OXFORD UNIVERSITY PRESS | BJA British Journal of Anaesthesia

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Journal:	*British Journal of Anaesthesia*
Manuscript ID	BJA-2016-00163-PM007.R2
Manuscript Type:	Clinical Investigation
Date Submitted by the Author:	30-May-2016
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Mesh keywords:	Baroreflex, Autonomic Nervous System, Postoperative Complications

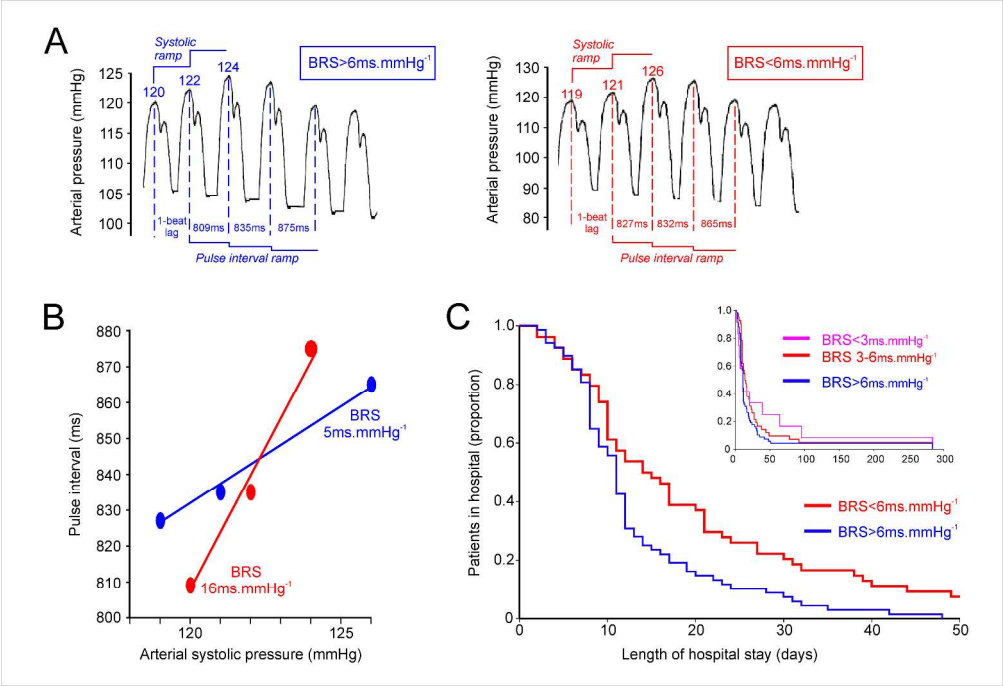

Figure 1. Baroreflex analysis and hospital stay. A. Schematic showing measurement and calculation of BRS. Using a validated sequence method technique (one beat lag), a baroreflex event is defined by 3 or more consecutive beats where the systolic blood pressure (SBP) and pulse interval (PI) change in 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 ms.mmHg-1. C. BRS<6ms.mmHg-1 was associated with prolonged hospital stay (hazard ratio:1.62 (95%CI:1.14-2.32); p=0.004; unadjusted log-rank analysis). Inset plot highlights length of stay in patients with BRS<3ms.mmHg-1.

470x322mm (300 x 300 DPI)

Subedited BJA-2016-00163-PM007.R2; accepted 26th June; 4 tables, 1 figures; 1 supplementary file

Baroreflex impairment and morbidity following major surgery

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Running title: Baroreflex function and postoperative outcome

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 risk of morbidity following trauma and sepsis. We hypothesized that baroreflex dysfunction contributes to excess postoperative morbidity following major surgery as a consequence of the inability to achieve adequate tissue oxygen delivery perioperatively.

Methods: In a randomised, controlled trial of goal-directed hemodynamic therapy (GDT) in higher-risk surgical patients (ISCRTN 76894700), baroreflex function was assessed using the spontaneous baroreflex sensitivity (BRS) method via an arterial line placed preoperatively, using a validated sequence method technique (one beat lag). BRS was calculated during the 6 h postoperative GDT intervention. BRS analyses were done by investigators blinded to clinical outcomes. The primary outcome was the association between postoperative baroreflex dysfunction (BRS<6 $mmHg.s^{-1}$, a negative prognostic threshold in cardiovascular pathology) and early postoperative morbidity. The relationship between baroreflex dysfunction and postoperative attainment of preoperative indexed oxygen delivery (DO_2I) was also assessed.

Results: Patients with postoperative baroreflex dysfunction were more likely to sustain infectious (RR 1.75 [95% CI: 1.07-2.85], P=0.02) and cardiovascular (RR 2.39 [95% CI: 1.22-4.71], P=0.008) morbidity. 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 DO_2 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.

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

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 comorbidities commonly associated with excess postoperative morbidity. Baroreflex autonomic dysfunction is an independent predictor of morbidity and mortality during critical illness.[1, 2] Several studies have found that baroreflex sensitivity values <6 ms.mmHg^{-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 epidemiologic 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 may be reduced by ensuring 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 (DO_2), which we have shown is associated with excess complications.

METHODS

We previously conducted a multicentre, randomized, double blinded trial (Trial Registration: *ISRCTN76894700*) at 4 hospitals in the United Kingdom.[12] A pre-specified analysis plan was published prior to trial completion at *www.ucl.ac.uk/anaesthesia/trials*. Adult patients undergoing major elective surgery expected to last for at least 2 hours were eligible for recruitment provided they satisfied the following high-risk criteria: a. ASA physical status ≥3; b. surgical procedures with an estimated/documented risk of postoperative morbidity (as defined by the PostOperative Morbidity Survey) exceeding 50%; c. modified Revised Cardiac Risk Score ≥3,[13] as defined by age ≥70 years, a history of cardiovascular disease (myocardial infarction, coronary artery disease, cerebrovascular accident, electrocardiographic evidence for established cardiac pathology), cardiac failure, poor exercise capacity (anaerobic threshold <11ml.kg.min^{-1} as assessed by cardiopulmonary exercise testing), renal impairment (serum creatinine ≥130 μmol/l) and/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 aimed at restoring/preserving each patients' individualized preoperative oxygen delivery or protocolised 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 preoperatively to permit calibrated cardiac output monitoring (LiDCO*Plus*, LiDCO Ltd, London, UK).[14] Haemodynamic data were recorded intraoperatively 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 six hours. Haemodynamic management in both randomisation arms (i.e. GDT and protocolised control group allocated patients) were managed exclusively by research staff during the postoperative study period. Prior to the intervention, in all patients, the Lidco lithium-based sensor was recalibrated to ensure accurate measurement of cardiac output. Oxygenation (SpO_2 ≥94%), haemoglobin (>80 $g.l^{-1}$), core temperature (≥36°C) and heart rate (<100 min^{-1}) and mean arterial pressure (60-90 mmHg), maintained using an alpha-1 adrenoceptor agonist as required) were protocolised standard of care measures. Crystalloid fluid (compound sodium lactate) was administered at 1 $ml{\cdot}kg{\cdot}h^{-1}$ 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 intravenous fluid and inotropic therapy according to an algorithm (Supplementary Figure 1) 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 intravenous infusion of dobutamine (1-20 $\mu g.kg.min^{-1}$ via central venous catheter) was commenced but strictly limited by heart rate parameters (<100 bpm, and/or ≤25% from baseline heart rate at the start of the intervention period). 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 ICU clinicians who could alter any aspect of patient care, provided the site principal and/or chief investigator was 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. after 24 h postoperatively) 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] (Figure 1A) obtained immediately preoperatively and for 6 hours postoperatively using a validated sequence method technique (one beat lag).[16] Baroreflex events across 3 or more consecutive beats were identified where the systolic blood pressure (SBP) and pulse interval (PI) 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, as they do not represent physiological baroreflex responses. The slope of the linear regression line of PI against SBP provided the BRS of each event in $ms.mmHg^{-1}$. Preoperative BRS was determined as the median slope value of all detected events. Median BRS values ≤ 6 $mmHg.s^{-1}$ for each hour of the postoperative period were defined as abnormal (baroreflex dysfunction), as BRS values ≤ 6 $ms.mmHg^{-1}$ are 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 $ms.mmHg^{-1}$), which has previously identified patients at the most extreme risk of death following 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/BRS data using the PostOperative Morbidity Survey, which assesses all-cause morbidity over the preceding 24 h period.[22] Failure to recover normally during the postoperative period was defined using the Clavien–Dindo scale, with ≥grade II complications representing clinically important deviations from projected postoperative recovery.[23] Thus, infectious morbidity was defined by microbiological confirmation and/or a deviation from normal postoperative care requiring antibiotic use beyond local, standardized prophylactic antibiotic therapy (i.e. after 24h post-operatively). The primary endpoint was all-cause morbidity (Clavien–Dindo ≥grade II complications) on postoperative day 2. Secondary outcomes were infectious morbidity on postoperative day 2, mean postoperative oxygen delivery (expressed as a percentage of each patients' preoperative oxygen delivery target) and length of hospital stay (adjusting for hospital deaths).

Statistical methods

Power analysis was based on the results of the POMO trial which showed that ~54% patients sustained significant morbidity (≥2, Clavien-Dindo scale)[23] by postoperative day 2.[12] On the basis of our previous work,[24] 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 alpha 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 baroreflex sensitivity <>6ms.mmHg^{-1}, timepoint (Suppl. Fig. 2) and randomization arm). Nonparametric data were analysed with the Mann–Whitney U-test. Relative risk (RR) and 95% 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 and/or modulate arterial baroreflex regulation, taking into account preoperative (absolute preoperative BRS value, albumin, diabetes mellitus, cardiovascular morbidity (incorporating history of ischaemic heart disease, heart failure, atrial fibrillation, stroke, anaerobic threshold <11ml.kg.min^{-1}), gender, age, type of surgery) and intraoperative (blood transfusion, lactate at end of the operation, epidural use, duration of operation) factors, using a hierarchical, 1-way forward switching model.[25] A full set of references supporting the choice of these factors is supplied in Supplementary table 1. A similar multivariate analysis was undertaken to explore the relationship between BRS and oxygen delivery postoperatively, again using a hierarchical, 1-way forward switching model.[25] All reported P values are two-sided. Statistical analyses were performed using NCSS 8 (Kaysville, UT). Median values (interquartile range) are presented, unless stated otherwise. Significance was accepted at P values ≤0.05.

RESULTS

Baroreflex dysfunction in higher-risk surgical patients

BRS was calculated throughout the whole perioperative period in 122/204 POM-O trial patients (Suppl. Figure 1). Preoperative recordings spanned a median duration of 39 minutes (IQR: 31-55), capturing a median 162 spontaneous events ((IQR: 90-271). Postoperative recordings spanned the entire 6-hour intervention period in all patients, with a median event rate of 174/h. Baroreflex dysfunction- as defined by BRS ≤6 ms.mmHg^{-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 mmHg.s^{-1}, a threshold associated with particularly poor prognosis in other disease states.[5, 21, 26]

**insert Table 1 here

Patients with preoperative BRS<6 mmHg.s^{-1} were more likely to have postoperative BRS<6 mmHg.s^{-1} (RR 2.6 (95% CI: 1.6-4.1), P=0.003). Because intraoperative management and surgery associated with specific anaesthetic interventions (e.g. hepatobiliary patients receiving epidural analgesia [27]) 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 comorbidities associated with autonomic dysfunction (diabetes mellitus, cardiac disease) and intraoperative management (Table 2). We found that preoperative BRS (P=0.0002; Suppl. Figure 2) was the only perioperative factor associated with postoperative BRS.

**insert Table 2 here

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, gender, body mass index, type of surgery, diabetic and cardiovascular morbidity (Table 2B). Intraoperatively, 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 intraoperatively, haemoglobin levels were similar between groups by the end of the operation and prior to the haemodynamic intervention. Baroreflex dysfunction was associated with higher lactate, which persisted throughout the postoperative intervention period. Postoperatively, DO_2I was 39% (95% CI: 11-68), P=0.001) lower than the preoperative target in baroreflex dysfunction patients not randomized to GDT (Table 3; Suppl. Figure 2).

**insert Table 3 here

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 (RR: 2.39 [95% CI: 1.22-4.71], P=0.008) morbidity 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; Figure 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.

**insert Table 4 here

**insert Figure 1 here

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 hospitalisation. 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 comorbidities 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,[28] coupled with the recognition that cardiovascular and autonomic function are frequently impaired in patients presenting for cancer surgery.[29]

Established cardiac dysfunction is strongly associated with excess postoperative morbidity and mortality.[30] Autonomic dysfunction is frequently observed in established cardiac failure, characterized by up-regulation of GPCR kinase (GRK)-2, which inhibits pro-contractile signalling by phosphorylating the beta-adrenoreceptor and inducing beta-arrestin binding. [31, 32] 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 likely contributes to the higher mortality observed in rats with baroreflex dysfunction following acute endotoxaemia.[33] In our study, patients with baroreflex dysfunction had a higher venous lactate at the end of the intraoperative period, suggesting tissue dysoxia may have developed in part as a consequence of lower oxygen delivery. Infectious complications after tissue trauma are likely exacerbated by reduced oxygen delivery and strongly linked to subsequent mortality.[34] Postoperative DO_2 was lower in patients with baroreflex dysfunction not randomized to GDT, and failure to achieve preoperative DO_2 was associated with lower BRS during the intervention period.

Despite GDT, higher venous lactate persisted in baroreflex dysfunction patients; these patients were more likely to acquire early postoperative morbidity necessitating interventions that deviate from normal surgical care. Our exploratory analysis of haemodynamic performance shows that sustained baroreflex dysfunction (i.e. preoperative BRS<6ms.mmHg^{-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 over why goal-directed haemodynamic management in critical illness does not appear to benefit patients with established, early sepsis/systemic inflammation.[35]

Defects in baroreflex function may occur in afferent neurons transmitting the information from baroreceptors, brainstem neurons or the parasympathetic efferent limb.[36] Laboratory models have demonstrated that loss of vagal parasympathetic activity exacerbates systemic inflammation in several organs, through immuno-neuromodulation of alpha-7 nicotinic receptors on tissue resident macrophages.[37] Furthermore, vagal denervation promotes persistent inflammation through failure to regulate resolution of inflammation.[38] The triad of inflammation, oxidative stress and impaired baroreflex sensitivity is well recognized in the chronic development of cardiometabolic disease.[39] In conscious rats, loss of baroreflex function impedes attenuation of peripheral (joint) inflammation, mediated by sympathetic neural drive.[40] 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.[41]

We found that established baroreflex dysfunction was associated with a higher incidence of intraoperative blood transfusion. This observation may be mechanistically linked, since haemostasis is influenced by parasympathetic neural activity. In experimental soft tissue injury, haemorrhage is reduced following vagal nerve stimulation.[42] Diminished efferent (parasympathetic) activity, which contributes to baroreflex dysfunction, is promoted by inflammatory mediators, opiates and anaesthetic agents.[43, 44] Further loss of parasympathetic neural activity triggered by haemorrhage, reperfusion and consequent inflammation during major surgery may therefore be particularly detrimental.[45]

Masking of the serial BRS analyses to outcomes is a significant strength of the study. In-depth hemodynamic 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 due to unanticipated ineligibility for analysis (atrial fibrillation, dysrhythmias), suboptimal waveform characterization, loss of data during downloading due to 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.[46, 47] There was no systematic pattern to patients being excluded, other than the failure of one monitoring device that 'dumped' the dataset whilst 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 may have been strengthened by complementary baroreflex assessment including the ramp technique, which requires using vasoactive drugs serially.[48] However, logistic and clinical restrictions precluded this additional approach.

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

Author Contributions: Conceived and designed the experiments: GLA. Performed the experiments: AT, NJ. Analysed the data: AT, NJ, GLA. Contributed reagents/ materials/ analysis tools: GLA. Wrote the first draft of the manuscript: GLA, AT. Contributed to the writing of the manuscript: GLA, AT. ATICMJE criteria for authorship read and met: GLA, AT, NJ. Agree with manuscript results and conclusions: AT, NJ, GLA.

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Acknowledgments: This work was supported by the Academy Medical Sciences/Health Foundation Clinician Scientist scheme (GLA). Part of this work was undertaken at UCLH/UCL who received a proportion of funding from the UK Department of Health's NIHR Biomedical Research Centres funding scheme. We acknowledge the support of the surgical teams and patients for participating in these studies.

Figure legends

Figure 1. Baroreflex analysis and hospital stay. A. Schematic showing measurement and calculation of BRS. Using a validated sequence method technique (one beat lag), a baroreflex events is defined by 3 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 $ms.mmHg^{-1}$. C. BRS<6ms.mmHg-1 was associated with prolonged hospital stay (hazard ratio:1.62 (95% CI:1.14-2.32); P=0.004; unadjusted log-rank analysis). Inset plot highlights length of stay in patients with BRS<3 $ms.mmHg^{-1}$.

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Table 1: Baseline characteristics for POM-O patients in whom BRS was calculated pre and postoperatively.

	BRS>6 ms.mmHg^{-1} (n=68)	**BRS<6 ms.mmHg^{-1} (n=54)**
Age, years	67 (8)	68 (8)
Male	38 (56)	34 (63)
Body mass index, 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	54 (79)	38 (70)
Creatinine >130 µmolL^{-1}	2 (3)	5 (9)
Diabetes mellitus	14 (21)	14 (26)
History of cardiovascular disease	47 (69)	42 (77)
Surgical procedure*		
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*		
University College London Hospital	24	21
Royal Free Hospital	36	19
Royal London Hospital	2	4
St Georges Hospital	6	10

Data presented as mean (SD), or n (%). * indicate % patients/group within each surgical category/hospital.

Table 2. Baroreflex dysfunction and postoperative oxygen delivery. Multivariate analysis assessing (a) Perioperative factors associated with postoperative BRS, (b) achievement of preoperative oxygen delivery target.

a. Perioperative factors associated with postoperative BRS.

Independent variable	Regression Coefficient β	Standard Error	T-Value	P value	Reject H0 at 5%?
Intercept	3.1844	4.6746	0.681	0.50	No
Preoperative					
Age	-0.0186	0.0373	-0.498	0.62	No
Gender	-0.5929	0.6191	-0.958	0.34	No
Body mass index	-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
Bllod transfusion	-1.211	0.7136	-1.697	0.09	No
Lactate, end op	-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 (% preoperative DO_2I value).

Independent variable	Regression Coefficient β	Standard Error	T-Value	P value	Reject H0 at 5%?
Intercept	76.5974	34.8664	2.197	0.03	Yes
Age	0.1571	0.4755	0.33	0.74	No
Postop BRS>6$ms.mmHg^{-1}$	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 op	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

Table 3: Perioperative haemodynamics and fluid therapy. Data presented as mean (SD), median (quartiles) or n (%). P values refer to two-way ANOVA comparing haemodynamic intervention X baroreflex type. Asterisk refers to between haemodynamic therapy group comparisons; A denotes significant difference for interaction between haemodynamic intervention X baroreflex type. B denotes significant difference between baroreflex types (BRS>6 v. BRS<6). All patients received 1 $ml.kg^{-1}.h^{-1}$ Ringers lactate crystalloid solution postoperatively.

	Control arm		Goal-directed therapy		
	BRS>6 (n=31)	**BRS<6 (n=22)**	**BRS>6 (n=37)**	**BRS<6 (n=32)**	**P value**
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
DO_2I, $ml.min^{-1}.kg^{-1}$	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, no. (%)	2 (6)	8 (36)^{B}	7 (19)	11 (34)^{B}	0.02
Hb, $g.L^{-1}$, end of op	105 (11)	108 (18)	103 (13)	110 (18)	0.31
Vasopressor, no.(%)	6 (19)	5 (23)	6 (16)	8 (25)	0.82
Lactate, $mmol.L^{-1}$	1.6 (1.0)	2.9 (1.3)^{B,*}	2.0 (1.1)	2.3 (1.6)^{B}	^{B}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
DO_2I, $ml.min.kg^{-1}$	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, no. (%)	3 (10)	6 (27)	7 (19)	11 (34)	0.11
Dobutamine, no. (%)	0	0	13 (35)*	12 (38)*	*<0.001
Lactate, $mmol.L^{-1}$	1.4 (0.6)	2.1 (0.8)^{B}	1.9 (1.6)	2.7 (1.8)^{B}	^{B}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
DO_2I, $ml.min^{-1}.kg^{-1}$	497 (174)	431 (132)^{A}	537 (164)*	599 (180)*	*<0.01; ^{A}0.04

Table 4. Morbidity on postoperative day 2, stratified by postoperative baroreflex sensitivity.

Data represented as number of patients (%) for respective BRS category. P values calculated using Fisher's exact test. ARR- absolute risk reduction.

	Normal baroreflex sensitivity (n=68)	Baroreflex dysfunction (n=54)	ARR (%) (95% CI)	P value
Clavien-Dindo >grade 2	27 (40)	36 (67)	27 (10 to 44)	0.003
POMS-defined morbidity				
Pulmonary	56 (82)	45 (83)	-1 (-12 to 14)	0.89
Infection	18 (26)	25 (46)	20 (3 to 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 to 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