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ORIGINAL

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Pre-operative tonometry is predictive for mortality and morbidity in high-risk surgical patients

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Abstract *Objective*: To determine whether a) pre-operative measurement of gastric intramucosal pHi is predictive for mortality and morbidity in high-risk surgical patients and b) peri-operative improvement of global oxygen delivery (DO_2) with fluids and dopexamine leads to increased gastric pHi and c) either improved global perfusion or improved splanchnic perfusion is related to the prevention of multiple organ failure (MOF).
Design: Retrospective analysis of a double-blind, placebo-controlled, randomised study.
Setting: General intensive care units from 14 hospitals.
Patients: Two hundred eighty-six high-risk surgical patients.
Interventions: Swan-Ganz and tonometer catheter placement; patients were stabilised pre-operatively using fluids, blood and/or oxygen to preset goals before receiving placebo or two doses of dopexamine (0.5 or 2.0 μg·kg·min) peri-operatively.
Measurements and results: Haemodynamic assessment (including DO_2 and oxygen consumption (VO_2)) was performed together with measurement of gastric mucosal pHi pre-operatively and directly, 2, 6, 12, 24 and 36 h post-operatively. Retrospectively, patients were divided pre-operatively into two sub-groups based on the optimal cut-off value for mortality of the first pHi measurement after induction of anaesthesia as calculated by a receiver operator characteristic (ROC) curve analysis – low pHi group (< 7.35) and normal pHi (≥7.35). Mortality in the low pHi, was higher than in the normal pHi, group (16.8 vs 2.3 %; $p = 0.0001$). In the normal pHi group dopexamine, which was given prior to the first pHi measurement, had no effect on pHi, while DO_2 increased significantly. In this group MOF score and number of patients with MOF remained similar for the treatment sub-groups. In the low pHi group gastric pHi increased significantly during dopexamine infusion ($p = 0.008$), despite the lack of an increase in DO_2 and VO_2. In this group the MOF score and the number of patients developing MOF decreased significantly with the use of dopexamine ($p = 0.04$). In both groups bicarbonate levels remained similar for the treatment sub-groups.
Conclusions: In high-risk surgical patients pre-operative measurement of pHi was predictive for mortality. The peri-operative response of pHi to dopexamine seemed to be dependent on pre-operative gastric pHi.

Key words Dopexamine · Gastric intramucosal pHi · Oxygen delivery · Oxygen consumption · Haemodynamic optimisation · High-risk surgical patient · Multiple organ failure

Introduction

Multiple organ failure (MOF) is the major cause of late death and serious morbidity following surgery [1, 2]. High-risk surgical patients are especially prone to the development of MOF [3].

One of the current hypotheses for cellular and organ dysfunction is based on the presence of unrecognised hypovolaemia, leading to regional dysoxia, which could be the main pathophysiological disturbance leading to MOF [4]. A normal compensatory mechanism to hypovolaemia is vasoconstriction, particularly in the skin and gut. Shoemaker found that, in critically ill surgical patients, increasing the oxygen delivery (DO_2) peri-operatively to values obtained in surviving surgical patients decreased the organ-failure-related mortality [3]. This has been confirmed by others in post-operative patients, as well as in patients after trauma, whereas patients with sepsis had no benefit from achieving supernormal values for oxygen transport [5, 6, 7, 8, 9]. Moreover, global hypovolaemia is a potent cause of gut mucosal hypoperfusion and the latter seems to be related to the development of MOF [10]. Correction of the gastric mucosal acidosis has been shown to reduce the incidence of organ failure in post-operative patients [11]. Thus, aiming peri-operatively at supernormal values for both global and regional perfusion parameters would be expected to reduce the incidence of post-operative organ failure.

In two trials using dopexamine and plasma volume expansion as a means of achieving supernormal values of DO_2 and oxygen consumption (VO_2) Boyd et al. and Wilson et al. reduced the mortality in post-operative patients [6, 12, 13, 14, 15]. However, Uusaro showed that after cardiac surgery splanchnic perfusion may remain inadequate despite correction of global haemodynamics [16].

Clearly global and regional haemodynamics do not always change in parallel [16, 17]. Thus, improving global perfusion does not necessarily lead to improvement of regional perfusion. Our hypothesis was that improving global oxygen transport is not necessarily associated with improvement in the gastric mucosal pHi. The database from the European multicentre study on dopexamine was used to test this hypothesis [18]. We report an analysis of peri-operative changes in regional and global perfusion in high-risk surgical patients in whom dopexamine, in addition to plasma volume expansion, was used to optimise the peri-operative haemodynamic status.

Patients and methods

Institutional ethics committee approval from all participating centres was obtained and patients or close relatives gave informed consent for enrolment in the study. The study has been conducted according to the principles established in Helsinki. Patients undergoing non-vascular, abdominal surgery of an expected duration of longer than or equal to 1.5 h, and fulfilling one or more of the high-risk criteria devised by Shoemaker [19] were randomised to one of three treatment groups. A total of 412 patients were included across 14 centres during a 20-month period from November 1994 to June 1996. The data for this analysis were obtained from the European multicentre study on dopexamine in high-risk abdominal surgical patients [18]. The main study showed that increasing DO_2 further by dopexamine after pre-operative fluid stabilisation did not improve overall survival.

Peri-operative treatment and assessment

Patients identified as 'high-risk' were admitted pre-operatively to the intensive care unit (ICU). At this time they received a pulmonary artery catheter and an intra-arterial catheter. During stabilisation fluids, blood products and/or oxygen were given if patients had a wedge pressure less than 10 mmHg, a cardiac index less than 2.5 $l \cdot min \cdot m^2$, mean arterial pressure less than 70 mmHg, a haemoglobin concentration of less than 10 g/dl or arterial oxygen saturation (SaO_2) less than 94 %. After stabilisation, patients were randomised in a blinded fashion to placebo or one of two doses of dopexamine (0.5 or 2.0 $\mu g \cdot kg \cdot min$).

In all centres, patients received a nasogastric tonometry tube, unless contra-indicated, after induction of anaesthesia and saline installed in the balloon for at least half an hour. The saline was removed after this equilibration time and analysed on a blood gas analyser system. The variability of the different blood gas analysers among the centres was assessed by testing different standard saline samples with known PCO_2. Standardised PCO_2 variability was not significantly different among the centres. The mean coefficient of variation among the different centres was 1.57 %. The measurement of pHi was used as an observational tool only and treatment was not directly aimed at changing the intramucosal pH. The use of acid suppression therapy was not protocolised in the study.

The dopexamine infusion was maintained during surgery and for the following 24 h. Fluids were given throughout this period as required to maintain filling pressures, as defined by the above-mentioned criteria. In addition to haemodynamic measurements, gastric intramucosal pHi was determined at regular intervals (pre-operatively, directly post-operatively, at 2 h, 6, 12, 24 and 30–36 h post-operatively). The dopexamine treatment was started in advance of the first pHi measurement. The actual median time between the start of the stabilisation and the first pre-operative pHi measurement was 3 h 33 min. The median time between the start of the stabilisation and the first post-operative pHi measurement was 5 h 33 min. After this time-point the 2-h post-operative time-point was determined after a median time of 2 h. For the 6, 12, 24 and 30–36 h post-operative time-points these figures were 6 h, 11 h 55 min, 23 h 45 min and 35 h 35 min, respectively.

Patient follow-up

Post-operatively patients were re-admitted to the ICU. The same goals as set pre-operatively were used post-operatively in order to optimise the haemodynamic condition of the patient. Any necessary treatment was permitted. The APACHE II and MOF scores (modified from Goris et al.) were calculated [20]. Patients having an MOF score above 4 were defined as having MOF. At 24 h the infusion rate of dopexamine or placebo was stepwise down-titrat-

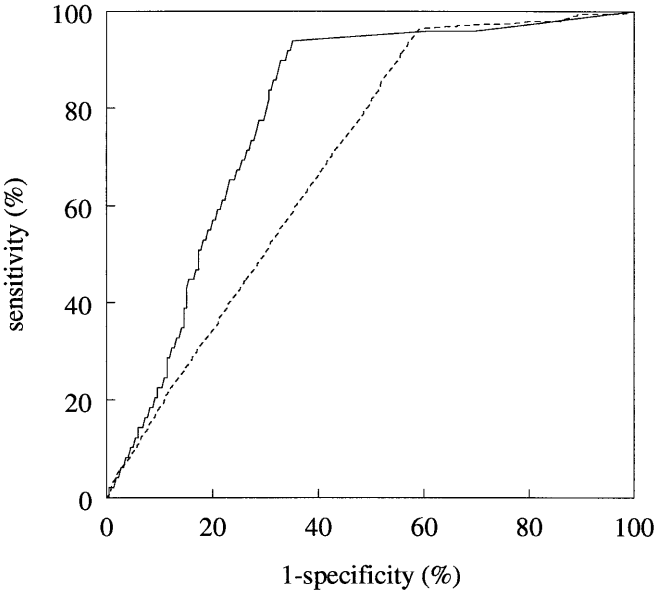

Fig. 1 Predictive value of pre-operative and peri-operative pHi as assessed by receiver operator characteristic (ROC) curves. The maximal value for the area under the ROC-curve is 1. This represents the best identification of the randomly chosen sick patient having the disease compared to a randomly chosen non-diseased patient. The area under the ROC curve from the pre-operative pHi ([arrowhorizex]) was significantly larger than the area under the curve from the peri-operatively (- – -)measured pHi ($p = 0.04$)

ed. After 30–36 h patients could be discharged from the ICU should their condition no longer require intensive care management. After discharge from the ICU, patients were monitored for 28 days or until final hospital discharge for morbidity and mortality. Organ failure was assessed by the MOF score on days 2–6, days 13, 20 and 27.

Patient sub-analysis

A retrospective analysis was performed on those patients in whom a pre-operative (after induction of anaesthesia) gastric pHi could be obtained ($n = 286$). Patients were divided into two sub-groups, based upon the optimal cut-off point value as analysed by an analysis of the ROC curve (see Statistics and Results sections) – 'normal pHi' and 'low pHi'. A pHi below 7.35 was considered in this population to be the optimal indication of a significant mucosal acidosis. Previously, pHi below this level has been demonstrated to be related to an increased risk of MOF and mortality [21, 22, 23].

Statistical analysis

Statistical analysis was performed using SPSS version 7.5. Data are presented as means ± standard deviation, or as absolute numbers with percentages and compared using Student's *t*-test or by chi-square test.

The predictive values of the pHi measurements for mortality obtained pre-operatively and during the total peri-operative period, were plotted using ROC curves and compared using a statistical method previously described (Fig. 1) [24, 25]. The areas under the ROC curve represent the probability that a randomly chosen individual deceased patient is correctly assessed for having a greater risk of death than a randomly chosen non-deceased individual patient. Thus, this gives an indication of the prognostic power in individual patients. The optimal cut-off value for the pre-operative value for mortality was calculated from the ROC curve analysis as that point with the greatest combined sensitivity and specificity. This cut-off value was used to divide the population into two subgroups [26]. The distribution of patients in the low and normal pHi groups among the different participating centres was compared using a chi-square test.

Since dopexamine was started prior to the first pHi measurement, pre-operative pHi values were first compared among the different treatment groups, using one-way ANOVA with Bonferoni post hoc analysis. Secondly, global and regional haemodynamic data and MOF scores among treatment groups, with the low and normal pHi groups analysed separately, were compared by a multiple-way analysis of variance (ANOVA), with one within-factor: time (repeated measures) and one between-factor: treatment with dopexamine (including three levels). Where appropriate, the last observation carried forward principle was used to replace missing data. The mean percentage of missing values was 6.2% (SD 3.4%). Error values of the multiple-way ANOVA are reported in Tables 1 and 2 as time-effect, to indicate the significance of the within-subject analysis, and treatment effect (see also Figs. 2 and 3) to indicate the significance of the interaction between repeated measures times dopexamine treatment. The Bonferoni post hoc analysis was performed to determine which particular point in time differed significantly among the three treatment groups and the significance at a level of 0.05 is reported as an asterisk in the tables and figures.

The combined and independent effects of the haemodynamic variables, which were significant on chi-square or multiple-way ANOVA analysis, were analysed using a logistic non-parametric multiple regression model (backward conditional). A p value less than 0.05 was considered statistically significant.

Results

Overall clinical data

Of the 412 patients in the overall study a total of 286 patients, in whom pre-operative gastric tonometry was measured, were included in the analysis. The remaining patients had no gastric tonometer placed (due to gastro/oesophageal surgery, $n = 98$) or the pre-operative measurement was not performed ($n = 28$). Overall outcome between the patients included in the sub-study and the patients excluded was comparable.

Optimal gastric intramucosal pHi cut-off value

The area under the ROC curve for the pre-operative measurement of pHi was 0.79 (Fig. 2). The area under the ROC curve for all time-points combined was 0.69 (SE = 0.013; CI 2.5-97.5% = 0.67-0.72), and significantly lower than the area under the ROC curve for the

Table 1 Peri-operative changes in global haemodynamic perfusion during treatment with dopexamine in patients with a normal pHi pre-operatively (DO_2 oxygen delivery (ml·min·m^2), VO_2 oxygen consumption (ml·min·m^2), HCO_3 arterial bicarbonate, *Lact.* arterial lactate, *Plac* placebo, *0.5* and *2.0* denote 0.5 and 2.0 μg·kg·min dopexamine, respectively, p_1 indicates p values of repeated time-measures, p_2 indicates the p value of the interaction by multiple-way ANOVA between repeated measures × dopexamine treatment)

Subgroups	Pre-dopex		Pre-op		Post-op (PO)		24 h PO		36 h PO		p_1	p_2
DO_2												
Plac	474	20	456[a,c]	20	381[a]	20	449[a,c]	21	464	22	0.006	0.05
0.5	522	20	583	25	476	22	527	21	523	22		
2.0	521	29	656	28	543	36	580	26	566	23		
VO_2												
Plac	107.5	6.4	98.3	7.6	76.1	4.6	97.5	5.4	82.6	5.7	0.25	0.61
0.5	114.8	6.7	97.6	9.0	77.1	4.6	112.4	5.3	103.1	5.7		
2.0	104.3	7.9	92.5	7.6	83.7	6.8	112.7	5.5	91.7	9.0		
HCO_3												
Plac			24.9	0.4	22.5	0.4	25.7	0.4	30.4	4.1	0.61	0.16
0.5			24.0	0.3	24.7	2.7	24.8	0.4	25.5	0.4		
2.0			23.8	0.4	22.7	0.5	24.7	0.4	25.3	0.4		
Lact.												
Plac	1.2	0.1	0.9[b]	0.1	1.1[b]	0.1	1.4	0.1	1.1	0.1	0.25	0.59
0.5	1.4	0.2	0.9	0.1	1.0	0.1	1.8	0.2	1.3	0.2		
2.0	1.1	0.1	1.2	0.1	1.6	0.1	1.8	0.2	1.2	0.1		

Values are shown as means ± standard error. Data were analysed using multiple-way ANOVA for all time-points

[a] $p < 0.05$ comparing placebo versus 0.5 μg·kg·min sub-groups

[b] $p < 0.05$ comparing 0.5 and 2.0 μg·kg·min sub-groups

[c] $p < 0.05$ comparing placebo versus 2.0 μg·kg·min sub-groups

Table 2 Peri-operative changes in global haemodynamic perfusion during treatment with dopexamine in patients with a low pHi pre-operatively (DO_2 oxygen delivery (ml·min·m^2), VO_2 oxygen consumption (ml·min·m^2), HCO_3 arterial bicarbonate, *Lact.* arterial lactate, *Plac* placebo, *0.5* and *2.0* μg·kg·min denote 0.5 and 2.0 dopexamine, respectively, p_1 indicates p values of repeated time-measures, p_2 indicates the p value of the interaction by multiple-way ANOVA between repeated measures × dopexamine treatment)

Subgroups	Pre-dopexamine		Pre-operative		Post-operative (PO)		24 h PO		36 h PO		p_1	p_2
DO_2												
Plac	518	19	458[c]	23	421	28	546	25	559	26	0.007	0.25
0.5	518	28	514	30	499	35	536	31	536	30		
2.0	477	34	590	34	541	37	534	27	572	37		
VO_2												
Plac	119.6	7.9	89.6	7.2	79.5[c]	6.4	121.0	7.2	90.2	8.5	0.006	0.99
0.5	118.7	8.5	80.6	4.8	86.3	8.3	106.6	6.6	105.8	7.8		
2.0	107.2	8.2	92.9	8.4	95.7	6.8	105.7	6.0	98.2	9.9		
HCO_3												
Plac			29.5	6.8	20.9	0.6	22.4	0.7	22.6	0.8[c]	0.51	0.52
0.5			22.9	0.5	21.4	0.7	24.0	0.6	24.7	0.6		
2.0			32.0	9.2	21.4	0.4	24.4	0.8	25.5	0.7		
Lact.												
Plac	1.0	0.1	0.9[b,c]	0.1	1.2[b,c]	0.1	1.8	0.2	1.1	0.1	0.19	0.02
0.5	0.9	0.1	0.9	0.1	1.1	0.1	1.4	0.2	1.2	0.2		
2.0	1.2	0.1	1.2	0.1	1.6	0.2	1.6	0.2	1.2	0.2		

Values are shown as means ± standard error

Data were analysed using multiple-way ANOVA for all time-points

[a] $p < 0.05$ comparing placebo versus 0.5 μg·kg·min sub-groups

[b] $p < 0.05$ comparing 0.5 and 2.0 μg·kg·min sub-groups

[c] $p < 0.05$ comparing placebo versus 2.0 μg·kg·min sub-groups

pre-operative measurement ($p = 0.04$). The optimal cut-off point for the pre-operatively measured pHi was 7.35, with a sensitivity of 86.4 % and a specificity of 63.6 %.

The low pHi group (113 patients, with a pre-operative gastric pHi mean of 7.26 (SD, 0.08)) had a significantly higher mortality than the normal pHi group (172 patients, with a mean of 7.47 (SD, 0.10)) (16.8 vs

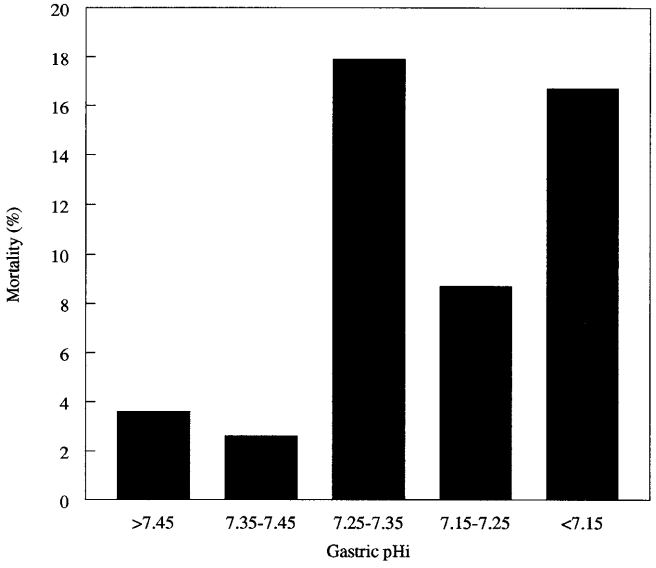

Fig. 2 Mortality figures by gastric pHi. Data are presented as percentages. Mortality associated with the pre-operatively pHi *(solid bars)* showed a biphasic pattern. $p = 0.0001$, mortality for patients with a pre-operative pHi < 7.35 versus mortality for patients with a pre-operative pHi≥7.35 by Chi-square test

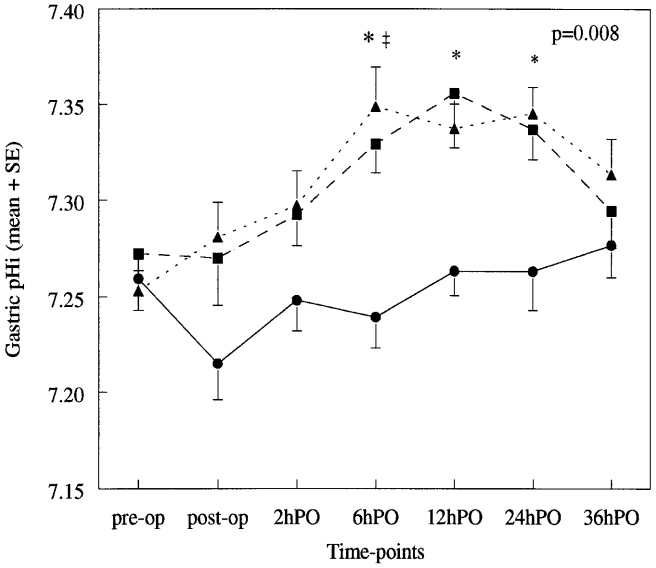

Fig. 3 Peri-operative gastric pHi in patients with low pre-operative pHi treated with dopexamine. Data are presented as means ± standard error. Data were compared using repeated measures ANOVA (p value indicates the interaction between the repeated time-point × dopexamine treatment; treatment-effect). Bonferroni correction was carried out comparing the three treatment sub groups. $^{*}p < 0.05$ comparing placebo ([arrowhorizex]● [arrowhorizex]) versus 0.5 μg·kg·min (- – -■- – -) sub-groups, $^{\#}p < 0.05$ comparing 0.5 and 2.0 μg·kg·min (···▲···) sub-groups, ‡$p < 0.05$ comparing placebo versus 2.0 μg·kg·min sub-groups

2.3 %; $p = 0.0001$). The mortality rates for the different pHi values are depicted in Fig. 1. The mortality rates for pre-operatively measured pHi showed a sudden increase in the group of patients with values below 7.35 compared to those with pre-operative pHi levels above 7.35.

Clinical data in low and normal pHi groups

There were no differences with respect to age, diagnosis and operation type between the low and normal pHi groups. Table 3 shows the demographics of patients in these two sub-groups. The distribution of patients in the low and normal pHi groups was not different among the different participating centres ($p = 0.3$). The distribution of pre-operative pHi values was similar in all participating centres.

In the group with a low pHi pre-operatively 39, 37, and 37 patients were randomised to receive placebo, 0.5 and 2.0 μg·kg·min dopexamine, respectively. In the normal pHi group, 58 patients were randomised to receive placebo, 61 patients were randomised to receive 0.5 μg·kg·min dopexamine, and 53 to receive 2.0 μg·kg·min dopexamine.

Although H_2-blockade was not routinely used in the study, the majority of patients received acid suppression therapy during surgery. The number of patients receiving this therapy was equally distributed among the normal and the low pHi groups (91/172 versus 65/113, $p = 0.44$). Moreover, the mean pre-operative pHi value was similar in the patients with and without acid suppression therapy (7.384 (SD, 0.139) versus 7.402 (SD, 0.137), $p = 0.31$).

Changes in pHi during dopexamine infusion

The first pHi measurement, performed after induction of anaesthesia, showed no differences among the treatment groups (placebo 7.398 (SD, 0.157), 0.5 μg·kg·min 7.390 (SD, 0.117), 2.0 μg·kg·min 7.390 (SD, 0.140); $p = 0.27$, Bonferoni-analysis, $p = 1.0$)

In the total group of patients with a low pHi pre-operatively, the pHi increased steadily following surgery, but remained below 7.35. However, the pHi in the placebo-treated patients in the low pHi group did not change significantly post-operatively compared to the pre-operative value ($p = 0.13$). In 84 % of the placebo-treated patients in the low pHi group, the pHi decreased below 7.35 during at least one time-point. These percentages were 64 and 65 % for patients in the 0.5 and 2.0 μg·kg·min dopexamine groups, respectively.

In the normal pHi group, gastric pHi dropped significantly ($p = 0.005$) in the placebo-treated patients during surgery and remained stable thereafter. Despite the fall

Table 3 Patient demographics

Variables	Normal pHi group	Low pHi group	*p* value
Number	172	113	
Age (years)	62 ± 14	63 ± 14	0.6
Sex (% male)	54.7	58.4	0.5
Height (cm)	167 ± 9	168 ± 11	0.4
Weight (kg)	69 ± 13	72 ± 16	0.2
Diagnosis *(n)**			
Carcinoma	96	56	
Malignant neoplasm	17	12	
Secondary malignancy	15	3	
Benign neoplasm	4	2	
Peritonitis	8	11	
Pancreatitis	7	5	
Enteritis/colitis	16	11	
Cholecystitis/cholangitis	1	2	
Duodenal ulcer	3	3	
Other diagnoses	13	14	0.2
Procedures *(n)**			
Resection intestine	94	77	
Splenectomy	3	1	
Biliary tract procedure	5	6	
Hepatectomy	24	7	
Pancreas resection	35	19	
Uninary tract procedure	3	4	
Genital tract procedure	4	3	
Other procedures	21	21	0.06
Acute/elective	36/172	28/113	0.4

*Patients may have more than one diagnosis or procedure performed

Values are shown as means ± standard deviation

between pre-operative and post-operative values, the mean post-operative values remained within normal limits (> 7.35). However, 41 % of the placebo-treated patients in the normal pHi group had a temporary drop of pHi below 7.35 during at least one time-point. These percentages were 45 and 49 % for patients in the 0.5 and 2.0 μg·kg·min dopexamine groups, respectively.

In the low pHi group, the addition of dopexamine resulted in a significant increase in the post-operative pHi, when compared to the placebo group ($p = 0.038$ for time-related influences and $p = 0.008$ for time × treatment-related influences by multiple-way ANOVA, see Statistics). In addition, gastric pHi reached normal values in patients receiving dopexamine, while this was not the case in placebo-treated patients (Fig. 3). When dopexamine was stopped after 24 h a significant decrease in gastric pHi from a mean of 7.34 to 7.30 was found when combining both treatment groups ($p = 0.03$).

The increase in gastric pHi associated with the use of dopexamine was not seen in the normal pHi group. Post-operatively, pHi remained similar in patients receiving dopexamine when compared to placebo (treatment-effect, $p = 0.072$) (Fig. 4).

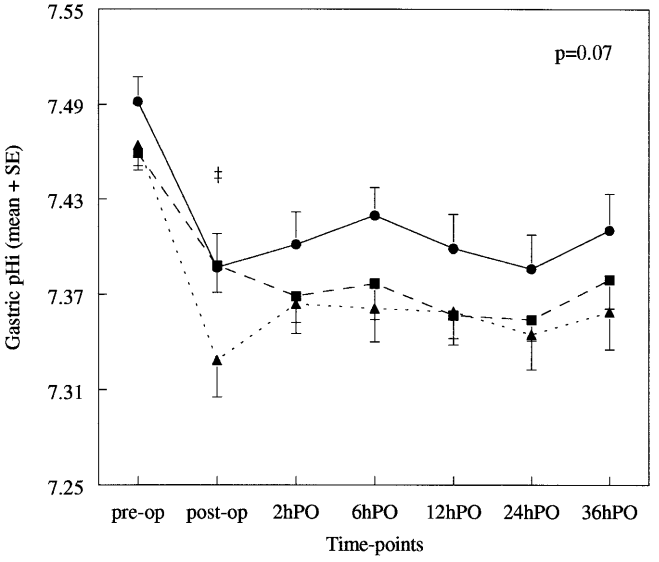

Fig. 4 Peri-operative gastric pHi in patients with a normal pre-operative pHi treated with dopexamine. Data are presented as means ± standard error. Data were compared using repeated measures ANOVA (p value indicates the interaction between the repeated time-point × dopexamine treatment; treatment-effect). Bonferroni correction was carried out to compare the three treatment sub-groups. ‡$p < 0.05$ comparing placebo ([arrowhorizex]● [arrowhorizex]) versus 2.0 μg·kg·min (···▲···) sub-groups; 0.5 μg·kg·min (- – -■- – -)

Global oxygen transport

Pre-operative haemodynamics prior to dopexamine infusion were similar in the two sub-groups, with respect to the MAP, wedge-pressure, DO_2, VO_2, mixed venous oxygen saturation, actual bicarbonate and lactate levels.

Global oxygen transport data for the normal pHi and low pHi groups are shown in Tables 1 and 2, respectively. In the normal pHi group the DO_2 was increased in the patients receiving dopexamine (treatment-effect, $p = 0.05$ for DO_2) (Table 1). In the low pHi group, the DO_2 and VO_2 were not altered by dopexamine (treatment-effect $p = 0.25$ and $p = 0.99$ for DO_2 and VO_2, respectively) (Table 2).

In the low pHi group dopexamine increased the arterial lactate (treatment-effect $p = 0.015$), whereas the arterial lactate levels remained similar among the three treatment groups in the normal pHi group.

In order to detect systemic acid-base status in the measurement of the gastric pHi, the arterial actual bicarbonate levels were compared between the treatment sub-groups in the low and normal pHi groups. No significant changes in arterial bicarbonate levels were seen over time (time-effect, $p = 0.65$ and 0.51), nor did treatment with dopexamine alter the arterial bicarbonate levels (treatment-effect, $p = 0.16$ and 0.32 for normal and low pHi groups, respectively).

The total volume of crystalloids and colloids infused in the patients during the peri-operative period was also equal in the low and normal pHi groups, as was use of inotropes other than dopexamine during the surgical procedure (data not shown).

Mortality

Logistic regression analysis, including pHi, DO_2 and treatment as variables in the equation, showed that both pHi and global DO_2 were predictive for the occurrence of mortality for all patients combined. The measurement of pHi when obtained pre-operatively was the most important determinant of mortality (pHi: B = –3.97, SE = 1.73, $p = 0.02$; DO_2: B = –0.003, SE = 0.002, $p = 0.04$, constant: B = 28.29, SE = 12.75, $p = 0.03$).

Survival was not improved by adding dopexamine in the sub-group with a low pHi. Day 28 mortality in patients with a low pHi receiving placebo treatment was 20.5 % (8/39), whereas it was 10.8 % (4/37) and 18.9 % (7/37) in patients with 0.5 and 2.0 μg·kg·min, respectively ($p = 0.5$). Mortality in the different sub-groups in patients with a normal pHi was 3.6 % (2/56), 1.6 % (1/61), and 1.9 % (1/53) for the placebo, 0.5 and 2.0 μg·kg·min treated patients, respectively ($p = 0.1$). The adjusted odds ratio for mortality of the low pHi group versus normal pHi group is 8.5, with an unadjusted odds ratio of 7.0 for the placebo-treated patients when comparing low and normal pHi groups and 7.3 and 12.1 for the 0.5 and 2.0 μg·kg·min treated patients, respectively (mean: 8.8).

Morbidity

The MOF score during the 27-day follow-up period in the low pHi placebo-treated patients was higher when compared with the normal pHi group (treatment-effect, $p = 0.001$). The mean MOF score after 24 h was 2.7 (SD, 2.6) in the low pHi group and 1.6 (SD, 1.4) in the normal pHi group ($p = 0.02$). Logistic regression analysis showed that in predicting the occurrence of MOF, the measurement of pre-operative gastric pHi was the most important predictor (pHi: B = –4.2, SE = 0.55, $p < 0.0001$; DO_2: B = –0.0009, SE = 0.0004, $p = 0.03$; constant: B = 29.5, SE = 4.06).

In the low pHi group the MOF score in patients with dopexamine was significantly lower during the follow-up period of 27 days compared to patients treated with placebo (time-effect, $p = 1.0$ and treatment-effect, $p = 0.04$). Additionally, in the low pHi group the number of patients with MOF was significantly higher in the placebo- versus dopexamine-treated patients (12/39 vs 3/37 and 2/37 for placebo, 0.5, and 2.0 μg·kg·min, respectively: $p = 0.003$). The effect of dopexamine was mainly seen in the cardiovascular, pulmonary, haemotological and renal components of the MOF score.

Multiple organ failure scores in the normal pHi group did not change during treatment with dopexamine (treatment-effect, $p = 0.26$). The number of patients with MOF was also similar (3/58, 6/81, and 10/53 for placebo, 0.5, and 2.0 μg·kg·min, respectively: $p = 0.07$).

Discussion

Reports in the literature concerning the use of supernormal values of global DO_2 as goals for haemodynamic management have produced varying results. A tentative conclusion can be made that trauma and high-risk peri-operative patients may benefit from such an approach, whereas septic ICU patients, in general, do not [5, 6, 7, 8, 9, 27]. Recent studies have indicated that not only global perfusion determines outcome [11, 28]. Within the ICU, there is current interest in focussing on regional, rather than global, perfusion parameters. This study represents an evaluation of the relationship between regional and global perfusion in a group of high-risk surgical patients undergoing haemodynamic optimisation, with or without the addition of dopexamine.

In this analysis, a low pHi pre-operatively was associated with significantly higher mortality and morbidity compared to a normal pHi. The relation between decreased pHi level and increased frequency of post-operative death and complications has been found previously [10, 21, 22], but to our knowledge this is the first study which found this association when the gastric pHi was determined prior to the surgical procedure. Apparently, high-risk surgical patients have signs of splanchnic intramucosal acidosis prior to the surgical intervention. The measurement of intramucosal PCO_2, from which the pHi is calculated, gives an indirect measurement of the adequacy of the mucosal or splanchnic blood flow. The pHi value represents a composite value which reflects several influences. Besides mucosal perfusion, systemic acid-base status and changes in metabolism influence the final pHi measurement. It is likely that changes in perfusion or volume status contribute to the pre-operative intramucosal acidosis. Patients undergoing elective major abdominal surgery are starved for at least 10 h to reduce the risk of aspiration. Moreover, the diseases for which the patients are operated upon have often caused weight loss, nausea or vomiting. All these factors can contribute to an increased risk of mucosal hypoperfusion and acidosis in the patient prior to surgery. In addition, previous data indicated that an intramucosal acidosis was associated with decreased gastric perfusion [29]. Unfortunately, we did not record more information on the systemic acid-base status to indicate that the changes in pHi were based on differences in the regional PCO_2 and not the arterial pH, as indicated by the Hend-

erson-Hasselbach equation. However, the lack of differences in the actual bicarbonate levels does suggest this.

The cut-off point of a pHi of 7.35 or lower as marker for the presence of intramucosal acidosis has not been validated extensively. However, both in this study and in previous studies this was able to identify a high-risk surgical population [21, 22, 23, 30]. The cut-off point in this study was based upon a ROC curve analysis. The area under the ROC curve of 0.79 indicated good predictive power in the individual patient. In this study the cut-off point of 7.35 showed a clear, distinctive low mortality (< 3 %) in patients with a pHi above 7.35 and a markedly higher mortality (> 16 %) in patients with a pHi below 7.35. Moreover, this study also indicated that the low pHi value was associated with an increased risk of MOF. Both mortality and the development of MOF were best predicted using the measurement of gastric pHi, when assessed using a logistic regression analysis. The measurement of the gastric intramucosal pHi, therefore, seems to be an adequate predictor of mortality in high-risk surgical patients when measured prior to surgery.

Although the patients in this study were already receiving dopexamine or placebo at the time of the first pHi measurement, the pre-operative pHi values were not different between placebo- and dopexamine-treated patients. However, the changes in pHi were strikingly different in the various treatment schedules in the post-operative period. In the low pHi group, both dopexamine-treated groups showed a significant increase in pHi post-operatively when compared with the placebo group. Moreover, the decrease in pHi after cessation of the dopexamine infusion may indicate a rebound phenomenon, although an exact explanation for this finding is difficult to give.

Although many studies using dopexamine have been published before, only two other studies investigated the effects of dopexamine on gastric pHi during major abdominal surgery. Müller et al. showed a decreased tissue PCO_2 in the small intestine during low-dose dopexamine (0.5 μg·kg·min) infusion, although the gastric pHi did not change significantly [31]. This latter observation may be related to the relatively short intra-operative infusion of dopexamine during 60 min. The effects of dopexamine in our study were found after 6 h. The study by Byers et al., including 30 patients out of the database of the main dopexamine study, displayed no differences in gastric pHi, although a significant decrease in the inflammatory response in the gastric mucosa was found during dopexamine infusion [32]. Two other studies in patients undergoing major abdominal surgery using dopexamine, by Boyd et al. and Wilson et al., did not include measurements of gastric intramucosal pHi [6, 15].

The other studies using dopexamine included patients with severe septic shock and yielded varying results of the effects of dopexamine [33, 34]. Gastric pHi decreased during dopexamine infusion in patients with septic shock, despite an increase in total splanchnic blood flow [33]. The causes for this dissociation between total splanchnic blood flow and gastric pHi are multifactorial and may be related to the presence of heterogeneous or inadequate blood flow within the hepatosplanchnic area during sepsis, or may be related to the Haldane effect [35]. It is also possible that the concomitant use of the vasoactive medications and sepsis-related changes in vasomotor auto-regulation may contribute to these findings [27, 36].

After cardiac surgery dopexamine improved gastric pHi in one study and decreased it, despite an increase in total splanchnic blood flow, in another. It is possible that the effects of dopexamine can also be modified by the type of surgery [37, 38, 39, 40].

In contrast to the low pHi group, in the normal pHi group no effect of the dopexamine treatment could be demonstrated, with mean pHi values remaining higher than 7.35. Both groups received fluids for correction of (global) hypovolaemia. We hypothesised that the low pHi group represents patients who were hypovolaemic prior to fluid loading but in whom correction of systemic hypovolaemia did not result in restoration of splanchnic flow. Edouard showed that transient normotensive hypovolaemia induces a splanchnic vasoconstriction that is sustained after normalising blood volume [41]. The further interpretation of the data presented is made difficult by the fact that the protocol did not include pHi measurements prior to fluid loading and the start of dopexamine treatment.

The group in which dopexamine appeared to show a beneficial effect on outcome was the low pHi group. The mean pHi values in the low pHi group did not return to normal levels in the placebo-treated patients, whereas after 6–12 h a normalisation was achieved in the dopexamine-treated patients. In these patients MOF scores and the occurrence of MOF were significantly lower compared to the placebo-treated patients, although mortality was not altered by dopexamine.

The change in pHi and MOF score was not associated with a change in global DO_2, a finding again supported by previous studies. In the study by Bach et al. dopexamine also improved splanchnic perfusion without a concomitant rise in DO_2 [38]. In a study by Ivatury et al. patients, following trauma, were actively resuscitated to either an DO_2 of more than 600 $l \cdot min \cdot m^2$ or a pHi of above 7.3 [27]. In this study improvement of DO_2 without improved splanchnic perfusion was associated with a high mortality.

In the normal pHi group, in which dopexamine had no beneficial effect on pHi, there was also no difference in MOF scores between the dopexamine- and placebo-treated patients.

In conclusion, in this large study population of patients undergoing high-risk surgical procedures, pre-oper-

ative measurement of gastric mucosal pHi is a good predictor of post-operative morbidity and mortality. The peri-operative response of pHi to dopexamine seemed to be dependent on pre-operative gastric pHi. In the low pHi group, an association between the effect of dopexamine on pHi and the effect on MOF was observed, independently of changes in global DO_2. In the light of the results of the studies published so far and the retrospective nature of this analysis, routine treatment of a low pre-operative gastric pHi by dopexamine cannot be recommended before the beneficial effects of such a treatment have been demonstrated in a prospective, randomised clinical trial.

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