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C. Hamilton-Davies
M. G. Mythen
J. B. Salmon
D. Jacobson
A. Shukla
A. R. Webb

Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry

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C. Hamilton-Davies[1] (✉) · J. B. Salmon · D. Jacobson · A. Shukla · A. R. Webb
University College London Hospitals
Department of Intensive Care,
The Middlesex Hospital, Mortimer Street,
London W1N 8AA, UK

M. G. Mythen
Department of Anesthesiology,
Duke University Medical Center, Durham,
NC 27710, USA

[1] *Mailing address:*
Department of Anaesthesia,
Harefield Hospital,
Hill End Road,
Harefield,
Middlesex UB9 6JH, UK
FAX: +44 (1895) 82 89 65

Abstract *Objective:* The gastrointestinal tonometer, which allows measurement of gastrointestinal mucosal CO_2 and subsequent derivation of gut intramucosal pH (pHi), has been demonstrated to be a sensitive predictor of outcome following major surgery. Current theory suggests that the origin of the low pH may be hypovolaemia. This study was designed to compare the temporal sequence of changes in tonometric readings with invasive blood pressure, stroke volume, heart rate, lactate and arterial blood gas measurements during progressive haemorrhage.
Design: Observational healthy volunteer study.
Setting: Intensive care unit at University College London Hospitals.
Subjects: Six healthy, medically qualified volunteers.
Interventions: After obtaining baseline measurements, the subjects were progressively bled 25 % (range = 21–31 %) of their blood volume over a period of 1 h in two approximately equal aliquots. Equilibration was allowed for 30 min following the bleed, after which further measurements were made and the blood was then retransfused over 30 min.
Measurements and main results: There was no consistent change in any of the haemodynamic variables other than gastric intramucosal CO_2 : arterial CO_2 gap ($PiCO_2$ – $PaCO_2$) after removal of the first aliquot of blood, although five of the six subjects also demonstrated a fall in pHi. After removal of the second aliquot of blood, $PiCO_2$ – $PaCO_2$ gap and pHi continued to indicate a worsening gastric intramucosal acidosis; stroke volume, as measured by suprasternal Doppler, demonstrated a marked fall, while all other variables measured had not altered consistently or to such a degree as to elicit a clinical response or cause suspicion of a hypovolaemic state. On retransfusion, all variables returned towards baseline.
Conclusions: This study demonstrates the value of tonometry as an early monitor of hypovolaemia and highlights the shortcomings of other more commonly measured clinical variables.

Key words Tonometer · Haemorrhage · Hypovolaemia · Splanchnic

Introduction

The gastrointestinal tonometer allows derivation of gut intramucosal pH (pHi) and has been demonstrated to be a sensitive predictor of outcome following major surgery [1, 2]. Also, in 80 critically ill patients, Doglio et al. showed pHi was a valuable prognostic indicator of outcome and that failure to correct the pHi within 12 h significantly worsened the prognosis [3].

The pHi is derived from a modified Henderson-Hasselbalch equation; increased production of CO_2 from anaerobic metabolism in addition to that due to aerobic metabolism reduces pHi. It is also suggested that increased intramucosal CO_2 may result from the failure to clear CO_2 due to poor regional perfusion; Landow et al. correlated gastric pHi with lactate concentration, pH and O_2 saturation measured directly from the hepatic vein [4]. The aetiology of low pHi remains uncertain, although current theory suggests that hypovolaemia is one major cause [5] and both animal and human studies support this [6, 7]. It has been shown that a 15% fall in total blood volume results in a reduction of approximately 40% in splanchnic blood volume with no change in any of the commonly measured cardiovascular variables, such as blood pressure or heart rate [8]. A study by Mythen and Webb [9] showed that in fluid-loading patients prior to cardiopulmonary bypass both pHi and outcome improved, further strengthening the case for hypovolaemia as a major aetiological factor in the development of a low pHi.

This study was designed to compare the information obtained from gastrointestinal tonometry with blood pressure, heart rate, lactate, stroke volume and arterial blood gas measurements during controlled, progressive haemorrhage. In particular, the speed of detection of hypovolaemia was assessed.

Materials and methods

This study was approved by the UCL Hospitals ethics committee. Subjects gave written informed consent and the study was conducted on the intensive care unit at UCL Hospitals. An intensivist of at least senior registrar level was present throughout the study. Subjects were enrolled between June 1994 and June 1995 and were healthy males aged 21–37 years. They were starved for 8 h prior to instrumentation and received two 150 mg doses of ranitidine in the preceding 12 h, as described by Heard et al. [10].

Monitoring consisted of electrocardiography, intra-arterial blood pressure via a 20-G cannula placed in the radial artery of the non-dominant hand, pulse oximetry, stroke volume measured non-invasively by means of the suprasternal Doppler [11] (ODM 1, Deltex, Chichester, UK). In addition to these monitors, a gastrointestinal tonometer (Sigmoid Tonomitor, Tonometrics, Worcester, Mass., USA) was passed nasogastrically for assessment of gut pHi. Position of the tonometer was confirmed by rapid injection of air down a fine-bore nasogastric tube sutured to the tonometer tip and auscultation over the epigastrium with a stethoscope.

Table 1 Details of healthy volunteers

Subject	Age (years)	Weight (kg)	Maximum estimated percentage blood loss
1	33	85	27
2	31	95	24
3	31	70	26
4	32	78	23
5	37	100	21
6	28	70	31
Mean	32	83	25.3

A 14-G cannula was inserted under local anaesthesia in the cephalic vein of the non-dominant arm.

Baseline measurements of heart rate, blood pressure, pHi, lactate, stroke volume and base deficit were taken 30 min after instrumentation. Baseline measurements were recorded every 30 min until two consecutive pHi measurements were made within the fluctuation due to random error. Results were then averaged and the mean reading displayed as the baseline. The baseline was achieved in all subjects by three sets of readings. All blood gas analyses in arterial blood and tonometer saline were made using the Radiometer ABL 300 (Radiometer, Copenhagen, Denmark) blood gas analyser, which was 3-point calibrated using standard carbonated saline (Alkoton, Alko Diagnostic Corp, Holliston, Mass., USA).

The gastrointestinal intramucosal : arterial CO_2 gap was calculated at each time point by calculating the difference between the simultaneous measurement of arterial and tonometer saline CO_2 corrected for equilibration time using the correction factor supplied by Tonometrics. Measurements were repeated at 30-min intervals until a stable baseline (T_0) was established prior to haemorrhage. Blood was then removed from the 14-G cannula over 60 min, into citrated blood collection bags, with sets of measurements made at 30 and 60 min immediately after termination of haemorrhage (T_1). A 30-min equilibration time was then permitted, after which a further set of measurements was made. Retransfusion of the removed blood was commenced following this set of measurements at point T_2 over a period of 30 min, after which a final set of data was recorded. The data are displayed graphically (Figs. 1–3) with baseline (T_0) readings compared with readings after removal of both aliquots of blood following termination of haemorrhage (T_1) by means of repeated measures ANOVA.

Results

Details of the six healthy subjects are given in Table 1. Blood volume changes were based on an estimated blood volume of 70 ml/kg. Readings subsequent to establishment of baseline and baseline averages for all subjects are given in Table 2.

Following the removal of the first aliquot of blood, the only variables to show any consistent change were pHi and gastrointestinal intramucosal : arterial PCO_2 gap, with the latter showing a significant increase from baseline ($p < 0.01$) (Fig. 1). After removal of the second aliquot of blood T_1 (mean = 25% of circulating blood volume, SD = 3.5%) pHi and PCO_2 gap continued to worsen, demonstrating a significant change ($p < 0.01$) from baseline (T_0). The only other significant change

Table 2 Individual data on healthy volunteers

Time (mins)	Subject					
	1	2	3	4	5	6
Heart rate (bpm)						
30 (base)	64	62	61	59	77	73
60	77	64	63	58	75	65
90	78	67	63	61	77	61
120	74	58	61	64	80	61
150	83	52	65	59	79	72
Systolic BP (mm Hg)						
30 (base)	128	126	135	120	138	168
60	168	156	158	154	158	145
90	153	146	140	137	150	65
120	130	132	126	118	136	140
150	147	136	130	140	160	160
Stoke volume (ml)						
30 (base)	98	110	106	99	85	72
60	98	113	103	92	85	53
90	74	113	80	85	84	35
120	96	100	108	95	72	53
150	129	127	100	110	92	72
pHi						
30 (base)	7.36	7.383	7.446	7.41	7.38	7.36
60	7.223	7.359	7.41	7.36	7.386	7.304
90	7.236	7.324	7.401	7.33	7.354	7.24
120	7.244	7.368	7.369	7.36	7.297	7.28
150	7.37	7.293	7.407	7.42	7.358	7.28
$PiCO_2$ – $PaCO_2$ (gap) (kPa)						
30 (base)	5.70–5.13 (0.57)	6.41–5.51 (0.90)	4.98–5.44 (– 0.46)	5.81–5.68 (0.13)	5.84–5.77 (0.07)	6.13–5.52 (0.60)
60	6.09–5.20 (0.89)	8.97–5.49 (3.48)	5.66–5.48 (0.18)	6.40–5.64 (0.76)	6.08–5.49 (0.59)	7.13–5.47 (1.66)
90	6.91–5.41 (1.50)	8.68–5.52 (3.16)	5.74–5.21 (0.53)	6.85–5.37 (1.48)	6.75–5.52 (1.23)	7.65–4.66 (2.99)
120	6.04–5.04 (1.00)	8.33–5.23 (3.10)	5.83–4.89 (0.94)	6.39–5.74 (0.65)	7.56–5.63 (1.93)	7.54–5.22 (2.32)
150	7.61–5.43 (2.18)	6.20–5.49 (0.17)	5.86–5.59 (0.27)	5.31–5.20 (0.11)	6.72–5.69 (1.03)	7.84–5.51 (2.33)
Base excess						
30 (base)	2.1	0.8	0.7	1.9	2	1.4
60	2.4	1.3	1.3	2.1	1.9	1.9
90	2.3	1.7	1.4	1.6	1.8	0.6
120	1.9	1.4	0.4	1.6	1.9	1.5
150	1.5	2.4	2.1	0.9	2.1	2.5
Lactate (mmol/l)						
30 (base)	1.3	0.8	0.6	1.2	1	1.1
60	1.4	0.7	0.8	1	0.8	0.9
90	1.6	0.6	0.7	1	0.8	0.9
120	1.5	0.8	0.7	0.8	0.9	1
150	1	0.6	0.6	0.9	0.7	0.8

was a fall in stroke volume by a mean of 16.5 ml (SD = 15 ml) ($p < 0.01$). Base deficit, lactate, heart rate and blood pressure failed to demonstrate either a significant or a consistent change, with all but one value remaining in the range which would fail to prompt therapeutic intervention. On retransfusion of the blood, the abnormalities observed in the pHi and PCO_2 gap tended to return to normal except in subject 2, where both pHi and the PCO_2 gap continued to worsen.

Only one subject demonstrated a clinically significant fall in blood pressure after removal of 31 % of his blood volume. The fall at this point was precipitous, requiring rapid blood replacement. There was no preceding or concurrent rise in heart rate, as might have been expected. Resuscitation was successful, with no sequelae. Of note, the blood pressure returned to baseline after only 200 ml of blood had been reinfused.

Discussion

This study clearly reiterates the poor warning of hypovolaemia given by the routinely used perioperative monitors of heart rate and blood pressure [12]. Central

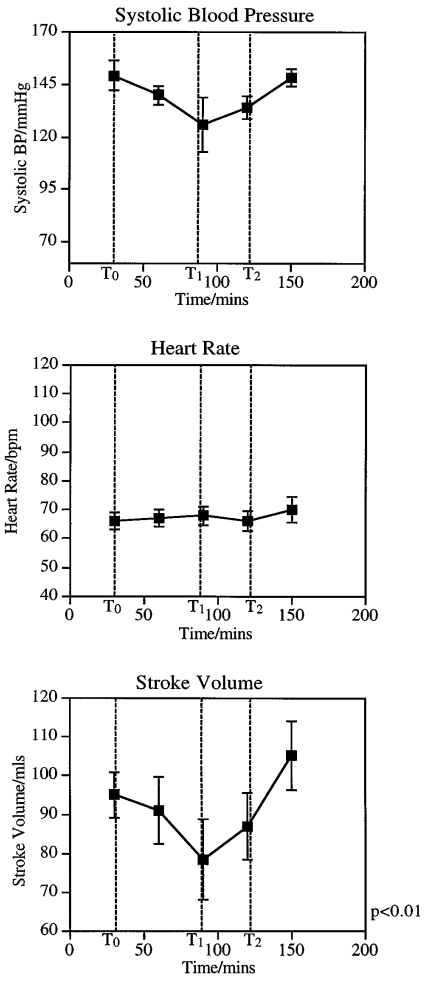

Fig. 1 The haemodynamic response to progressive hypovolaemia in healthy volunteers. T_0 baseline, T_1 end of bleed, T_2 prior to retransfusion. p value = significance of end of bleed relative to baseline as derived using repeated measures ANOVA

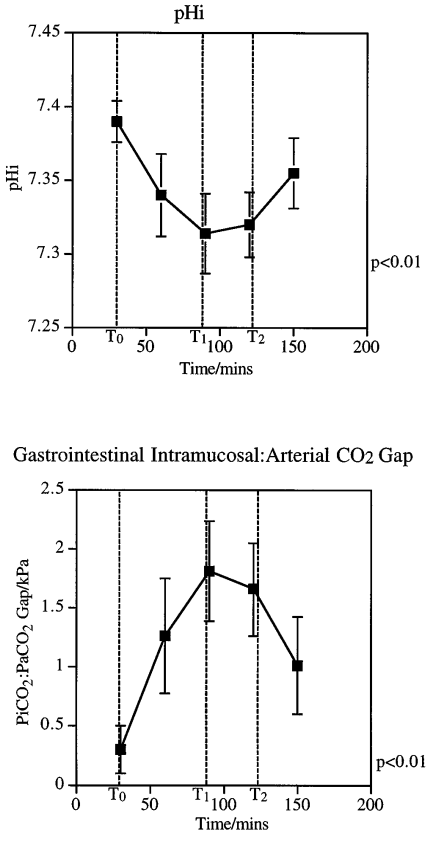

Fig. 2 The tonometric response to progressive hypovolaemia in healthy volunteers. T_0 baseline, T_1 end of bleed, T_2 prior to retransfusion. p value = significance of end of bleed relative to baseline as derived using repeated measures ANOVA. Tonometric gastrointestinal intramucosal : arterial CO_2 gap also shows significant fall after removal of first aliquot of blood

venous pressure monitoring has already been demonstrated to be an unreliable indicator of volume status in conditions of increased vascular tone, such as high catecholamine states or post-surgical hypothermia [13]. In addition to this, central catheter placement is not without morbidity [14].

In spite of the mean rise in heart rate of 17%, in no subject did the absolute rate constitute a clinically significant tachycardia. Subject 6 showed no change in blood pressure until more than 30% of his blood volume had been removed, at which point the pressure fell dramatically over seconds, requiring immediate retransfusion. Prior to this point, the subject stated that he had no symptoms of hypovolaemia, despite the alterations in pHi and PCO_2 gap and the noted fall in stroke volume. Had this situation occurred in the face of rapid ongoing surgical bleeding, the outcome may well have been fatal. One possible explanation for this failure of the heart rate to compensate for the fall in stroke volume is that the subject did not demonstrate a reasonable autonomic response. However, there was nothing in the subject's medical history to make us suspect autonomic disease. The oesophageal Doppler has been shown to be sensitive to changes in left ventricular filling [15] but has not been compared to other techniques, such as intrathoracic blood volume or transthoracic echo in detection of preload changes. It is possible that these techniques may offer earlier warning of reduced preload, but further investigation is needed.

Base excess and lactate measurements gave no indication of the acute hypovolaemic state of the subjects, probably indicating that the time course for these to become abnormal is longer than the period of the study. Current theory points to the gut as the first area to suffer hypoperfusion as a result of acute hypovolaemia [8, 16, 17]. If lactate production or localised acidosis occurs in this region, it will be subjected to a large dilutional

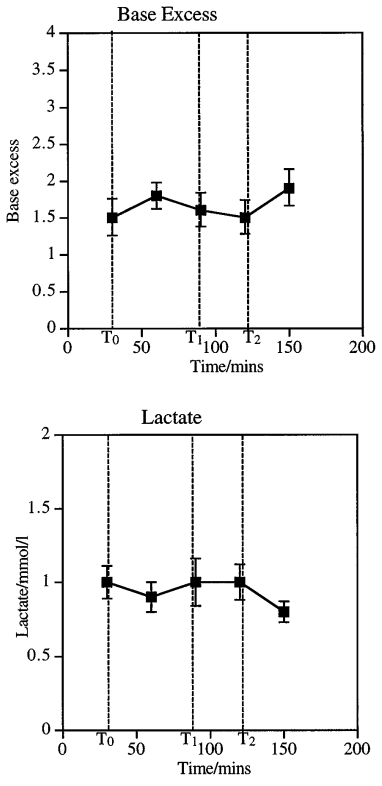

Fig. 3 The base deficit and lactate response to progressive hypovolaemia in healthy volunteers. T_0 baseline, T_1 end of bleed, T_2 prior to retransfusion. p value = significance of end of bleed relative to baseline as derived using repeated measures ANOVA

factor during measurement of whole body arterial lactate or base deficit. Also lactate is metabolised largely by the liver, and as long as perfusion to this organ is preserved, local changes in gut lactate production will be masked until production outstrips hepatic metabolism.

In all subjects the PCO_2 gap was the most sensitive predictor of hypovolaemia and was the only measure to increase in all subjects after removal of the first aliquot of blood. This agrees with work by Schlichtig [18]. One of the criticisms of gastrointestinal pHi as a measure of gastrointestinal mucosal perfusion has been that arterial bicarbonate can be substituted for intramucosal bicarbonate in a Henderson-Hasselbalch equation to determine pHi [19]. It is difficult to follow this concept in an organ that is supposedly underperfused at the time when tonometry is supposed to be most beneficial, and when bicarbonate would be expected to be consumed as a buffer. Despite these arguments, direct measurement of pHi has shown good correlation with tonometrically derived pHi [20, 21]. However, derivation of pHi seems to add nothing to the information obtained from the $PiCO_2 - PaCO_2$ gap.

pHi measurement proved to be the second best indicator of hypovolaemia and had fallen in five of the six subjects after removal of the first aliquot of blood, although this value fell below 1 SD of the mean in only two of the six subjects. The ability of the pHi measure to identify a numerically abnormal figure in only four of the six subjects after removal of both aliquots of blood may result from the 30-min CO_2 equilibration time required with the tonometer. This may be rectified, to a large degree, by the introduction of the continuous reading gas-filled Tonocap (Datex, Helsinki, Finland), which purports to give a near real-time indication of intramucosal PCO_2 levels.

Other techniques are available for monitoring splanchnic perfusion, such as Duplex Doppler, indocyanine green clearance, measurements of lignocaine metabolite levels, etc. However, these techniques require highly specialised equipment, are cumbersome and would severely hinder the surgeon during abdominal or thoracic procedures and thus are best used in non-operative situations, such as in the intensive care unit.

Gastrointestinal tonometry clearly represents a useful addition to currently used perioperative monitors of hypovolaemia. This study demonstrates that $PiCO_2$ measurement is a relatively sensitive indicator of hypovolaemia. Unlike in previous studies in surgical patients or critically ill patients, we have been able to demonstrate that tonometry can detect hypovolaemia before there are any symptoms.

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