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Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost

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Abstract. *Objectives:* To determine CO and gastric mucosal perfusion in patients during elective major surgery; to seek a relationship with subsequent outcome.
Design: Prospective descriptive study.
Setting: University hospital.
Patients: 51 patients undergoing elective major surgery of an anticipated duration of greater than 2 h who were at risk of developing gut mucosal hypoperfusion and post-operative organ failure.
Measurements and results: CO was determined by oesophageal Doppler measurement of aortic blood flow. Gastric mucosal perfusion was determined by tonometric assessmment of gastric mucosal pH (pHi). Blood pressure and urine flow were measured. At the end of surgery no patients were oliguric or hypotensive. Post-operatively morbidity, mortality, duration and cost of stay in the ITU and hospital were assessed. There were 32 patients with evidence of gastric mucosal ischaemia at the end of surgery (pHi < 7.32) despite maintenance of CO. This group of patients spent a mean of 4.7 (range 0–33) days in the ITU, 14 developed major complications (7 with multiple organ failure [MOF] and 6 died. In 19 patients gut mucosal perfusion was maintained during surgery (pHi ≥ 7.32); these patients demonstrated an increase in CO of 48.4% (95% confidence interval 21.3–75.6) and spent a mean of 1.0 (range 0–4) days in the ITU. Only one developed a major complication and none died. The total cost of post-operative care for the 51 patients was estimated at £ 356650. Mean cost per patient in the low pHi group was significantly greater at £ 8845 (range £ 600–£ 42700) compared to £ 3874 (range £ 2600–£ 9600) in the normal pHi group. The total·cost of post-operative care for the 7 patients who developed MOF was £ 171450 i.e. 48% of the total cost.
Conclusion: A low gastric pHi measured during the intra-operative period in a group of patients undergoing major (mainly cardiovascular) surgery is associated with increased post-operative complications and cost.

Key words: Tonometry – Oesophageal Doppler – Post-operative morbidity – MOF – Cost analysis

The primary function of the cardio-respiratory system is to supply sufficient oxygen to the tissues to meet their metabolic requirements. Failure to do so results in anaerobic metabolism, an oxygen debt and tissue acidosis. Global indices of the adequacy of tissue perfusion such as blood pressure (BP), heart rate (HR), CO, urine flow, arterial pH (pHa) or lactate concentration may not reflect regional perfusion [1–5]. In experimental models the intramucosal pH of the gut (pHi) is a reliable index of local tissue perfusion [6–8]. The gastric pHi can be measured easily and reproducibly using a silicone balloon tonometer placed in the lumen of the stomach [5]. In addition, a reliable and relatively non-invasive measurement of CO is now possible using a continuous-wave oesophageal Doppler device measuring blood flow in the descending thoracic aorta [9].

An abnormally low pHi is associated with increased morbidity and mortality in patients undergoing cardiac and major vascular surgery and in patients admitted to the ITU [5, 10–13]. The maintenance of a normal pHi is associated with reduced mortality in the ITU [12, 13]. Gut mucosal hypoperfusion is an early consequence of hypovolaemia and inadequate CO and is demonstrable long before systemic blood pressure falls [14, 15]. Undetected hypovolaemia and other low CO states may thus lead to inadequate tissue oxygenation and possibly subsequent complications which may not become apparent until several days post-operatively. It is postulated that the integrity of the gut mucosa is compromised by ischaemia and this leads to translocation of bacteria and endotoxin from the gut lumen [16, 17]. The subsequent stimulation of inflammatory pathways can eventually lead to the characteristic tissue destruction seen in MOF. Indeed,

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animal models of haemorrhagic shock have shown a late mortality (after 48 h) from organ failure following apparently adequate resuscitation [18]. MOF remains a common cause of death despite advances in intensive care medicine with over 90% of patients with MOF dying if more than 3 organs are involved for more than 3 days [19, 20].

We therefore decided to measure CO and gastric pHi during elective major surgery using gastric tonometry and the oesophageal Doppler. Changes in these variables were then compared with the development of post-operative complications.

Patients and methods

The study was approved by our local ethics committee and all patients gave written informed consent. Patients were studied if they were i) having elective major surgery of an anticipated duration of greater than 2 h which required the routine placement of a urinary catheter, an arterial catheter and central venous catheter and ii) at risk of developing gut mucosal hypoperfusion (i.e. patients having cardiac and vascular surgery) [5, 10] and at risk of developing post-operative organ failure according to the criteria of Shoemaker et al. [21]. The following exclusion criteria were observed: age less than 18 years; pregnancy; coagulopathies; perforated viscus; oesophageal or gastric pathology; oesophageal or gastric surgery. All patients were given Ranitidine 150 mg p.o. on the night before and on the morning of surgery to increase the precision of the assessment of gastric pHi [22]. All patients were anaesthetised using a balanced general anaesthetic technique. Depth of anaesthesia was maintained at a constant level as judged by standard clinical criteria until the last set of study variables had been recorded. Otherwise, no attempt was made to influence the anaesthetic or surgical management of the patients.

Heart rate and blood pressure were measured directly via a 20 g radial artery cannula and right atrial pressure (RAP) directly via a 14 g internal jugular catheter 15–20 min after induction of anaesthesia, before the first surgical stimulus, and at the end of surgery following the completion of skin closure. Hypotension was defined as a mean blood pressure of less than 60 mmHg. Urine flow was measured hourly. Oliguria was defined as a urine output of less than 0.5 ml/kg/h. The following non-routine techniques were used: immediately after induction of anaesthesia a tonometer (Sigmoid Tonomitor, Tonometrics Inc., Bethesda, MD) was introduced into the patient's stomach having been sutured to a fine-bore nasogastric tube with catgut. Correct placement was confirmed by the injection of air down the nasogastric tube while auscultating over the epigastrium. The tonometer was used to measure PCO_2 in the stomach following an equilibration period of 60 min and again at the end of surgery, following the completion of skin closure. The pHi was calculated by inserting the values of gastric PCO_2 and the arterial bicarbonate determined by arterial blood gas analysis (Radiometer 300 L, Copenhagen, Denmark) into a modified Henderson-Hasselbach equation (Eq 1) as described and validated previously [5, 23].

$$\mathrm{pHi} = 6.1 + \log_{10}\left(\frac{\text{arterial } [\mathrm{HCO_3^-}]}{\mathrm{PCO_2}(\text{tonometer}) \times \mathrm{K}}\right) \qquad (1)$$

where K is a time dependent equilibration constant provided by the manufacturer. A pHi = 7.32 was taken as the lower limit of normality [5, 22]. Particular note was made of bicarbonate administration as this can effect the interpretation of the calculated pHi [24].

An oesophageal Doppler probe (ODM 1, Deltex, Chichester, UK) was inserted via the patient's mouth and positioned approximately 35–40 cm from the teeth where well defined aortic blood flow signals were detected. Doppler estimated CO and stroke volume (SV) were recorded at 15–20 min after induction of anaesthesia (before the first surgical stimulus) and again at the same time as the final pHi measurement. The oseophageal Doppler system used in our study measures velocity waveforms of descending aortic blood flow. Using an internal nomogram an estimation of volumetric CO could be made to approximately 85–90% accuracy when compared with thermodilution; the coefficient of variation has been shown to be considerably lower for the Doppler system [9]. CO data were indexed to body surface area. Theatre personnel were blind to the results of all non-routine techniques.

Post-operative complications were recorded – a major complication being defined as one that resulted in an overall post-operative hospital stay of greater than 14 days or death [25]. Organ failure was determined according to the criteria proposed by Knaus and Wagner [20]. The cost of post-operative care was calculated according to the following daily rates: £ 600 for a one day post-operative ITU stay; £ 1050 per day if the stay was greater than 24 h and £ 400 per day on a general ward (as estimated by our Hospital finance department to include salaries, drugs and supplies but excluding capital costs and overheads).

Study group size was estimated with reference to our pilot study (unpublished observations) and previous studies [5, 10]. Statistical analysis was performed after 51 patients had been studied (6 months data collection). Data are shown as mean (95% confidence interval) or mean (median) [range]. Changes in cardiovascular variables were analysed with the paired Student's *t*-test within groups and the unpaired Student's *t*-test between groups. Demographic characteristics were analysed with an unpaired Student's *t*-test or χ^2 test. A p value of <0.05 was considered significant.

Results

A total of 51 patients were studied. There were 32 patients (63%) who had evidence of gastric mucosal ischaemia (pHi < 7.32) and the end of surgery. Of these 32, forming the low pHi group, 12 (23%) also had a low pHi at 1 h. None of the other 19 patients, forming the normal pHi group, showed mucosal ischaemia at 1 h. No patients were given bicarbonate during the study period. Distribution of surgical procedures between low and normal pHi groups are shown in Table 1. There were no significant differences in demographic characteristics between the two groups as shown in Table 2. The cardiovascular changes are shown in Table 3 with individual

Table 1. Distribution of surgical procedures. Patients grouped according to pHi at end of surgery

Surgical procedure	pHi at end of surgery	
	≥7.32 (n = 19)	<7.32 (n = 32)
Coronary artery by-pass grafts	7	14
Re-do coronary artery by-pass grafts	–	1
Coronary artery by-pass grafts and aortic valve replacement	1	2
Aortic valve replacement	4	1
Mitral and tricuspid valve replacement	–	2
Aortic, mitral and tricuspid valve replacement	1	–
Mitral valve replacement	–	1
Re-do aortic and mitral valve replacement	–	2
Re-do mitral and tricuspid valve replacement	–	3
Ventricular aneurysectomy (recent MI)	1	–
Major vascular surgery involving cross clamping of the aorta	1	4
Major vascular surgery not involving cross clamping of the aorta	1	1
Cystectomy for invasive carcinoma	1	1
Whipple's procedure	2	–

Table 2. Demographic characteristics of study population and duration of operation. Patients grouped according to pHi at end of surgery. Mean (median) [range]

	pHi ≥ 7.32 (n = 19)	pHi < 7.32 (n = 32)
Male	11	24
Female	8	8
Age (years)	62 (64) [28 – 82]	62 (64) [27 – 79]
Weight (kg)	71.3 (68) [46 – 99]	73.3 (75) [46 – 102]
Height (cm)	167.4 (170) [145 – 187]	168.2 (170) [128 – 183]
Duration of surgery (min)	202.0 (180) [120 – 350]	232.7 (240) [130 – 330]

Cl data plotted in Fig. 1. There were no significant differences between groups in baseline values of HR, BP, RAP, SV or Cl. None of the 51 patients were oliguric or hypotensive at the end of surgery. The low pHi group showed no significant change in BP or Cl from baseline to the end of surgery. However, there was a significant rise in HR ($p = 0.0006$) and RAP ($p = 0.009$) and a fall in SV ($p = 0.006$). The normal pHi group showed no significant change in BP or HR but a highly significant increase in both Cl (48.4%, 95% confidence interval 21.3% – 75.6%. $p = 0.001$) and SV (31.3%, 95% confidence interval 9.6% – 52.5%, $p = 0.007$).

The patients in the low pHi group spent an average of 4.7 (median 1.0) [range 0 – 33] days in the ITU and 15.1 (median 9.5) [range 1 – 97] days in hospital. Of these 32 patients, 14 developed major post-operative complications of whom 6 subsequently died (Table 4). Two patients having cardiac surgery died in the immediate post-operative period; one from uncontrollable bleeding, the other from heart failure which became resistant to inotropic support. The sensitivity of the pHi measured at the end of surgery for predicting subsequent complications was 93.3% with a specificity of 50%. The sensitivity of pHi at 1 h for predicting complications was 53.3% with a specificity of 88.9%. Only 2 patients developed overt gastrointestinal complications. Seven patients developed MOF of whom 4 (57%) subsequently died. Only one patient had a pulmonary artery catheter placed preoperatively compared to 7 post-operatively (6 with MOF and 1 with cardiac failure). Of the 51 patients 12 had a low baseline pHi at 1 h after induction of anaesthesia. Of these 12 patients 8 developed post-operative complications of whom 4 subsequently died. The 19 patients who did not develop evidence of gastric mucosal ischaemia (pHi > 7.32) by the end of surgery spent an average of 1.0 (median 1.0) [range 0 – 4] day in the ITU and 8.9 (median 7.0) [range 6 – 24] days in hospital. Of these patients only one developed a major post-operative complication and none died. The total cost of post-operative care for all 51 patients was £ 356650. Mean cost per patient in the low pHi group was £ 8845 (median £ 4900) [range £ 600 – £ 42700] compared to £ 3874 (median £ 3000) [range £ 2600 – £ 9600] in the normal pHi group. The total cost of post-operative care for the 7 patients who developed MOF was £ 171450, i.e. 48% of the cost of all 51 patients.

Discussion

The aim of this study was to measure CO and gastric pHi during elective major surgery and to compare changes in these variables to the development of post-operative complications, in particular MOF. Irrespective of the initiating stimulus (surgery, cardiopulmonary bypass, bacterial infection) the morphology of necropsy specimens in both animal models and patients with MOF is remark-

Table 3. Mean (95% confidence interval) changes in cardiovascular variables from baseline to end of surgery. There were no significant differences in baseline variables between groups

	Baseline	End of surgery	p value
Normal pHi group (n = 19)			
Heart rate (beats/min)	71 (64 – 79)	77 (72 – 83)	0.14
Systolic BP (mmHg)	117 (109 – 125)	121 (110 – 132)	0.49
Mean BP (mmHg)	79 (72 – 85)	82 (74 – 89)	0.52
Right atrial pressure (mmHg)	5.3 (2.6 – 8.0)	5.8 (2.7 – 8.9)	0.77
Cardiac output (l/min)	4.3 (3.8 – 4.8)	6.4 (5.0 – 7.7)	0.001
Stroke volume (ml)	63 (55 – 72)	85 (65 – 99)	0.007
Gastric intramucosal pH	7.39 (7.36 – 7.42)	7.37 – 7.40)	0.13
Arterial pH	7.42 (7.39 – 7.43)	7.41 (7.38 – 7.44)	0.85
Urine flow (ml/kg/h)		1.42 (0.94 – 1.54)	
Low pHi group (n = 32)			
Heart rate (beats/min)	74 (65 – 83)	89 (83 – 95)	0.0006
Systolic BP (mmHg)	114 (107 – 121)	120 (115 – 126)	0.09
Mean BP (mmHg)	78 (73 – 83)	81 (76 – 86)	0.27
Right atrial pressure (mmHg)	4.3 (2.8 – 5.8)	8.1 (6.3 – 9.9)	0.009
Cardiac output (l/min)	4.7 (4.0 – 5.3)	4.5 (4.0 – 4.9)	0.54
Stroke volume (ml)	67 (57 – 78)	53 (46 – 60)	0.006
Gastric intramucosal pH	7.34 (7.31 – 7.37)	7.20 (7.16 – 7.25)	0.0001
Arterial pH	7.38 (7.35 – 7.40)	7.33 (7.30 – 7.35)	0.01
Urine flow (ml/kg/h)		1.13 (0.85 – 1.41)	

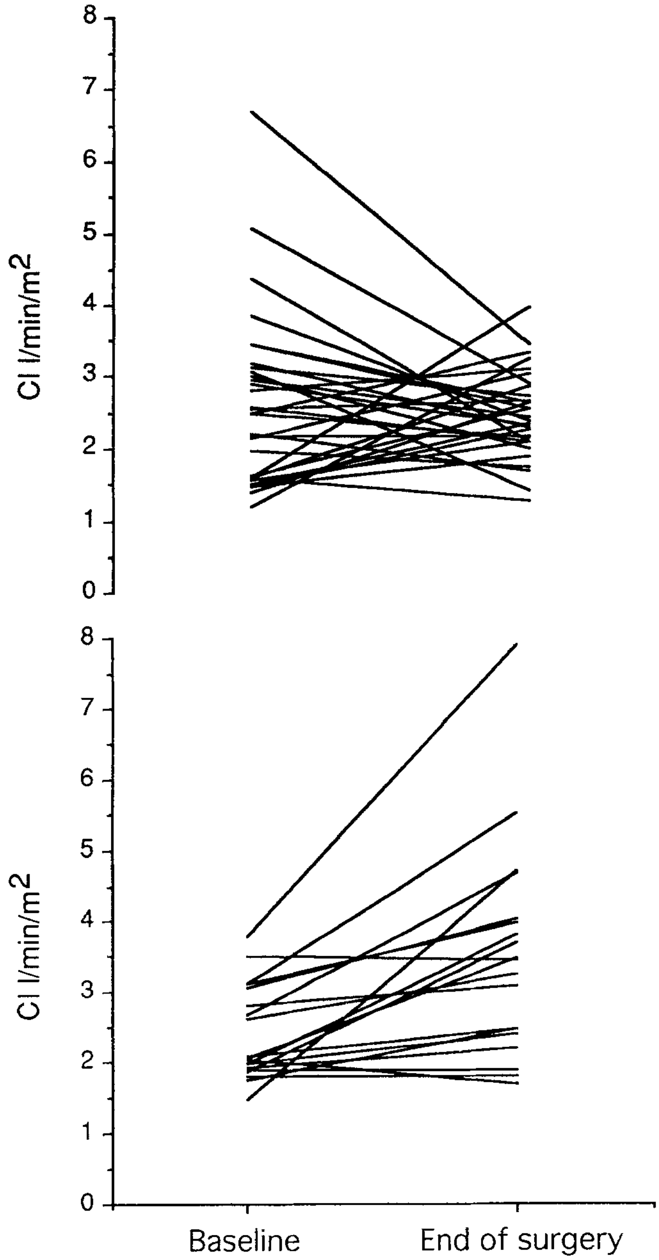

Fig. 1. Change in cardiac index from baseline to end of surgery. The *upper graph* shows the individual changes recorded in patients who had a pHi < 7.32 at the end of surgery ($n = 32$). The *lower graph* shows the individual changes in the patients who had a pHi ≥ 7.32 at the end of surgery ($n = 19$)

ably constant suggesting a final common pathway. Post-operative organ dysfunction involves the whole organism with tissue destruction distant from the site of surgery secondary to uncontrolled activation of inflammatory pathways. Established MOF remains an essentially incurable disease [20]. Therefore, attention needs to be focused on prevention. Tissue trauma at the site of major surgery is a necessary evil. Thus, we have turned our attention to a more detailed assessment of the patient's haemodynamic state in the peri-operative period in the hope that a compounding and potentially avoidable insult may be identified. We therefore decided to study a relatively non-homogeneous group of patients undergoing elective major surgery who were at risk of developing gut mucosal hypoperfusion or post-operative organ dysfunction [5, 10, 21]. These were mainly patients undergoing cardiac and vascular surgery the final distribution being representative of the case mix of elective major surgery seen in our institution.

An abnormally low gastric mucosal pH was found at the end of surgery in 63% of patients in this study. In agreement with previous studies of patients undergoing major surgery pHi measurement was predictive of post-operative major complications and mortality [4, 5, 10] and more sensitive than other forms of monitoring such as blood pressure or urine flow measurement [5]. We also measured pHi at 1 h after induction of anaesthesia. Our original intention was that this would form a baseline measurement, allowing 1 h for equilibration of gastric CO_2 with the tonometer saline. While we were unable to demonstrate a normal "baseline" pHi in all patients it is of interest that this measurement was able to predict post-operative complications though with less sensitivity than the pHi taken at the end of surgery. The lack of difference in other baseline cardiovascular variables taken prior to the beginning of surgery suggests that the volaemic status was not markedly different between the two pHi groups at that stage. It is therefore likely that the pHi at 1 h represented the effects of cardiovascular deterioration in that hour.

The function of the cardio-respiratory system is to maintain an adequate supply of oxygen to all tissues. Failure to achieve this results in tissue hypoxia and cellular dysfunction. In our study the group of patients who showed evidence of gut mucosal ischaemia during surgery, and had a poor outcome, demonstrated no change in Cl. The group that maintained gut mucosal perfusion demonstrated a significant and spontaneous increase in Cl (48.4 ± 13%) with 37% of patients achieving greater than 50% increase in Cl. It is likely that increasing cardio-respiratory variables to greater than normal levels is a pre-requisite to the perfusion of areas such as the gut mucosa during states of increased demand [26–28]. These patients maintained gut mucosal perfusion without intervention. It is not yet clear, however, which therapeutic interventions would be most useful for increasing global cardio-respiratory variables and, indeed, whether such manoeuvres would necessarily result in better gut mucosal perfusion and a reduction in complications.

Previous studies aiming to reduce the incidence of post-operative complications have relied on supra-normal cardiovascular goals [21]. The assumption is that an increased total body oxygen consumption is synonymous with increased oxygen utilization in all tissues to satisfy a presumed increase in oxygen demand. Interestingly, many of the patients who developed gut mucosal hypoperfusion in our study did so inspite of an increase in Cl (Fig. 1). In contrast many patients who maintained gut mucosal perfusion demonstrated minimal change in Cl. We do not have data for total body oxygen transport or consumption but we can point out that adequacy of the global circulation does not guarantee adequacy of perfusion in vulnerable tissues such as the gut mucosa.

Table 4. Post-operative complications

Sex	Age (years)	Ht (cm)	Wt (kg)	Surgical procedure	Duration of postoperative stay: ITU	Duration of postoperative stay: Hospital	Complications	Outcome	Estimated cost of post-op care	PA catheter: pre-op	PA catheter: post-op	Baseline pHi <7.32
pHi<7.32 at end of surgery												
M	71	168	82	AAA repair	2	22	Respiratory failure/ persistent dyspnoea	Survived	£9700			+
F	79	153	59	MVR	9	9	MODS	Died	£9450		+	+
F	50	150	47	Mesenteric re-vascularisation	9	97	MODS (infarcted ileum and colon resected on day 10)	Survived	£42700		+	
F	77	128	55	AAA repair	1	21	Pseudo-obstruction	Survived	£8600			+
M	67	180	75	CABG (re-do)	33	33	MODS	Died	£34650		+	
M	69	166	68	AVR	1	14	Wound infection[a]	Survived	£5800			+
M	70	180	85	Femoro-popliteal by-pass (re-do)	0	21	Wound-infection[a]	Survived	£8400			
M	27	182	79	AVR/MVR (re-do)	1	21	Complete heart block/CVA	Survived	£5700			+
F	73	153	46	MVR/TVR (re-do)	1	1	Re-sternotomy – uncontrolable surgical bleeding	Died	£600			+
M	71	168	71	MVR/CABG	20	20	MODS	Died	£21000	+		+
F	68	170	73	MVR/TVR	21	30	MODS	Survived	£25650		+	
M	76	168	58	Cystectomy	19	19	MODS	Died	£19950		+	
M	58	174	91	CABG	1	1	Cardiac failure	Died	£600		+	+
M	63	165	94	CABG	13	24	MODS	Survived	£18050		+	
pHi≥7.32 at end of surgery												
F	68	170	70	Femoro-femoral arterial bypass	0	24	Wound dehiscence	Survived	£9600			

[a] Wound infection was determined according to the criteria of Peel and Taylor [33]

AAA, Abdominal aortic aneurysm; MVR, mitral valve replacement; AVR, aortic valve replacement; CABG, coronary artery by-pass grafts; TVR, tricuspid valve replacement; MODS, multiple organ dysfunction syndrome

This is supported by animal and, more recently, human data from various authors [4–8, 29]. Gastric intramucosal pH has been shown to monitor indirectly the adequacy of oxygen delivery to the splanchnic bed – an area that is particularly vulnerable to an inadequate CO. Although doubts have been raised regarding some of the assumptions made in the calculation of the pHi when normocapnia is not maintained or bicarbonate is administered [24] the tonomitor has repeatedly demonstrated its value as a clinical monitor [5, 10, 12, 13, 29]. The gastric tonometer is an easy to use, reliable and safe means of measuring peripheral perfusion [6–8] in a part of the body whose viability may be critical in the evolution of MOF [16, 17]. Early intervention is crucial as treatment using pHi as a therapeutic index was associated with a 25% increase in survival of patients admitted to the ITU with a normal pHi [13]. However, no benefit was demonstrated if the admission pHi was abnormal. It is clear that gut mucosal perfusion must be maintained in the operative period to achieve normality on admission to the intensive therapy unit. This requires an early pro-active approach to treatment, particularly since pHi may become abnoral early in the course of surgery.

A reduction in splanchnic blood volume is an immediate response to hypovolaemia as increased sympathetic tone diverts blood to more vital organs such as the brain, heart and kidneys. Price demonstrated that a 15–20% reduction in total blood volume was associated with no significant change in BP, CO or central blood volume in healthy volunteers and thus no reduction in perfusion of the vital organs (e.g. kidneys) although there was a 40% reduction in splanchnic blood volume [14]. Similarly, the patients who developed gut mucosal hypoperfusion in this study maintained their BP, CO and urine flow. However, they did show a reduction in SV and increase in HR consistent with hypovolaemia and a compensatory increase in sympathetic tone. Patients having major surgery are at particular risk of hypovolaemia. Pre-operative preparation may include prolonged starvation and the administration of enemas. During surgery there is bleeding and oedema formation due to tissue trauma, increased evaporation from exposed surfaces and from the lungs due to the administration of dry anaesthetic gases. It is well known that hypovolaemia can be marked before blood pressure falls [14, 15]. Yet blood pressure measurement remains the most commonly used method for the peri-operative assessment of cardiac function in the UK [30]. The patients that developed gut mucosal hypoperfusion also demonstrated a significant increase in RAP from baseline to the end of surgery. The measurement of a normal central venous or even pulmonary artery wedge pressure will not exclude hypovolaemia without assessing the dynamic effect of a fluid challenge since the venous system constricts in response to increased sympathetic tone [31]. Baek et al. demonstrated this point in high risk post-operative patients. Of the patients with high RAP measurements, more than half showed a decrease in RAP and PAWP in response to volume loading. Pulmonary and total vascular resistances fell and CO increased [32]. Since hypovolaemia is such a powerful factor in the reduction of gut mucosal perfusion it is likely that volume substitution will be most useful.

In conclusion, a low gastric pHi measured during the intra-operative period is associated with increased post-operative complications and cost. The oesophageal Doppler system used in combination with the gastric tonometer allowed both quantitative and qualitative assessment of cardiac function relatively non-invasively. Rather than the empirical approach used in 'goal directed therapy' it may be possible to augment patients' cardiorespiratory systems with the aim of maintaining gut mucosal perfusion and thus reducing post-operative morbidity, mortality and cost. We are investigating this 'gut directed therapy' in a prospective randomised study.

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