantly, the response of the PCO_2 gap to fluid challenge was related to baseline PCO_2 gap, the PEEP level, and cumulative doses of vasopressors. This suggests that the patients who had a decrease in PCO_2 gap were more severely ill and may have had more severe alterations in splanchnic blood flow. Physiologically, it could be expected from the curvilinear relationship between ΔPCO_2 and flow that, for a given VCO_2, a similar absolute change in blood flow results in greater changes in ΔPCO_2 within the lowest range than in the highest range of flow. Although we did not measure splanchnic blood flow in the present study, we have previously reported that changes in PCO_2 gap during dobutamine administration occurs only in patients with low fractional splanchnic blood flow [28]. In support of this hypothesis, PEEP levels were higher in patients in whom PCO_2 gap decreased during fluid challenge, and high PEEP levels, in contrast to low to moderate PEEP levels, can decrease splanchnic blood flow [29, 30].

Importantly, changes in PCO_2 gap were not predicted by changes in CI, which is in accordance with several studies that have underlined the lack of a relationship between splanchnic blood flow or gastric mucosal blood flow and systemic hemodynamic measurements [31, 32]. This illustrates the complex relationship between CI, splanchnic blood flow, mucosal blood flow, and mucosal PCO_2. It is very likely that underlying hypovolemia was undiagnosed due to compensatory mechanisms. Hamilton-Davies et al. [10] reported, during graded hypovolemia in healthy volunteers, that the PCO_2 gap increased already after the first aliquot of blood withdrawal, whereas stroke volume, heart rate, and arterial pressure remained constant, illustrating the fact that compensatory mechanisms induced blood-flow redistribution from the splanchnic to the central compartment. It is likely that alpha-adrenergic agents can even further exacerbate this phenomenon. Accordingly, the usual signs of hypovolemia may be absent and the response in PCO_2 gap can be dissociated from the response in CI.

Other mechanisms could explain the absence of a decrease in PCO_2 gap in some patients. Firstly, blood-flow redistribution can occur during septic shock, between organs as well as among organs, and this may not always be reversed by fluid administration. In endotoxic shock models, fluid administration increased CI and mesenteric blood flow without decreasing gastric mucosal PCO_2 [13, 14]. Secondly, the amount of colloids, here limited to 500 ml of HES, may have been insufficient to increase mucosal blood flow; however, PAOP increased in almost all patients (22 of 24) and we did not consider further fluid administration at this point. Thirdly, the increased PCO_2 gap may be secondary to ischemia–reperfusion. Nielsen et al. [33] demonstrated that oxidants derived from xanthine oxidase injured the gastric microcirculation during reperfusion, which prolonged mucosal ischemia. In a small group of trauma patients, Barquist et al. [34] demonstrated that a "splanchnic"-antioxidant therapy (xanthine oxidase inhibitor, hydroxyl radical scavenger, isoproterenol) associated with fluid resuscitation could more adequately restore gastric mucosal pH and even decrease multiple organ dysfunction syndrome. Fourthly, a washout phenomenon could have resulted in transient CO_2 tissue release during reperfusion. We think this was unlikely since we did not observe any rebound increase in $PgCO_2$ during fluid administration, using 10-min intervals with the Tonocap device.

Finally, the Haldane effect [35] could explain how an increase in blood flow resulting in an increase in mucosal O_2 saturation could increase $PgCO_2$. According to the Haldane effect, at any PCO_2 oxygenated blood has a lower CO_2 content than reduced blood [36]; hence, for a given CO_2 content, PCO_2 will be higher at a higher hemoglobin saturation. This phenomenon may result in a paradoxical increase in PCO_2 gap, despite an increase in mucosal blood flow. Nevertheless, although several factors alone or in combination may explain the variation of the effects of fluid challenge on PCO_2 gap, the predominant factor seems to be an inadequate mucosal perfusion at baseline.

Errors in measurements, including jejunal reflux, can sometimes occur during gastric tonometry [37]; however, these are minimized using gas tonometry. It is very unlikely that these errors in measurements played a significant part in our findings. Firstly, our measurements were within values reported in other studies using gastric tonometry [8, 38]. Secondly, minor changes occurred in patients with low PCO_2 gap at baseline and PCO_2 gap markedly decreased when it was elevated at baseline. Errors in measurements would have been random and do not explain these systematic changes.

The present study used only HES solution, so that we cannot exclude the possibility that other fluids could have resulted in different effects [17]. The HES molecules may affect endothelial cell activation, through mechanisms that are not completely understood. HES solutions have been associated with preserved microvascular cross-sectional area in experimental sepsis [39]. In septic

patients, the infusion of HES solutions can be associated with reduced release of circulating soluble adhesion molecules, suggesting a reduction in endothelial cell activation and injury [40]. Interestingly, a study by Boldt et al. indicated that pHi improved in septic patients resuscitated with HES but not in patients treated with albumin solutions [41]. In addition, volume resuscitation with HES solutions may improve pHi in patients undergoing major surgery [11, 42]. On the other hand, Castro et al. [43] reported that HES solutions may compromise erythrocyte rheology and impair mucosal perfusion in septic animals. In patients submitted to cardiopulmonary bypass, Sumpelmann et al. [44] reported that pump priming with HES resulted in more frequent hemolysis and more severe morphological alterations in red blood cell shape than gelatins or albumin. In addition, Asfar et al. [17] reported that HES administration slightly increased PCO_2 gap while gelatin solutions improved mucosal CO_2; hence, the specific effects of HES solutions on gastric mucosal PCO_2 remain to be established.

Conclusion

In conclusion, the effects of fluid challenge on gastric mucosal PCO_2 are variable and cannot be predicted from changes in cardiac output and oxygen delivery. On the contrary, this response was related to baseline PCO_2 gap; hence, a decrease in PCO_2 gap after fluid challenge should suggest that gastric mucosal hypoperfusion was present at baseline. Therefore, volume replacement may be tried in the presence of an increased PCO_2 gap to rule out gastric mucosal hypoperfusion even when global hemodynamic variables are not grossly abnormal. On the other hand, there are many other factors capable of influencing the PCO_2 gap so that one cannot feel secure about recommending the use of gastric tonometry as the only guide to fluid therapy in septic patients.

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