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Gastric intramucosal pH-guided therapy in patients after elective repair of infrarenal abdominal aneurysms: is it beneficial?

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Abstract Objective: To determine if gastric intramucosal pH (pHi)-guided therapy reduces the number of complications and length of stay in the intensive care unit (ICU) or the hospital after elective repair of infrarenal abdominal aortic aneurysms.

Design: Prospective, randomized study.

Setting: Surgical intensive care unit (SICU) of a University Hospital.

Patients: Fifty-five consecutive patients randomized to group 1 (pHi-guided therapy) or to group 2 (control).

Interventions: Patients of group 1 with a pHi of lower than 7.32 were treated by means of a prospective protocol in order to increase their pHi to 7.32 or more.

Measurements and results: pHi was determined in both groups on admission to the SICU and thereafter at 6-h intervals. In group 2, the treating physicians were blinded for the pHi values. Complications, APACHE II scores, duration of endotracheal intubation, fluid and vasoactive drug treatment, treatment with vasoactive drugs, length of stay in the SICU and in the hospital and hospital mortality were recorded. There were no differences between groups in terms of the incidence of complications. We found no differ-

ences in APACHE II scores on admission, the duration of intubation, SICU or hospital stay, or hospital mortality. In the two groups the incidence of pHi values lower than 7.32 on admission to the SICU was comparable (41% and 42% in groups 1 and 2, respectively). Patients with pHi lower than 7.32 had more major complications during SICU stay ($p < 0.05$), and periods more than 10 h of persistently low pHi values (< 7.32) were associated with a higher incidence of SICU complications ($p < 0.01$).

Conclusions: Low pHi values (< 7.32) and their persistence are predictors of major complications. Treatment to elevate low pHi values does not improve postoperative outcome. Based on these data, we cannot recommend the routine use of gastric tonometers for pHi-guided therapy in these patients. Further studies are warranted to determine adequate treatment of low pHi values that results in beneficial effects on the patient's postoperative course and outcome.

Key words Abdominal aortic aneurysma · Postoperative complication · Intramucosal pH · Tonometer · Gastrointestinal ischemia

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Introduction

A low gastric intramucosal pH (pHi) obtained at the end of a major surgical procedure [1–3] or on admission to a surgical intensive care unit (SICU) [4–6] has been demonstrated to predict postoperative complications such as sepsis, multiple organ dysfunction syndrome (MODS) and cardiac failure. Moreover, pHi-guided therapy has been reported to improve patients' outcomes in a general intensive care unit (ICU) population [7] and in trauma patients [8, 9].

Repair of infrarenal abdominal aortic aneurysm (AAA) is a procedure that can cause major postoperative complications and even death. The reported in-hospital mortality for elective AAA repair ranges from 5% [10, 11] to 12% [12], whereas the incidence of major complications such as acute renal failure, bleeding, ileus, cardiac failure, infection and myocardial infarction is reported to be 4–9% [12]. Major postoperative intestinal ischemia has been diagnosed in 1% of patients after elective AAA repair with a mortality rate of 50% [13]. In addition, there is a 15% incidence of adverse cardiac events in these patients during the postoperative period [14].

The aim of this prospective study, therefore, was to test whether pHi-guided treatment in the SICU is beneficial for the postoperative course of patients scheduled for elective AAA repair by reducing the number of patients with postoperative complications.

Materials and methods

After institutional approval and written informed consent, 55 consecutive patients were prospectively studied. All patients were scheduled for elective repair of an infrarenal AAA.

Patient groups

Before surgery, patients were randomized into one of two groups. In group 1 (treatment group) the pHi was determined at regular intervals and pHi-values lower than 7.32 were treated by the attending physician according to a predefined treatment flow chart (Fig. 1). The gastric mucosal carbon dioxide tension was measured (ABL 620, Radiometer, Copenhagen, Denmark) and pHi calculated [15]. In cases with a pHi of below 7.32 the physicians in charge treated the patient to restore this to above 7.32. In group 2 (control group) the pHi values were obtained as in group 1, however, the attending physicians were blinded for pHi values and treatment was performed according to the usual clinical guidelines: hemodynamics were stabilized primarily by means of intravenous fluids (Hetastarch, Ringer's lactate). As soon as possible, ventilation was changed from continuous mandatory ventilation with various levels of positive end-expiratory pressure to pressure support ventilation. The criteria for extubation were: when the body temperature exceeded 36°C, the patient was awake and responsive with a mean arterial pressure above 70 mm Hg, urine output above 0.5 ml/kg per hour, arterial pH more than 7.35 and arterial pCO₂ below 7.0 kPa, and there were no signs of other potential complications such as myocardial ischemia.

Study protocol

Starting on the day of surgery, each patient was given 40 mg omeprazole intravenously at 24-h intervals to reduce proton production in the stomach, which might potentially interfere with pHi measurements [16]. After the induction of general anesthesia, the nasogastric tonometer (TRIP TGS catheter, Tonometrics, Bethesda, Md, USA) was inserted. Correct placement of the tonometer was confirmed by auscultation over the stomach as air was injected through the tonometer or aspiration of typical gastric content. General anesthesia was induced with 5 mg/kg thiopentone and 2 µg/kg fentanyl. After muscle relaxation, the patient's trachea was intubated. Anesthesia was maintained with isoflurane and fentanyl up to 15 µg/kg. No combination of general and regional anesthesia was used. Carbon dioxide tension of the gastric mucosa was measured after admittance to the SICU and thereafter at 6-h intervals. The tonometer was removed after the patient had been extubated.

Measurement of pHi was performed according to the guidelines provided by the manufacturer of the tonometer. The tonometer's silicone balloon was filled with 2.5 ml 0.9% sodium chloride solution. After equilibration for 60 min, the solution was aspirated from the balloon; the first milliliter was discarded and blood gas analysis was immediately performed on the remaining 1.5 ml and an arterial blood sample. pHi was calculated based on the Henderson Hasselbalch equation:

$$\text{pHi} = 6.1 + \log \left(\frac{[\text{arterial bicarbonate}]}{[\text{time corrected tonometric carbon dioxide} \times 0.03]} \right)$$

A pHi value above 7.34 was considered to be normal [2, 17]. In group 1, pHi values below 7.32 were treated by the attending physicians. The pHi values, exact treatment and the physician's hypothesis for the low pHi were recorded. Treatment included intravenous fluid bolus (Ringer's lactate, colloids, packed red cells) and initiation or extension of pharmacologic therapy according to a predefined treatment flow chart (Fig. 1) based on a pathophysiologic concept [18]. It was also at the discretion of the treating physician to order additional diagnostic measures such as transesophageal echocardiography, pulmonary artery catheters, abdominal ultrasound or additional pHi measurements. In group 2, treatment consisted of standard procedures guided by conventional diagnostic measures, as is common practice in our institution.

In addition to pHi values, the following data were prospectively collected: duration of the surgical procedure, APACHE II score [19] on admission to the SICU and on day 3 of SICU treatment, duration of intubation, daily fluid requirement in milliliters, days of treatment with vasoactive drugs (patients with two vasoactive drugs were counted twice) and postoperative complications. After a patient's discharge to the ward, complications on the ward, total length of hospital stay or death were recorded retrospectively.

Complications were defined as a condition that required new therapeutic interventions or diagnostic procedures. The complications were divided into a major and a minor category. Major complications were defined as myocardial infarction, sustained myocardial ischemia (> 4 h), nosocomial infection according to the Center for Disease Control criteria [20], organ insufficiency according to Knaus [21] and surgical complications requiring a second laparotomy. In addition, we prospectively grouped patients based on pHi values on admission to the SICU to compare the incidence of complications in patients with normal (pHi > 7.32), to those having low (pHi < 7.32), values.

Statistics

The data are presented as means and standard deviations (SD) or ranges. Continuous variables were compared between groups

Flow chart for correction of low pH_i values

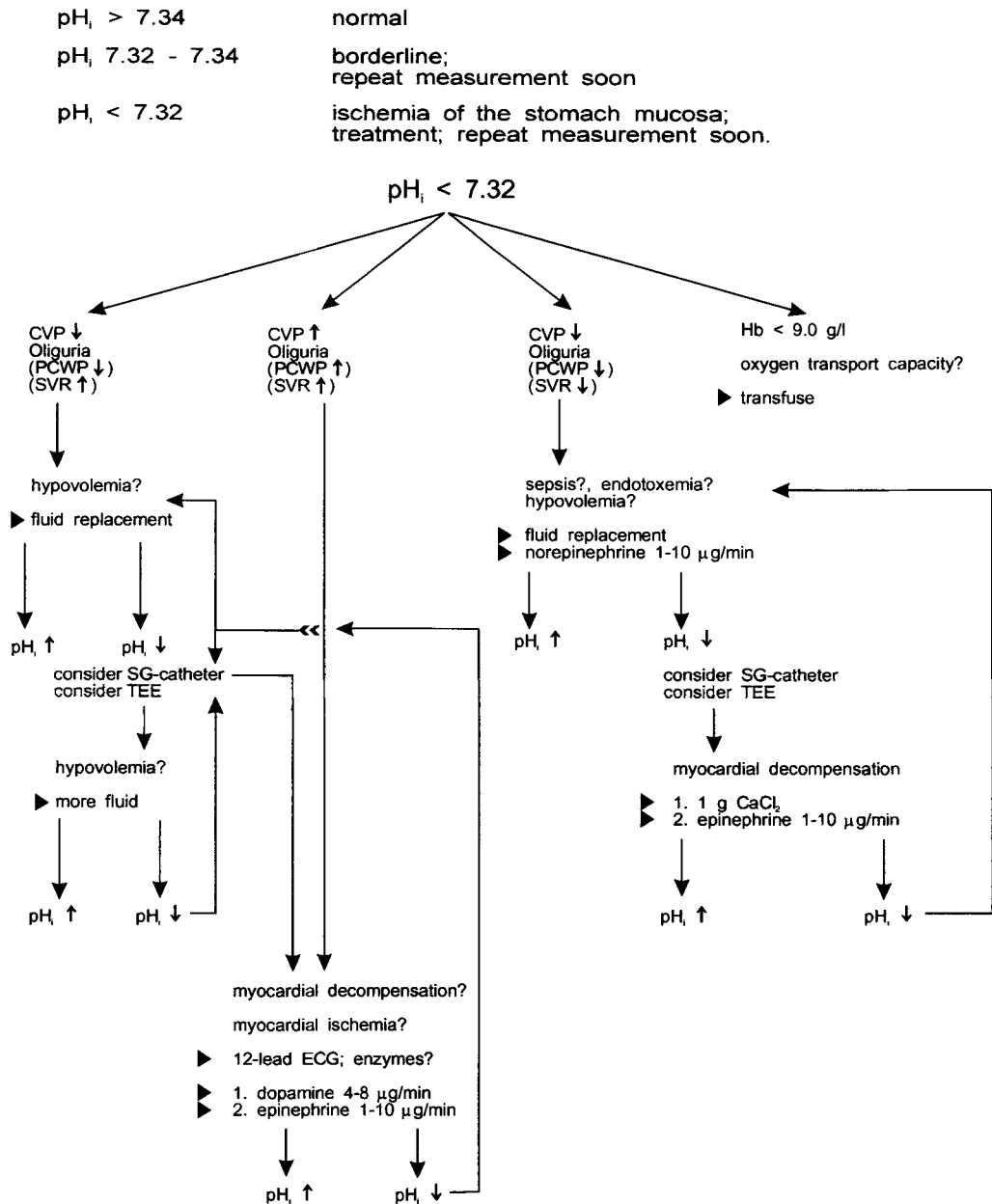


Fig. 1 The patients in group 1 were assigned to one of three groups depending on their pH_i value: 1) $pH_i > 7.34$, no intervention necessary. Check pH_i after 6 h. 2) pH_i between 7.32 and 7.34, borderline, intervention not yet necessary. Check pH_i after 0–2 h. 3) $pH_i < 7.32$, pathologic value, intervention necessary. The attending physician had to treat the patient according to the flow chart. Primarily, the volume statuses of the patients were adjusted. The central venous pressures and urine outputs served as individual guidelines, however no absolute target values had to be reached. Additional volume was given in the form of packed red cells, if the he-

moglobin concentration decreased below 9.0 g/l. The physicians were free to request more invasive diagnostic measures, such as pulmonary artery catheters or transesophageal echocardiography. The pH_i value had to be checked immediately after the intervention and, if it had not yet increased, further diagnostic and/or therapeutic measures had to follow according to the flow chart until the pH_i value was 7.32 or higher.

(*CVP* central venous pressure, *PCWP* pulmonary capillary wedged pressure, *SVR* systemic vascular resistance, *SG* Swan-Ganz, *TEE* transesophageal echocardiography)

Table 1 Preoperative patient data (ASA class American Society of Anesthesiologists physical status class [39], POVD peripheral occlusive vascular disease). No difference between groups 1 and 2 (unpaired Student's *t*-test, Mann-Whitney U test, Fisher's exact test)

	Group 1 (n = 29)		Group 2 (n = 26)	
Age (years)	64	± 10	67	± 9
ASA class	3 ^a	± 0.5	3 ^a	± 0.6
Coronary heart disease	13	(45%)	13	(50%)
Previous myocardial infarction	9	(31%)	11	(42%)
Arterial hypertension	18	(62%)	16	(62%)
Diabetes mellitus	1	(3%)	2	(8%)
POVD	17	(59%)	13	(50%)

^a median 3 (range 2–4)

using the two-sided unpaired Student's *t*-test, while comparison of scores was performed using the Mann-Whitney U test. Contingency tables were tested using Fisher's exact test. A *p* value less than 0.05 was considered significant.

Results

There were no differences between groups with respect to age or previous medical conditions (Table 1) or durations of the operative procedures and APACHE II scores on admission to the SICU (Table 2). There were also no differences between groups in terms of duration of intubation, perioperative fluid requirement, durations of the SICU and hospital stays. Patients in group 1 received more vasoactive drugs on postoperative day 1 compared to group 2 (*p* < 0.05). APACHE II scores on postoperative day 3 were higher (*p* < 0.05) in group 2 patients (Table 2).

Table 2 Intraoperative and postoperative data

	Group 1 (n = 29)		Group 2 (n = 26)	
	mean	SD	mean	SD
Duration of operation	189	77	193	73
APACHE II (admission)	11 ^a	4	13 ^b	5
APACHE II (SICU day 3)	11 ^c	7	19 ^{d, e}	4
Days on SICU	3 ^g	9	4 ^k	7
Days intubated	3 ^h	9	3 ^l	6
Total days in hospital	18 ⁱ	10	18 ^m	10
Total intraoperative fluids (ml)	8824	4048	9404	4812
Total fluids (ml; SICU day 1)	4862	2131	4812	4399
Total fluids (ml; SICU day 3)	3669	1822	3462	1560
Vasoactive drugs (SICU day 1)	20 (69%) ^f		10 (38%)	
Hospital mortality	1 (3%)		2 (8%)	

^a, 9 (4–24) [median (range)]; ^b, 12 (5–24) [median (range)]; ^c, 10 (3–21) [median (range)]; ^d, *p* < 0.05 (group 1: *n* = 6; group 2: *n* = 5; Student's *t*-test); ^e, 18 (15–25) [median (range)]; ^f, *p* < 0.05 (Fisher's exact test; patients receiving two vasoactive drugs were counted

The incidence and severity of complications for the two groups are shown in Table 3. There were no statistically significant differences. However, there were more major complications in patients with pHi values below 7.32 on admission to the SICU (*p* < 0.05), while this difference did not reach statistical significance within treatment groups (Table 4). There was a high incidence of pHi values lower than 7.32 in both groups (41% and 42% in groups 1 and 2, respectively). This incidence increased within 48 h to 55% (group 1) and 65% (group 2) (not significant).

In group 1, pHi remained normal (≥ 7.35) in 13 patients during the measuring period. A total of 22 episodes of pHi values below 7.32 were observed in 16 patients (55%). Nineteen of these episodes (86%) were treated with additional intravenous fluids while in eight episodes (36%), in addition to fluids, a new vasoactive drug was started or the dosage of the vasoactive drugs had to be increased, and in one episode the use of an antiarrhythmic drug was chosen. During three episodes of low pHi values (< 7.32), the attending physician requested an additional diagnostic measure: one transesophageal echocardiography, one abdominal ultrasound and one 12-lead electrocardiogram. In three episodes (14%), the physicians questioned the validity of the low pHi values because of the good clinical recovery and the normal values of all other monitoring parameters of the patient. In each of these cases the pHi measurement was repeated immediately and revealed normal values in all instances.

To determine whether the treatment regime was followed adequately in group 1 patients, we compared the difference of the total amount of intravenous fluids given during the first SICU day between patients with pHi below 7.32 and patients with pHi of 7.32 or higher. There was a significant difference in the total amount

twice); ^g, 1 (1–48) [median (range)]; ^h, 1 (0–48) [median (range)]; ⁱ, 14 (10–54) [median (range)]; ^k, 2 (1–33) [median (range)]; ^l, 1 (0–33) [median (range)]; ^m, 14 (9–49) [median (range)]

Table 3 Number of patients with postoperative complications and their nature. For every location (SICU or ward) the patients were assigned either to the group with major or minor complications.

There were no differences in the number of patients with complications between groups 1 and 2 (Fisher's exact test)

Complications		Group 1 (n = 29)		Group 2 (n = 26)	
SICU	Major	3	10 %	4	15 %
	Minor	6	21 %	3	12 %
Ward	Major	4	14 %	4	15 %
	Minor	6	21 %	7	27 %
Total	Major	7	24 %	8	31 %
	Minor	12	41 %	10	38 %

Table 4 Subgroups defined by pHi on admission to the SICU

Complications		Group 1 (n = 29)		Group 2 (n = 26)		Total (n = 55)	
		pHi ≥ 7.32 (n = 17)	pHi < 7.32 (n = 12)	pHi ≥ 7.32 (n = 15)	pHi < 7.32 (n = 11)	pHi ≥ 7.32 (n = 32)	pHi < 7.32 (n = 23)
SICU	Major	0	3 ^a	1	3	1	6 ^b
	Minor	5	1	3	0	8	1
Ward	Major	3	1	3	1	6	2
	Minor	4	2	5	2	9	4

^a, $p = 0.06$ compared with $pHi \geq 7.32$; ^b, $p < 0.05$ compared with $pHi \geq 7.32$ (Fisher's exact test)

of fluids ($pHi < 7.32$: $5833 \text{ ml} \pm 2340 \text{ ml}$; $pHi \geq 7.32$: 4176 ± 1725 ; $p < 0.05$).

In group 1, 10 episodes (45 %) of pHi values lower than 7.32 had a duration of less than 5 h, seven episodes (32 %) lasted between 5 and 10 h and five episodes (23 %) persisted over 10 h. All three patients in group 1 who had major complications during their SICU stay also had prolonged periods (i.e., > 10 h) of gastrointestinal mucosal ischemia. None of the individuals with short episodes ($n = 17$) of pHi values below 7.32 sustained major complications in the SICU ($p < 0.01$ prolonged versus short episodes of low pHi).

Discussion

Postoperative complications after AAA repair often occur and are undesired because they can lead to MODS. In spite of a variety of treatment regimens, the outcome

of patients with MODS has not improved, and this syndrome is the leading cause of SICU deaths [22]. Gastrointestinal mucosal ischemia is considered to be one of the triggering events for the development of MODS. Early treatment of gastrointestinal mucosal ischemia is of crucial importance because the risk of serious complications increases with the duration of ischemia [4]. For these reasons, monitoring and correction of pHi may be a rational approach to treat gastrointestinal ischemia and, thus, to prevent MODS [17].

The main findings of this study were: 1) The incidence of postoperative gastrointestinal mucosal ischemia is high, 2) low pHi values on admission to the SICU and prolonged periods of pHi below 7.32 are associated with more major complications, 3) the use of pHi as a guide for postoperative SICU therapy after resection of AAA is not superior to routine treatment.

We found an incidence of about 40 % of patients with pHi values below 7.32 on admission to the SICU. The

reported incidences of gastrointestinal mucosal ischemic episodes (as indicated by low pHi values obtained from gastric or sigmoid tonometers) after AAA repair range from 10 to 100%; however, the data are difficult to compare because of differences in definitions of pathologic pHi values and measuring sites: either in the stomach or in the large bowel [3, 23–25].

The results of the present study corroborate previous findings that demonstrate low pHi values on admission to the SICU are associated with an increased incidence of postoperative complications [1–6]. Our data are also in line with results suggesting that prolonged periods of low pHi values are associated with an increased risk for an adverse SICU outcome [4]. However, in contrast to previous studies [7–9], we were unable to demonstrate a beneficial effect of pHi-guided therapy on mortality and the incidence of complications. One explanation for the discrepancy may be the differences in mortality rates in controls. Gutierrez et al. [7] reported an excessively high in-hospital mortality of 58% in controls with a pHi of 7.35 or higher at the time of admission to the ICU. An alternative explanation may be the differences in the study populations: Gutierrez et al. investigated a heterogeneous ICU population with a high incidence of organ failures on admission and, consequently, higher APACHE II scores, while Ivatury et al. studied trauma victims with hospital mortalities between 30% and 50% [8, 9].

Another explanation for our failure to demonstrate beneficial effects of pHi-guided therapy may be that the therapeutic steps used to correct low pHi values were inadequate or were not accurately performed. Our flow chart is consistent with recent work demonstrating that certain therapies, mainly the infusion of various vasoactive drugs, are able to change pHi [26–33]. However, these studies were performed in septic patients, and the end points for treatment were improvement of splanchnic blood flow and oxygen transport variables. For example, infusion of dopexamine has been demonstrated to increase pHi in septic patients [27] whereas epinephrine causes a decrease of pHi in similar patients [33]. None of these studies provided information as to whether an increase in pHi had any beneficial effect on patient outcome. The patients in group 1 with a pHi below 7.32 during the first SICU day received more fluids than patients with a pHi of 7.32 or above, demonstrating, in part, that our treatment regimen was followed adequately. Why the total amount of fluids administered to group 1 and 2 patients was not statistically different remains unclear. We hypothesize that the conventional, indirect signs of hypovolemia, such as decrease of urine output, in our group 2 patients were sufficient to trigger adequate treatment with fluids and, therefore, knowledge of the pHi values was not mandatory for treating hypovolemia in these patients.

In healthy volunteers, hypovolemia (25% reduction of intravascular blood volume) is associated with a de-

crease in pHi that is fully reversible after restoration of intravascular volume [34]. Based on these data and the fact that postoperative hypovolemia is common after infrarenal AAA repair, we hypothesized that a decrease in pHi in our patients most likely reflects intravascular hypovolemia. We, therefore, decided to treat patients with low pHi values by administering additional fluid and/or vasoactive drugs. Using these measures, we successfully treated 77% of the low pHi episodes within 10 h. In the remaining episodes, however, failure to correct pHi within 10 h was associated with major complications during the SICU stay, a finding consistent with previously reported data [4]. For this reason we feel that the failure to correct pHi in these patients reflects inadequacy of our treatment regimen. On the other hand, we are unaware of any therapeutic option in addition to those we used that has been demonstrated either to increase low pHi values or to have a beneficial effect on the patient's postoperative course. In order to eliminate these uncertainties in the future, it will be necessary to investigate carefully the effects of various treatment regimes on pHi in different patient categories.

Possibly the sample size in this study was too small to exclude a type-2 statistical error. The reason we used a small sample size is because, at the time the study was planned, no data were available on the potential reduction of complications by pHi-guided therapies so a prospective determination of the sample size was not possible. Our data showed a reduction of 5% for group 1 compared with group 2 in the number of patients with major complications (Table 3), which was statistically not significant. A retrospective analysis of this reduction revealed that a sample size of 1000–1250 patients in each group would have been necessary to reach statistical significance (Power 95%, $\alpha = 0.05$, two-tailed). These numbers demonstrate that if there is an effect of pHi-guided therapy on major postoperative complications in this patient category, this effect is very small.

Available data on complications following AAA repair are limited to retrospective analyses and do not include the use of pHi-guided therapy modalities. Järvinen et al. [12] reported 30-day postoperative complications after elective AAA surgery in 226 patients. He found an overall complication incidence of 47%, but focused on selected complications without rating severity. Diehl et al. reported that in 17% of the patients with AAA repair, one or more postoperative complications occurred with an "operative mortality" of 5.1% [10]. The list of complications in this study was comparable to our definition of "major complications" and included acute renal failure, pulmonary insufficiency, myocardial infarction, bleeding, congestive heart failure and colon ischemia. Unfortunately, the authors did not differentiate between complications in the SICU and on the ward. It is also unclear how long the patients were followed, and the term "operative mortality" is not clearly

defined. For these reasons, comparison of our data with those of the above-mentioned studies is difficult.

The results of the present study raise several points. First, the clinical significance of low pHi values of short duration is still not known. Second, the pHi value at which treatment should be initiated needs to be established [3]. Third, are there any alternative treatment regimens for low pHi values that have a beneficial effect on patient outcome? Fourth, patient categories, for example, patients in more serious conditions, i.e. with APACHE II scores higher than 20, who may benefit from pHi-guided therapy need to be identified. Finally,

it remains to be established whether improvements in gastric tonometry, such as the use of recirculating gas tonometry [35–37] or different bases for calculations (tonometric minus arterial CO₂ tension instead of calculated pHi value [38]) favorably affect pHi-guided therapies in critically ill patients.

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