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Baroreflex impairment and morbidity after major surgery

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Abstract

Background: Baroreflex dysfunction is a common feature of established cardiometabolic diseases that are most frequently associated with the development of critical illness. Laboratory models show that baroreflex dysfunction impairs cardiac contractility and cardiovascular performance, thereby increasing the risk of morbidity after trauma and sepsis. We hypothesized that baroreflex dysfunction contributes to excess postoperative morbidity after major surgery as a consequence of the inability to achieve adequate perioperative tissue oxygen delivery.

Methods: In a randomized controlled trial of goal-directed haemodynamic therapy (GDT) in higher-risk surgical patients, baroreflex function was assessed using the spontaneous baroreflex sensitivity (BRS) method via an arterial line placed before surgery, using a validated sequence method technique (one beat lag). The BRS was calculated during the 6 h postoperative GDT intervention. Analyses of BRS were done by investigators blinded to clinical outcomes. The primary outcome was the association between postoperative baroreflex dysfunction (BRS <6 mm Hg s^{-1}, a negative prognostic threshold in cardiovascular pathology) and early postoperative morbidity. The relationship between baroreflex dysfunction and postoperative attainment of preoperative indexed oxygen delivery was also assessed.

Results: Patients with postoperative baroreflex dysfunction were more likely to sustain infectious {relative risk (RR) 1.75 [95% confidence interval (CI): 1.07–2.85], *P*=0.02} and cardiovascular morbidity [RR 2.39 (95% CI: 1.22–4.71), *P*=0.008]. Prolonged hospital stay was more likely in patients with baroreflex dysfunction [unadjusted hazard ratio 1.62 (95% CI: 1.14–2.32), log-rank *P*=0.004]. Postoperative O_2 delivery was 36% (95% CI: 7–65) lower in patients with baroreflex dysfunction in those not randomly assigned to GDT (*P*=0.02).

Conclusions: Baroreflex dysfunction is associated with excess morbidity, impaired cardiovascular performance, and delayed hospital discharge, suggesting a mechanistic role for autonomic dysfunction in determining perioperative outcome.

Clinical trial registration: ISCRTN76894700.

Key words: autonomic nervous system; baroreflex; postoperative complications

Established cardiometabolic disease, including heart failure and diabetes mellitus, is strongly associated with increased risk of perioperative morbidity. Autonomic dysfunction is frequently subclinical and a feature of preoperative co-morbidities commonly associated with excess postoperative morbidity. Baroreflex autonomic dysfunction is an independent predictor of

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Editor's key points

- Autonomic dysfunction is associated with baroreflex impairment or failure.
- This study found that baroreflex impairment was associated with tissue ischaemia and postoperative complications.
- Autonomic dysfunction thus seems to contribute to postoperative morbidity.
- Interventions that restore or protect baroreflex function may improve outcome.

morbidity and mortality during critical illness.[1 2] Several studies have found that baroreflex sensitivity values <6 ms mm Hg^{-1} are associated with poorer outcomes.[3–7] In part, this may reflect diminished parasympathetic (vagal) activity associated with baroreflex dysfunction.[8] Laboratory and clinical epidemiological data show that augmented vagal activity limits inflammation and organ injury, including cardiovascular morbidity and mortality.[9 10] In addition, we have shown in experimental models that baroreflex dysfunction promotes cardiac oxidative stress, thereby reducing inotropic reserve and impairing cardiac function.[11] Our translational laboratory studies have also suggested a mechanistic link between parasympathetic dysfunction, impaired cardiac contractility, and excess postoperative morbidity.[11]

As part of a randomized controlled trial exploring whether postoperative morbidity might be reduced by ensuring that individualized preoperative oxygen delivery was maintained,[12] we prospectively tested the hypothesis that baroreflex dysfunction plays a role in the development of postoperative morbidity. We postulated, on the basis of our laboratory and complementary translational clinical findings,[11] that baroreflex dysfunction contributes to impaired perioperative cardiac performance, thereby preventing postoperative achievement of preoperative oxygen delivery, which we have shown is associated with excess complications.

Methods

We previously conducted a multicentre, randomized, double-blinded trial (trial registration: ISRCTN76894700) at four hospitals in the UK.[12] A prespecified analysis plan was published before trial completion at www.ucl.ac.uk/anaesthesia/trials. Adult patients undergoing major elective surgery expected to last for at least 2 h were eligible for recruitment provided they satisfied the following high-risk criteria: (i) ASA physical status ≥III; (ii) surgical procedures with an estimated or documented risk of postoperative morbidity (as defined by the PostOperative Morbidity Survey) exceeding 50%; and (iii) modified Revised Cardiac Risk Score ≥3,[13] as defined by age ≥70 yr, a history of cardiovascular disease (myocardial infarction, coronary artery disease, cerebrovascular accident, ECG evidence for established cardiac pathology), cardiac failure, poor exercise capacity (anaerobic threshold <11 ml kg min^{-1} as assessed by cardiopulmonary exercise testing), renal impairment (serum creatinine ≥130 μmol l^{-1}), or diabetes mellitus. Intraoperative management was undertaken by consultant anaesthetists, according to their usual practice. Patients were randomly assigned to either postoperative goal-directed haemodynamic therapy (GDT) aimed at restoring or preserving each patient's individualized preoperative oxygen delivery or protocolized care in a 1:1 ratio, stratified by operation type (STATA software). Central random allocation was undertaken, with assignments concealed by envelope. Patients, attending physicians, and critical care staff were blinded to the patients' treatment assignments. Apart from the trial statistician and the data-monitoring committee, all treating physicians and other investigators remained blinded to the trial results until follow-up was completed.

Procedures

A radial arterial line was inserted before surgery to permit calibrated cardiac output monitoring (LiDCO*Plus*; LiDCO Ltd, London, UK).[14] Haemodynamic data were recorded during surgery and available for use by operating room staff. The intervention period commenced once the patient reached the critical care environment after surgery and continued for 6 h. Haemodynamic management in both randomization arms (i.e. GDT- and protocolized control group-allocated patients) were managed exclusively by research staff during the postoperative study period. Before the intervention, in all patients, the LiDCO lithium-based sensor was recalibrated to ensure accurate measurement of cardiac output. Oxygenation (peripheral oxygen saturation ≥94%), haemoglobin (>80 g l^{-1}), core temperature (≥36°C), heart rate (<100 beats min^{-1}), and mean arterial pressure (60–90 mm Hg), maintained using an α_1-adrenoceptor agonist as required, were protocolized standard-of-care measures. Crystalloid fluid (compound sodium lactate) was administered at 1 ml kg^{-1} h^{-1}, with additional fluid administered according to protocol. Postoperative analgesia was provided by thoracic epidural or patient-controlled opiate analgesia. The goal-directed therapy intervention group patients received i.v. fluid and inotropic therapy according to an algorithm (Supplementary data, Fig. S1) targeting each patient's individualized preoperative oxygen delivery value. If the preoperative oxygen delivery target was not met after the first hour of stroke volume optimization using gelatine colloid, an i.v. infusion of dobutamine (1–20 μg kg min^{-1} via central venous catheter) was commenced but strictly limited by heart rate parameters (<100 beats min^{-1}, ≤25% from baseline heart rate at the start of the intervention period, or both). A syringe with saline or dobutamine, unidentifiable to all staff other than research personnel, was connected via extension tubing to the central venous catheter of all patients. Cardiac output monitoring was not used in the protocolized standard-of-care group, but all variables were recorded. Calculation of oxygen delivery values was delayed until the end of the trial in the control group. All other aspects of clinical care were managed by intensive care unit clinicians, who could alter any aspect of patient care provided the site principal, chief investigator, or both were informed if haemodynamic management during the study intervention period was involved directly. Postoperative management adhered to enhanced recovery hospital protocols. Antibiotic use beyond prophylactic administration (i.e. >24 h after surgery) was a deviation from normal postoperative care.

Determination of baroreflex sensitivity

Spontaneous baroreflex sensitivity (BRS) was measured in surgical patients from the intra-arterial pressure recording[15] (Fig. 1A) obtained immediately before surgery and for 6 h after surgery using a validated sequence method technique (one beat lag).[16] Baroreflex events across three or more consecutive beats were identified where the systolic blood pressure and pulse interval changed in tandem and were highly correlated (r>0.85). Sequential changes in systolic pressures that occurred with directionally opposite changes in pulse interval were excluded from analysis,

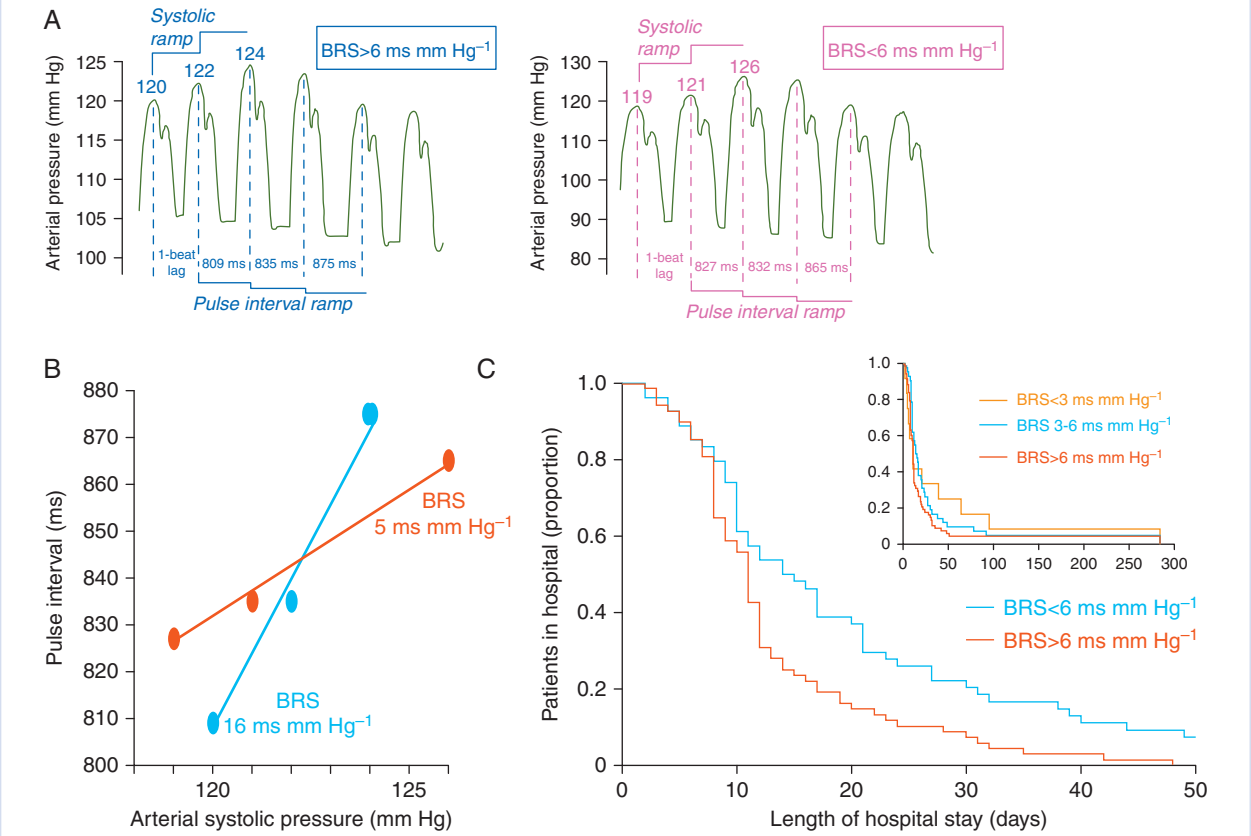

Fig 1 Baroreflex analysis and hospital stay. (A) Schematic diagram showing measurement and calculation of baroreflex sensitivity (BRS). Using a validated sequence method technique (one beat lag), a baroreflex event is defined by three or more consecutive beats where the systolic blood pressure (SBP) and pulse interval (PI) changed in tandem and are highly correlated (r>0.85). (B) The slope of the linear regression line of PI against SBP generates the BRS of each event in milliseconds per millimetre of mercury. (B) Baroreflex sensitivity <6 ms mm Hg^{-1} was associated with prolonged hospital stay [hazard ratio:1.62 (95% confidence interval: 1.14–2.32); P=0.004; unadjusted log-rank analysis]. Inset plot highlights length of stay in patients with BRS <3 ms mm Hg^{-1}.

as they do not represent physiological baroreflex responses. The slope of the linear regression line of pulse interval against systolic blood pressure provided the BRS of each event in in milliseconds per millimetre of mercury. Preoperative BRS was determined as the median slope value of all detected events. Median BRS values ≤6 mm Hg s^{-1} for each hour of the postoperative period were defined as abnormal (baroreflex dysfunction), because BRS values ≤6 ms mm Hg^{-1} have been consistently associated with negative outcomes in preceding population-based studies[3 5 17–20] We also assessed the incidence of markedly depressed baroreflex sensitivity (≤3 ms mm Hg^{-1}), which has previously identified patients at the most extreme risk of death after myocardial infarction.[5 21] To avoid bias, all baroreflex analyses were undertaken by investigators blinded to clinical outcomes.

Clinical outcomes

Morbidity was collected prospectively by assessors blinded to the intervention and BRS data using the PostOperative Morbidity Survey, which assesses all-cause morbidity throughout the preceding 24 h period.[22] Failure to recover normally during the postoperative period was defined using the Clavien–Dindo scale, with ≥grade 2 complications representing clinically important deviations from projected postoperative recovery.[23] Thus, infectious morbidity was defined by microbiological confirmation, a deviation from normal postoperative care requiring antibiotic use beyond local, standardized prophylactic antibiotic therapy (i.e. beyons 24 h after surgery), or both. The primary end point was all-cause morbidity (Clavien–Dindo ≥grade 2 complications) on postoperative day 2. Secondary outcomes were infectious morbidity on postoperative day 2, mean postoperative oxygen delivery (expressed as a percentage of each patient's preoperative oxygen delivery target), and length of hospital stay (adjusting for hospital deaths).

Statistical methods

Power analysis was based on the results of the POM-O trial, which showed that ~54% patients sustained significant morbidity (≥grade 2, Clavien–Dindo scale)[23] by postoperative day 2.[12] On the basis of our previous work,[11] we estimated that significant morbidity would be >1.5 times more likely to occur in patients with baroreflex dysfunction, which occurs in ~35% patients. Thus, the sample size required for an α-value of 0.05 and 80% power would be ≥119 patients. For continuous data, normality of distribution was assessed and, where appropriate, analysed with balanced-design ANOVA [taking into account BRS <6 or >6 ms mm Hg^{-1}, time point (Supplementary data, Fig. S2), and

randomization arm]. Non-parametric data were analysed with the Mann–Whitney *U*-test. Relative risk (RR) and 95% confidence interval (CI) were estimated. Length of hospital stay was estimated using the Kaplan–Meier method and analysed using the Cox proportional hazard model. Multivariate analysis was undertaken to establish whether there was a significant relationship between postoperative baroreflex dysfunction and perioperative factors associated with outcome,modulation of arterial baroreflex regulation, or both, taking into account preoperative [absolute preoperative BRS value, albumin, diabetes mellitus, cardiovascular morbidity (incorporating history of ischaemic heart disease, heart failure, atrial fibrillation, stroke, and anaerobic threshold <11 ml kg min^{-1}), sex, age, and type of surgery] and intraoperative factors (blood transfusion, lactate at end of the operation, epidural use, and duration of operation), using a hierarchical, one-way forward switching model.[24] A full set of references supporting the choice of these factors is supplied in Supplementary data, Table S1. A similar multivariate analysis was undertaken to explore the relationship between BRS and oxygen delivery after surgery, again using a hierarchical, one-way forward switching model.[24] All reported *P*-values are two sided. Statistical analyses were performed using NCSS 8 (Kaysville, UT, USA). Median values (interquartile range) are presented, unless stated otherwise. Significance was accepted at $P \leq 0.05$.

Results

Baroreflex dysfunction in higher-risk surgical patients

Baroreflex sensitivity was calculated throughout the whole perioperative period in 122/204 PostOperative Morbidity–Oxygen delivery (POM-O) trial patients (Supplementary data, Fig. S1). Preoperative recordings spanned a median duration of 39 min (IQR: 31–55), capturing a median of 162 spontaneous events ((IQR: 90–271). Postoperative recordings spanned the entire 6 h intervention period in all patients, with a median event rate of 174 h^{-1}. Baroreflex dysfunction, as defined by BRS ≤6 ms mm Hg^{-1}, was present in 54 of 122 patients (44%); clinical characteristics are shown in Table 1. We identified 13 patients (11%) with BRS values <3 mm Hg s^{-1}, a threshold associated with particularly poor prognosis in other disease states.[5 21 25]

Patients with preoperative BRS <6 mm Hg s^{-1} were more likely to have postoperative BRS <6 mm Hg s^{-1} [RR 2.6 (95% CI: 1.6–4.1), *P*=0.003]. Given that intraoperative management and surgery associated with specific anaesthetic interventions (e.g. hepatobiliary patients receiving epidural analgesia)[26] are known to affect baroreflex regulation, we also assessed which factors were associated with higher BRS values at the end of the postoperative intervention period. We performed a multivariable analysis taking into account co-morbidities associated with autonomic dysfunction (diabetes mellitus, cardiac disease) and intraoperative management (Table 2). We found that preoperative BRS (*P*=0.0002; Supplementary Data, Fig. S2) was the only perioperative factor associated with postoperative BRS.

Perioperative cardiovascular performance

Postoperative achievement of the individualized oxygen delivery target was associated with higher BRS and randomization to goal-directed therapy, taking into account age, sex, BMI, type of surgery, and diabetic and cardiovascular morbidity (Table 2B). During surgery, similar volumes of fluid and requirement for pressor (norepinephrine) support were observed in patients with normal BRS and baroreflex dysfunction, irrespective of which trial arm they were subsequently assigned to randomly (Table 3). The proportion of patients with baroreflex dysfunction was similar between study arms (Table 3). Although patients with baroreflex dysfunction were more likely to receive packed red cells during surgery, haemoglobin concentrations were similar between groups by the end of surgery and before the haemodynamic intervention. Baroreflex dysfunction was associated with higher plasma lactate concentration, which persisted throughout the postoperative intervention period. After surgery, oxygen delivery was 39% (95% CI: 11–68; *P*=0.001) lower than the preoperative target in patients with baroreflex dysfunction not randomized to GDT (Table 3; Supplementary Data, Fig. S2).

Table 1 Baseline characteristics for PostOperative Morbidity–Oxygen delivery (POM-O) trial patients in whom baroreflex sensitivity was calculated before and after surgery. Data are presented as the mean (SD) or *n* (%). [a]The percentage of patients per group within each surgical category or hospital. BRS, baroreflex sensitivity

Characteristic	BRS >6 ms mm Hg^{-1} (*n*=68)	BRS <6 ms mm Hg^{-1} (*n*=54)
Age (yr)	67 (8)	68 (8)
Male	38 (56)	34 (63)
BMI (kg m^{-2})	26.1 (4.1)	28.5 (5.5)
Haemoglobin (g l^{-1})	123 (14)	129 (19)
Albumin (g dl^{-1})	43 (4)	41 (5)
Malignancy [*n* (%)]	54 (79)	38 (70)
Creatinine >130 μmol l^{-1}	2 (3)	5 (9)
Diabetes mellitus [*n* (%)]	14 (21)	14 (26)
History of cardiovascular disease [*n* (%)]	47 (69)	42 (77)
Surgical procedure[a] [*n* (%)]		
Upper gastrointestinal	14 (54)	12 (46)
Liver resection/ hepatobiliary	37 (65)	20 (35)
Lower gastrointestinal	11 (48)	12 (52)
Vascular	6 (38)	10 (62)
Hospital[a]		
University College London Hospital	24	21
Royal Free Hospital	36	19
Royal London Hospital	2	4
St George's Hospital	6	10

Baroreflex dysfunction and postoperative outcome

Patients with baroreflex dysfunction sustained more episodes of significant (Clavien–Dindo grade ≥2) morbidity by postoperative day 2 [RR: 1.68 (95% CI: 1.19–2.44), *P*=0.003]. Baroreflex dysfunction was associated with more infectious [RR: 1.75 (95% CI: 1.07–2.85), *P*=0.02] and cardiovascular morbidity [RR: 2.39 (95% CI: 1.22–4.71), *P*=0.008] by postoperative day 2 (Table 4). Throughout the perioperative stay, fewer patients with normal BRS sustained (≥grade 2) Clavien–Dindo-defined morbidity [RR: 0.73 (95% CI: 0.58–0.92), *P*=0.009] Prolonged hospital stay was more likely in patients with baroreflex dysfunction [unadjusted hazard ratio: 1.62 (95% CI: 1.14–2.32), log-rank *P*=0.004; Fig. 1]. Cox regression analysis identified baroreflex dysfunction [RR: 0.54 (95% CI: 0.35–0.83)], achievement of preoperative oxygen delivery target [RR: 0.65 (95% CI: 0.43–0.98)], and type of surgery [RR: 0.41 (95% CI: 0.20–0.86)] as significant predictors of prolonged hospital stay.

Table 2 Baroreflex dysfunction and postoperative oxygen delivery. Multivariate analysis assessing perioperative factors associated with postoperative BRS (A) and achievement of preoperative oxygen delivery target (B). BRS, baroreflex sensitivity; $D_{O_2}I$, indexed oxygen delivery; GI, gastrointestinal

Independent variable	Regression coefficient β	Standard error	T-value	P-value	Reject H0 (α<0.05)
A. Perioperative factors associated with postoperative BRS					
Intercept	3.1844	4.6746	0.681	0.50	No
Preoperative					
Age	−0.0186	0.0373	−0.498	0.62	No
Sex	−0.5929	0.6191	−0.958	0.34	No
BMI	−0.0589	0.0622	−0.948	0.35	No
Preoperative albumin	0.1123	0.0664	1.693	0.09	No
Cardiac morbidity	−0.4401	0.6562	−0.671	0.5	No
Diabetes mellitus	−0.7982	0.7933	−1.006	0.32	No
Hepatobiliary surgery	1.4997	0.8567	1.751	0.08	No
Upper GI surgery	−0.5455	0.9864	−0.553	0.58	No
Vascular surgery	1.7551	1.5509	1.132	0.26	No
Preoperative BRS	0.4745	0.1242	3.82	0.0002	Yes
Intraoperative					
Duration of operation	−0.0022	0.0033	−0.663	0.50	No
Epidural	1.3221	0.7236	1.827	0.07	No
Blood transfusion	−1.211	0.7136	−1.697	0.09	No
Lactate, end operation	−0.4192	0.2649	−1.582	0.11	No
Vasopressor	−0.7537	0.7562	−0.997	0.32	No
Postoperative					
Trial intervention	−0.0871	0.5905	−0.147	0.88	No
B. Factors positively associated with higher oxygen delivery (% of preoperative $D_{O_2}I$ value)					
Intercept	76.5974	34.8664	2.197	0.03	Yes
Age	0.1571	0.4755	0.33	0.74	No
Postoperative BRS >6 ms mm Hg^{-1}	16.8889	8.1576	2.07	0.04	Yes
Cardiac morbidity	−4.7209	8.8376	−0.534	0.59	No
Diabetes mellitus	−7.1517	9.4787	−0.755	0.45	No
Lactate, end operation	1.6747	3.1388	0.534	0.59	No
Goal-directed therapy	17.9531	7.7602	2.313	0.02	Yes
Surgery type	3.2863	9.2815	0.354	0.72	No

Discussion

Our data show that patients with baroreflex dysfunction undergoing elective major surgery sustain more morbid events (characterized by cardiac and infectious complications) and experience prolonged hospitalization. These data suggest, for the first time, that baroreflex autonomic dysfunction may contribute to the development of postoperative morbidity. Baroreflex dysfunction was not more prevalent in co-morbidities linked to autonomic dysfunction such as diabetes mellitus. This is perhaps unsurprising given the emerging link between autonomic dysfunction and a range of cardiometabolic pathologies,[27] coupled with the recognition that cardiovascular and autonomic function are frequently impaired in patients presenting for cancer surgery.[28]

Established cardiac dysfunction is strongly associated with excess postoperative morbidity and mortality.[29] Autonomic dysfunction is frequently observed in established cardiac failure, characterized by upregulation of G-protein-coupled receptor (GPCR) kinase-2, which inhibits procontractile signalling by phosphorylating the β-adrenoreceptor and inducing β-arrestin binding.[30 31] Impaired baseline function and inotropic responses in laboratory models of baroreflex autonomic dysfunction are consistent with impaired common GPCR signalling pathways underlying this defect.[11] Cardiovascular compromise is likely to contribute to the higher mortality observed in rats with baroreflex dysfunction after acute endotoxaemia.[32] In our study, patients with baroreflex dysfunction had a higher venous lactate concentration at the end of the intraoperative period, suggesting that tissue dysoxia might have developed in part as a consequence of lower oxygen delivery. Infectious complications after tissue trauma are likely to be exacerbated by reduced oxygen delivery and strongly linked to subsequent mortality.[33] Postoperative oxygen delivery was lower in patients with baroreflex dysfunction not randomized to GDT, and failure to achieve preoperative oxygen delivery was associated with lower BRS during the intervention period. Despite GDT, higher venous lactate concentrations persisted in patients with baroreflex dysfunction; these patients were more likely to acquire early postoperative morbidity, necessitating interventions that deviated from normal surgical care. Our exploratory analysis of haemodynamic performance shows that sustained baroreflex dysfunction (i.e. preoperative BRS <6 ms mm Hg^{-1} persisting into the postoperative period) occurs regardless of haemodynamic management. These findings mirror those of recent haemodynamic trials in sepsis, where targeting many aspects of oxygen delivery that were broadly similar to those pursued in the POM-O trial failed to improve outcome. These data therefore provide a new line of enquiry that contributes to the debate about why goal-directed haemodynamic management in critical illness does not appear to benefit patients with established, early sepsis or systemic inflammation.[34]

Defects in baroreflex function may occur in afferent neurons transmitting the information from baroreceptors, brainstem

Table 3 Perioperative haemodynamics and fluid therapy. Data are presented as the mean (SD), median (quartiles), or *n* (%). *P*-values refer to two-way ANOVA comparing haemodynamic intervention × baroreflex type. *Comparisons between haemodynamic therapy groups. †Significant difference for interaction between haemodynamic intervention × baroreflex type. ‡Significant difference between baroreflex types (BRS >6 *vs* <6 ms mm Hg^{-1}). All patients received 1 ml kg^{-1} h^{-1} Ringers lactate crystalloid solution after surgery. BRS, baroreflex sensitivity; $D_{O_2}I$, indexed oxygen delivery; Hb, haemoglobin

Parameter	Control arm		Goal-directed therapy		*P*-value
	BRS >6 ms mm Hg^{-1} (*n*=31)	BRS <6 ms mm Hg^{-1} (*n*=22)	BRS >6 ms mm Hg^{-1} (*n*=37)	BRS <6 ms mm Hg^{-1} (*n*=32)	
Preoperative					
Haemoglobin (g l^{-1})	126 (15)	132 (11)	121 (14)	126 (20)	0.71
Cardiac output (ml min^{-1})	6.1 (1.5)	6.8 (1.6)	5.9 (2.0)	6.2 (1.8)	0.62
$D_{O_2}I$ (ml min^{-1} kg^{-1})	550 (157)	607 (140)	516 (166)	559 (171)	0.26
Intraoperative					
Crystalloid (ml kg^{-1} h^{-1})	13.3 (8.2)	9.1 (2.9)	10.7 (4.9)	10.5 (5.7)	0.22
Colloid (ml kg^{-1} h^{-1})	2.4 (0–5.4)	2.3 (0.7–3.6)	1.8 (0–3.7)	1.6 (0–4.1)	0.68
Blood [*n* (%)]	2 (6)	8 (36)‡	7 (19)	11 (34)‡	0.02
Hb (g l^{-1}), end of operation	105 (11)	108 (18)	103 (13)	110 (18)	0.31
Vasopressor [*n* (%)]	6 (19)	5 (23)	6 (16)	8 (25)	0.82
Lactate (mmol l^{-1})	1.6 (1.0)	2.9 (1.3)*‡	2.0 (1.1)	2.3 (1.6)‡	0.03‡; <0.01*
Cardiac output (ml min^{-1})	5.6 (2.5)	6.3 (3.1)	5.2 (2.3)	5.2 (1.4)	0.40
$D_{O_2}I$ (ml min kg^{-1})	483 (197)	518 (255)	470 (223)	451 (147)	0.48
Postoperative					
Colloid (ml kg^{-1} h^{-1})	1.8 (1.6)	2.0 (1.8)	3.0 (1.6)*	2.9 (2.1)*	0.005*
Blood [*n* (%)]	3 (10)	6 (27)	7 (19)	11 (34)	0.11
Dobutamine [*n* (%)]	0	0	13 (35)*	12 (38)*	<0.001*
Lactate (mmol l^{-1})	1.4 (0.6)	2.1 (0.8)‡	1.9 (1.6)	2.7 (1.8)‡	0.003‡
Cardiac output (ml min^{-1})	6.1 (2.0)	6.0 (1.7)	6.8 (2.1)*	7.4 (2.1)*	0.006*
$D_{O_2}I$ (ml min^{-1} kg^{-1})	497 (174)	431 (132)†	537 (164)*	599 (180)*	<0.01*; 0.04†

Table 4 Morbidity on postoperative day 2, stratified by postoperative baroreflex sensitivity. Data are represented as number of patients (%) for respective baroreflex sensitivity category. *P*-values were calculated using Fisher's exact test. ARR, absolute risk reduction; CI, confidence interval; POMS, PostOperative Morbidity Survey

Morbidity	Normal baroreflex sensitivity (*n*=68)	Baroreflex dysfunction (*n*=54)	ARR (%) (95% CI)	*P*-value
Clavien–Dindo >grade 2	27 (40)	36 (67)	27 (10–44)	0.003
POMS-defined morbidity				
Pulmonary	56 (82)	45 (83)	−1 (−12 to 14)	0.89
Infection	18 (26)	25 (46)	20 (3–37)	0.02
Renal	61 (90)	46 (85)	−5 (−16 to 7)	0.45
Gastrointestinal	42 (62)	37 (69)	7 (−10 to 24)	0.44
Cardiovascular	10 (15)	19 (35)	21 (5–36)	0.008
Neurological	7 (10)	10 (19)	8 (−4 to 21)	0.19
Wound	2 (3)	3 (6)	3 (−5 to 10)	0.47
Haematological	7 (10)	7 (13)	3 (−9 to 14)	0.65
Pain	58 (85)	43 (80)	−6 (−19 to 8)	0.41

neurons, or the parasympathetic efferent limb.[35] Laboratory models have demonstrated that loss of vagal parasympathetic activity exacerbates systemic inflammation in several organs, through immuno-neuromodulation of α7 nicotinic receptors on tissue-resident macrophages.[36] Furthermore, vagal denervation promotes persistent inflammation through failure to regulate resolution of inflammation.[37] The triad of inflammation, oxidative stress, and impaired baroreflex sensitivity is well recognized in the chronic development of cardiometabolic disease.[38] In conscious rats, loss of baroreflex function impedes attenuation of peripheral (joint) inflammation, mediated by sympathetic neural drive.[39] Thus, acute inflammation superimposed on a lack of established baroreflex 'reserve' may further detrimentally impair the neural anti-inflammatory armamentarium, which consequently jeopardizes metabolic homeostasis.[40]

We found that established baroreflex dysfunction was associated with a higher incidence of intraoperative blood transfusion. This observation may be mechanistically linked, because haemostasis is influenced by parasympathetic neural activity. In experimental soft tissue injury, haemorrhage is reduced after vagal nerve stimulation.[41] Diminished efferent (parasympathetic) activity, which contributes to baroreflex dysfunction, is promoted by inflammatory mediators, opiates, and anaesthetic agents.[42 43] Further loss of parasympathetic neural activity triggered by haemorrhage, reperfusion, and consequent inflammation during major surgery may therefore be particularly detrimental.[44]

Masking of the serial BRS analyses to outcomes is a significant strength of this study. In-depth haemodynamic characterization was also undertaken blinded to BRS data. Collecting the BRS data serially as part of a randomized controlled trial offers a further mechanistic insight into the role of autonomic dysfunction. Limitations include the exclusion of patients because of unanticipated ineligibility for analysis (atrial fibrillation, dysrhythmias), suboptimal waveform characterization, and loss of data during downloading because of hardware dysfunction. Our study compares favourably with similar translational studies conducted in 'real-world' clinical scenarios, where the acquisition and analysis of complex waveform data is typically associated with ~30% exclusion rates.[45 46] There was no systematic pattern to patients being excluded, other than the failure of one monitoring device that 'dumped' the data set while saving to an external storage device. Exclusions occurred randomly throughout the study and from all recruiting sites. Spontaneous baroreflex sensitivity is a useful 'real-world' measure of baroreflex, but these data might have been strengthened by complementary baroreflex assessment, including the ramp technique, which requires using vasoactive drugs serially.[47] However, logistic and clinical restrictions precluded this additional approach.

In summary, our findings suggest that baroreflex dysfunction might contribute to the development of postoperative morbidity. These data present an alternative mechanistic paradigm through which existing or novel pharmacological approaches may be explored in an effort to limit the excess morbidity and mortality after significant tissue trauma and systemic inflammation.

Authors' contributions

Conceived and designed the experiments; contributed reagents/materials/analysis tools: G.L.A.
Performed the experiments: A.T., N.J.
Analysed the data; ATICMJE criteria for authorship read and met; agree with manuscript results and conclusions: A.T., N.J., G.L.A.
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Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

None declared.

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