DOI: 10.1093/bja/aeg212

BJA

Influence of thoracic epidural analgesia on cardiovascular autonomic control after thoracic surgery

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Background. Thoracic epidural analgesia (TEA) is effective in alleviating pain after major thoracoabdominal surgery and may also reduce postoperative mortality and morbidity. This study investigated cardiovascular autonomic control in patients undergoing elective thoracic surgery and its modulation by continuous TEA.

Methods. Thirty-eight patients were randomly assigned to receive patient-controlled analgesia (PCA group) or thoracic epidural analgesia (TEA group) with doses of bupivacaine (0.25% during operation, 0.125% after operation) and fentanyl (2 μg ml^{-1}). Heart rate variability (HRV), baroreflex function and pressure response to nitroglycerine and phenylephrine were assessed before operation, 4 h after the end of surgery (POD 0) and on the first and second postoperative days (POD 1 and POD 2).

Results. Early after surgery, all HRV variables and baroreflex sensitivities were markedly decreased in both groups. In the TEA group, total HRV and its high-frequency components (HF) increased towards preoperative values at POD 1 and POD 2, whereas the ratio of low to high frequencies (LF/HF) was significantly reduced (mean (SD), –44 (15)% at POD 0, –38 (17)% at POD 1, –37 (18%) at POD 2) and associated with blunting of the postoperative increase in heart rate and blood pressure. In the PCA group, the ratio of LF/HF remained unchanged and the decrements in HRV variables persisted until POD 2. In the two groups, baroreflex sensitivities and pressure responses recovered preoperative values at POD 2.

Conclusions. In contrast with PCA management, TEA using low concentrations of bupivacaine and fentanyl blunted cardiac sympathetic neural drive, resulting in vagal predominance, while HRV variables were better restored after surgery.

Br J Anaesth 2003; **91**: 525–31

Keywords: anaesthetic techniques, epidural; heart, heart rate; reflexes, baroreceptor; surgery, thoracic; sympathetic nervous system

Accepted for publication: May 19, 2003

Over the last three decades, epidural analgesia using local anaesthetics, opioids and α_2-agonists has gained widespread popularity for the control of postoperative pain.[1 2] Importantly, continuous epidural anaesthesia has been associated with reduced 30-day mortality after various types of surgery and a lower incidence of pulmonary thromboemboli, deep-vein thrombosis, respiratory depression and pulmonary complications.[3 4] These beneficial perioperative effects have been attributed to attenuation of the neuroendocrine response, modulation of the prothrombotic state, improved diaphragmatic function and optimal analgesia without undue sedation.

Thoracic epidural analgesia (TEA) with small doses of local anaesthetics and opioids is the most effective method of providing dynamic pain relief after major abdominal and thoracic surgical procedures.[5] Consequently, patients with TEA are able to mobilize earlier than those managed with parenteral opioids. However, TEA carries the potential risk of cardiovascular depression and hypotension due to local anaesthetic-induced negative inotropic effects, impaired

compensatory vasoconstriction and inhibition of cardiac sympathetic fibres originating at the first to fifth thoracic levels.[6]

In this randomized controlled study, cardiovascular autonomic control, assessed by power spectral analysis of the heart rate (HR) and baroreflex function, was compared in two groups of patients receiving either TEA or i.v. patient-controlled analgesia (PCA) after thoracic surgery.

Materials and methods

The study was approved by the institutional review board and informed consent was obtained in each case. The sample size calculation was based on data obtained previously.[7] Thirty-two patients had to be evaluated in order to show a difference greater than or equal to 1.2 standard deviations between the two groups with a power of 90% and a level of significance of 5%.

Thirty-eight male patients undergoing lung resection for cancer were randomized to receive either combined general anaesthesia with TEA (TEA group) or general anaesthesia followed by PCA (PCA group). Exclusion criteria were the presence of coronary artery disease, congestive heart failure, hypertension, renal insufficiency (creatinine clearance <40 ml min^{-1}), diabetes mellitus, autonomic dysfunction, coagulation abnormalities, recent infections, chronic alcohol consumption and cardiac rhythm other than sinus; patients undergoing pneumonectomy were excluded secondarily.

All patients were premedicated with midazolam 7.5 mg orally and 0.1 morphine mg kg^{-1} subcutaneously. Upon arrival in the operating theatre, they received an i.v. fluid bolus of lactated Ringer's solution (10 ml kg^{-1}). ECG, intra-arterial pressure, end-tidal carbon dioxide, pulsed oxygen saturation (Sp_{O_2}), blood gases and bispectral index (BIS) were monitored perioperatively. In the TEA group, a 19-gauge epidural catheter was inserted before operation at the vertebral level between T4 and T5 and, after a 3-ml test dose of lidocaine 2% with epinephrine 5 μg ml^{-1}, bupivacaine 0.25% was given in divided doses to achieve a cephalad limit of sensory block to cold sensation (alcohol swab) up to T2.

In both groups, anaesthesia was induced i.v. with fentanyl 100 μg and thiopental 4–6 mg kg^{-1}; tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1} and anaesthesia was maintained with isoflurane 0.5–1.5 MAC to target BIS values between 30 and 50. Patients were ventilated mechanically with an air–oxygen mixture to achieve arterial oxygen saturation ⩾92% and an end-tidal carbon dioxide tension of 35–40 mm Hg. A double-lumen tube was inserted to allow one-lung ventilation, and pulmonary resection was performed by the same surgeon through a mini-thoracotomy.

Intraoperative analgesia was maintained with an epidural infusion of bupivacaine 0.25% and fentanyl 4 μg ml^{-1} at the rate of 0.1 ml kg^{-1} h^{-1}. In the PCA group, patients received i.v. fentanyl 200 μg before skin incision and additional doses at the discretion of the attending anaesthetist.

Urinary and evaporative losses were replaced with lactated Ringer's solution and blood losses were compensated by equal volumes of hydroxyethyl starch 5% and/or packed erythrocytes to keep the haemoglobin concentration ⩾90 g $litre^{-1}$. Body temperature was maintained at ⩾36°C using fluid and air warming devices. At the end of the procedure, muscle relaxants were antagonized (glycopyrrolate 8 μg kg^{-1} and prostigmine 30 μg kg^{-1}) and the trachea was extubated after confirming the return of adequate spontaneous respiration, responses to verbal command and the ability to maintain a 5-s head lift.

After operation, patients were monitored for 48 h in the postanaesthesia care unit (PACU). In addition to i.v. ketorolac (30 mg per 8 h), patients received either i.v. morphine via a PCA pump (PCA group) or an epidural infusion of bupivacaine 0.125% and fentanyl 2 μg ml^{-1} (TEA group). The analgesic regimen was adjusted to achieve a visual analogue score <3/10 during deep inspiration. Oral intake and light food were resumed within 6–10 h after surgery and glucose 5% in saline was infused to ensure diuresis ⩾0.5 ml kg h^{-1}. Oxygen was administered to maintain Sp_{O_2} ⩾92%. Spirometry and deep breathing manoeuvres were performed regularly and patients were mobilized to the chair on the first postoperative day (POD 1) and started to walk on POD 2.

During and after operation, any episode of haemodynamic impairment lasting longer than 1 min and requiring treatment was identified. Hypotension, defined as systolic arterial pressure (SAP) <90 mm Hg, was treated by decreasing the administration of isoflurane (0.25% decrements) and/or i.v. phenylephrine followed by the infusion of lactate–Ringer solution 250 ml. Hypertension, defined as SAP >160 mm Hg, was treated by increasing inhaled isoflurane (0.25% increments), adjustment of the analgesic regimen, i.v. nitroglycerine (NTG), or any combination of them. Tachycardia, defined as HR >100/min, was treated with i.v. metoprolol.

Cardiac autonomic function was assessed by heart-rate variability (HRV) analysis and calculation of the baroreflex slope after bolus administration of phenylephrine (PHE) and NTG. Vascular pressure responsiveness was estimated by the changes in SAP induced by bolus administration of PHE and NTG.

Data were collected during four 10-min periods with stable haemodynamic and respiratory conditions: in awake patients, before anaesthesia induction and epidural anaesthesia (preop), 4 h after the end of surgery (POD 0) and on the morning of POD 1 and POD 2. In the TEA group, the cephalad and caudal limits of sensory block were recorded before each test.

The ECG signal was fed into a purpose-built R-wave detector to generate a series of successive RR intervals with an accuracy of 1 ms. The invasive radial artery pressure signal was simultaneously recorded and analogue-to-digital

Table 1 Patients and surgical characteristics (mean (range), mean (SD), or absolute value)

	PCA group (n=18)	TEA group (n=17)
Age (yr)	58 (44–71)	59 (47–69)
Body mass index	24.4 (3.2)	23.4 (3.6)
FEV_1 (litre)	2.2 (0.3)	2.3 (3.6)
FVC (litre)	3.1 (0.5)	3.3 (0.6)
Pa_{O_2} at room air (kPa)	10.1 (0.9)	9.9 (0.7)
Duration of surgery (min)	58 (5)	59 (4)
Duration of one-lung ventilation (min)	58 (5)	59 (4)
Extent of surgical resection (n)		
Lobectomy	16	15
Exploratory thoracotomy	1	2

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

converted using a 16-bit board with a temporal resolution of 1000 Hz and an amplitude resolution of 12 bits (Lab-view; National Instruments, Austin, TX, USA). Spectral estimation of RR interval variability was obtained from stationary regions of 8-min recordings containing repeated segments of more than 100 successive RR intervals with less than 2% ectopy. When present, extrasystolic beats were deleted and replaced by appropriately spaced values; missed beats were inserted by interpolation. After detrending of the signal (first degree), an autoregressive algorithm was used to obtain a spectral density estimate of RR interval variability. Spectral density was calculated as the area under the curve of two frequency bands: low frequency (LF, from 0.05 to 0.15 Hz) and high frequency (HF, from >0.15 to 0.6 Hz), and was expressed in absolute units in milliseconds squared. In addition, the LF/HF ratio was calculated as an index of sympathovagal balance. Transfer function analysis confirmed the absence of respiratory-dependent oscillations of HR in the LF component, whereas a significant relationship was found between respiration and the HF component.

To examine the baroreflex control of HR, interbeat interval responses to vasoconstrictor-induced hypertension and vasodilator-induced hypotension were analysed. All RR intervals were paired with the SAP values of the preceding beat and the baroreflex sensitivity was defined as the slope obtained by regression analysis of the linear portion of the curve (excluding values when R<0.9) and expressed as the change in RR interval in ms mm Hg^{-1} of change in SAP. Blood pressure was raised and lowered by alternating (randomly) bolus injections of PHE (50 μg, with 50 μg increments) and NTG (50 μg, with 50 μg increments) until SAP increased or decreased by at least 25 mm Hg, respectively, or until a maximum of 200 μg had been given. SAP and HR were allowed to return to baseline levels between vasoactive drug injections. The magnitude of the increase and decrease in SAP after PHE and NTG was expressed as the percentage change per 100 μg drug.

Data are presented as mean (SD) or median (range). Two *a priori* hypotheses were tested: (i) HRV variables and baroreflex function are unchanged after surgery compared with the preoperative period; and (ii) there is no difference between the TEA and PCA groups on cardiac autonomic control. The spectral variables were analysed after logarithmic transformation to improve skewness and kurtosis. Data were analysed using two-way analysis of variance followed by Bonferroni *post hoc* correction for multiple comparisons. Significance was assumed at P<0.05.

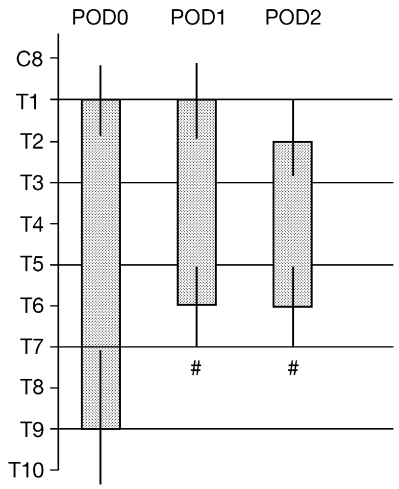

Fig 1 Limits of sensory blockade achieved during continuous infusion of bupivacaine 0.125% at POD 0, POD 1 and POD 2. P<0.05 compared with POD 0.

Results

Complete data were obtained in 35 patients (TEA group, n=17; PCA group, n=18); three patients in the TEA group were excluded because of incomplete epidural blockade. The two groups were similar with respect to patient characteristics and surgical data (Table 1) and perioperative fluid balance (TEA *vs* PCA: +120 (40) *vs* +165 (55) ml during operation, +280 (120) *vs* +315 (145) at POD 1, –80 (45) *vs* –105 (65) ml at POD 2).

In the TEA group, bupivacaine infusion rate was significantly greater at POD 0 (12.4 (3.6) mg h^{-1}) than at POD 1 (9.3 (2.6) mg h^{-1}) and at POD 2 (8.7 (2.3) mg h^{-1}) and resulted in greater sensory blockade at POD 0 (Fig. 1).

During operation, despite similar BIS values (45 (12) for TEA *vs* 47 (13) for PCA), patients with combined epidural and general anaesthesia (TEA group) required lower doses of i.v. fentanyl and a lower concentration of inhaled isoflurane; in addition, fewer episodes of hypertension and more frequent hypotensive events requiring treatment were encountered than in the PCA group (Table 2).

After operation, the visual analogue score for pain did not differ between the two groups (≤3/10). However, the incidence of hypertensive and tachycardic episodes requiring treatment with NTG or metoprolol was lower in the TEA than in the PCA group. As shown in Fig. 2, HR and MAP increased after operation in the PCA group compared with preoperative values (P<0.001), whereas postoperative HR

Table 2 Perioperative anaesthetic management and adverse haemodynamic events in patients undergoing thoracic surgery (mean (SD) or absolute value). Doses of fentanyl included i.v. and peridural routes. *P<0.05 between TEA and PCA groups

	PCA group (n=18)	TEA group (n=17)
Intraoperative period		
Fentanyl (μg)	350 (115)	200 (95)*
Isoflurane (%)	1.4 (0.8)	0.9 (5)*
Hypotension (patients, episodes)	3, 5	17, 37*
Phenylephrine (μg)	45 (40)	250 (150)*
Hypertension (patients, episodes)	5, 12	0*
Nitroglycerine (μg)	125 (100)	0*
Tachycardia (patients, episodes)	2, 5	2, 3
Metoprolol (mg)	8 (6)	2 (3)*
Postoperative period		
Morphine (mg)	98 (82–166)	–
Bupivacaine (mg)	–	601 (56)
Fentanyl (mg)	–	1.09 (0.11)
Hypotension (patients, episodes)	2, 3	4, 6
Phenylephrine (μg)	39 (64)	55 (63)
Hypertension (patients, episodes)	8, 18	1, 2*
Nitroglycerine (μg)	357 (251)	18 (44)*
Tachycardia (patients, episodes)	9, 19	2, 2*
Metoprolol (mg)	5 (4)	0.5 (1.2)*

and MAP did not differ from preoperative values in the TEA group.

During the four study periods, respiratory rate and arterial carbon dioxide tension did not differ and were similar in the two groups (data not shown). In the immediate postoperative period (POD 0), there were significant decreases in total HRV (–72 (18)% in PCA, –67 (17)% in TEA), the HF component (–81 (19)% in PCA, –57 (22)% in TEA) and the LF component (–76 (21)% in PCA, –82 (23)% in TEA) compared with preoperative values (Fig. 3).

In the PCA group, these indices of HRV remained decreased at POD 1 and POD 2 and the LF/HF ratio was unchanged throughout the four study periods. In the TEA group, total HRV and HF increased at POD 1 and POD 2, although they remained lower than preoperative values; the LF/HF ratio was significantly reduced compared with preoperative values (–44 (15)% at POD 0, –38 (17)% at POD 1, –37 (18)% at POD 2). In the PCA group, total HRV and HF were significantly lower at POD 1 and POD 2 than in the TEA group.

At POD 0, NTG administration (depressor test) induced a larger decrease in MAP and baroreflex sensitivity in the TEA group than in the PCA group (Fig. 4). In contrast, PHE administration (pressor test) produced similar hypertensive responses throughout the four study periods, and baroreflex sensitivity was transiently decreased at POD 0 in the two groups (–78 (27)% in the PCA group, –75 (34)% in the TEA group; not significant). At POD 2, baroreflex sensitivities and pressure responses to NTG and PHE were similar to preoperative values in both groups.

In the PCA group, postoperative elevations in HR were negatively correlated with decreases in total HRV, HF and baroreflex slope during the NTG test.

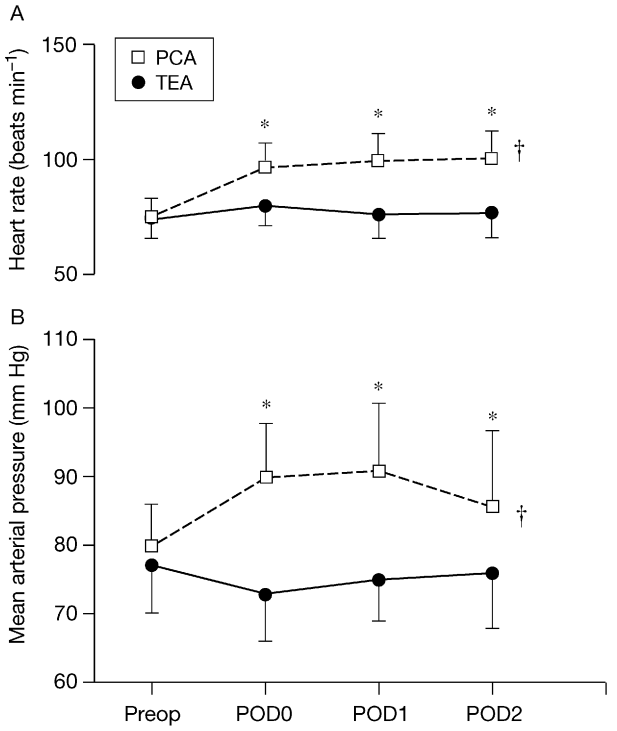

Fig 2 Perioperative time course of heart rate (A) and mean arterial pressure (B) in patients receiving patient-controlled analgesia (PCA) or thoracic epidural analgesia (TEA) before surgery (preop), 4 h after extubation (POD 0) and on the first and second days after surgery (POD 1 and POD 2 respectively). *P<0.05 between the two groups; †P<0.05 within a group.

Discussion

The present study demonstrated large decrements in baroreflex sensitivity and in the frequency domain indices of HRV after elective thoracic surgery. Compared with i.v. PCA, continuous TEA resulted in: (i) blunting of the postoperative increase in blood pressure and HR; (ii) a sustained reduction in LF/HF ratio; (iii) transient exaggerated hypotension associated with reduced cardiac acceleration in response to NTG; and (iv) partial recovery of HRV variables within 48 h after surgery.

In the PCA group, we observed transient blunting of the arterial baroreceptor–HR reflex (POD 0) and decrements in HRV variables for (at least) 2 days after surgery.

Residual effects of inhaled anaesthesia and neuromuscular reversal agents were expected to produce short-lasting impairments in baroreflex function and in beat-to-beat RR oscillations. After minor surgery, autonomic cardiac function has been shown to recover to the preoperative level within 2–3 h after withdrawal of isoflurane and the administration anticholinergic agents.[8–10] The administration of cyclooxygenase blockers, such as ketorolac, could further attenuate baroreflex responses, because endogenous prostaglandins have been shown to enhance tonic activity of arterial baroreceptor and to facilitate acute baroreceptor resetting in experimental conditions.[11]

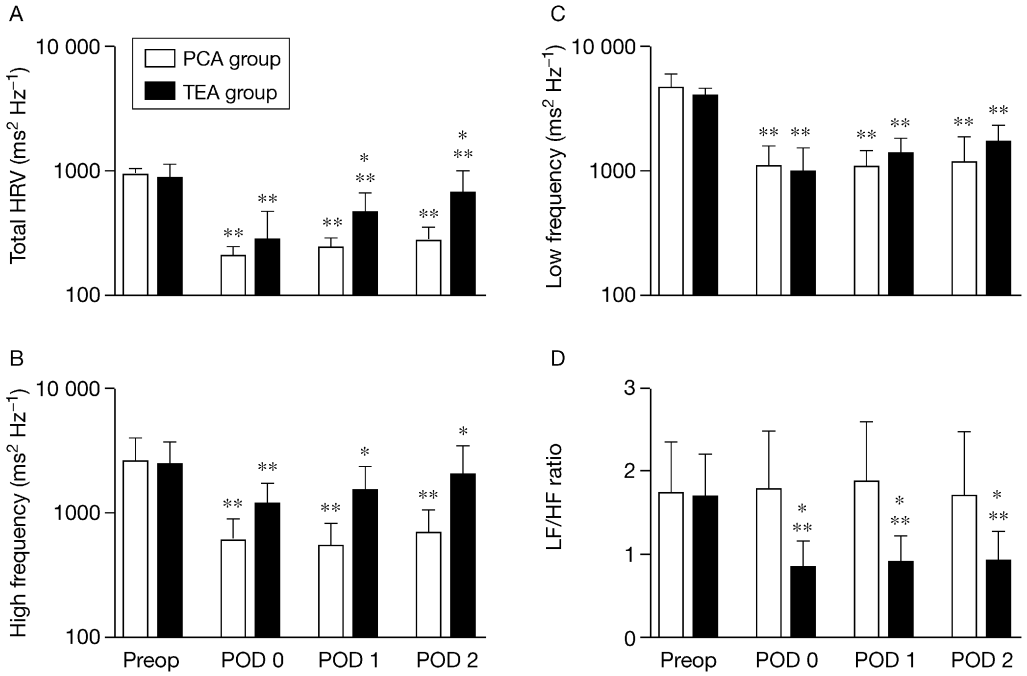

Fig 3 Perioperative time course of heart-rate variability (HRV) variables in the PCA group and TEA group. (A) Total HRV. (B) High-frequency component. (C) Low-frequency component. (D) low-frequency/high-frequency ratio (LF/HF). *P<0.05 between the two groups; **P<0.05 compared with preoperative value.

Despite satisfactory analgesia and gas exchange, HR and blood pressure both increased after operation. Interestingly, changes in HR were negatively correlated with those observed in the frequency domain and with baroreflex depressor sensitivity (NTG test), further confirming that changes in HR can be used as a crude index of sympathovagal balance.[12 13] Moreover, postoperative tachycardia associated with decrements in all HRV variables could also be explained by 'apraxic surgical injuries' of both sympathetic and parasympathetic neural fibres, leading to a temporary state of 'denervated heart'.[14]

In agreement with other reports, postoperative HF and LF spectra decreased by approximately 40%, with no change in LF/HF ratio.[12–14] The reduced HF power (0.15–0.6 Hz) reflected the attenuated parasympathetic control of HR (respiratory conditions being unchanged). Likewise, the reduced baroreflex sensitivity also reflected low parasympathetic reactivity, because the sigmoidal HR–SAP relationship is determined mainly by firing of vagal cardiac motoneurons in proportion to afferent baroreceptor inputs.[15]

Interpretation of the decreased LF power (0.05–0.15 Hz) and the unchanged LF/HF ratio is less straightforward. Under controlled physiological stimulation (e.g. head tilt, mental stress), the LF component is influenced by both sympathetic and parasympathetic activities and an increased LF/HF ratio reflects acute sympathetic hyperactivity.[16] Under pathological conditions such as surgery, HRV is modulated by additional neural interactions and reflexes, hormonal influences and by the functional integrity of the β-adrenergic receptor (e.g. receptor density, postsynaptic transduction, receptor phosphorylation). Amar and colleagues[13] demonstrated that postoperative alterations in most HRV variables were directly correlated with down-regulation and desensitization of β-adrenergic receptors, suggesting a functional uncoupling between cardiac sympathetic (hyper)activity and the sinus node. Additional mediators of the surgical stress response, such as angiotensin II, adrenocorticotropic hormone and cytokines, contribute to further impairment of beat-to-beat oscillations and pressure baroreflex sensitivity.[17–19] Taken together, these data strongly support the concept that surgical trauma markedly interferes with cardiovascular autonomic control.

The unchanged perioperative LF/HF ratio probably resulted from the combined effects of reduced vagal tone, sympathetic hyperactivity and altered β-adrenergic responsiveness. Whether these alterations in HRV variables represent transient autonomic dysfunction or natural adaptive mechanisms to the acute surgical stress is unknown and remains a topic of debate.

During operation, management with continuous TEA using bupivacaine 0.25% and low doses of fentanyl produced a 40% reduction in isoflurane requirements to achieve a similar depth of anaesthesia. Complete sensory and motor deafferentation resulting from neuraxial blockade has been shown to enhance the potency of volatile anaesthetic agents or sensitivity to them, or both, resulting in lower minimal anaesthetic concentration during surgical trauma (MAC-sparing effects).[20]

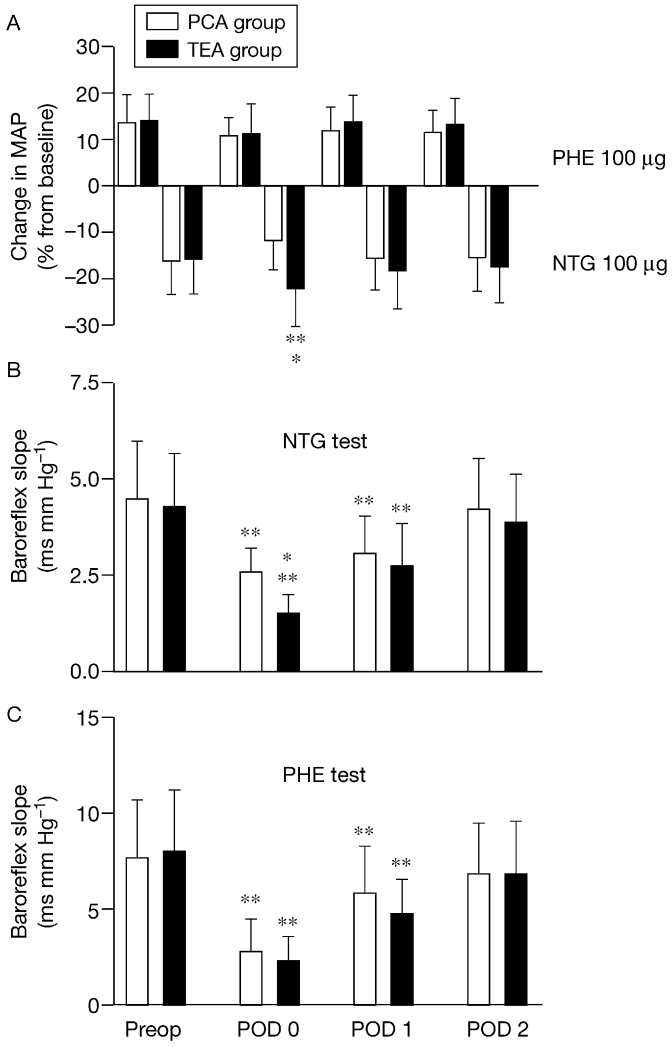

Fig 4 Perioperative change in vascular pressure response and baroreflex sensitivity after i.v. administration of phenylephrine (PHE) and nitroglycerine (NTG) in the PCA group and TEA group. (A) Change in mean arterial pressure (MAP). (B) Baroreflex sensitivity calculated during the depressor test (NTG). (C) Baroreflex sensitivity calculated during the pressor test (PHE). *P<0.05 between the two groups; **P<0.05 compared with preoperative (preop) value. POD 0, 4 h after extubation; POD 1, first day after surgery; POD 2, second day after surgery.

This study is the first to assess in humans recovering from major non-cardiac surgery the effects of preganglionic cardiac sympathetic block on HRV in the frequency domain, baroreflex sensitivity and vascular pressure response. Previous studies in awake unstressed subjects showed that high TEA did not alter the sensitivity of the arterial baroreceptor–HR reflex, or the fractional spectral power in the LF and HF domain,[21–23] whereas under acutely stressful conditions, such as myocardial ischaemia, mental stress, head tilt and cardiac sympathectomy (by means of TEA or pharmacological β-block), the increase in HR is blunted and the LF/HF ratio is markedly reduced.[24]

In our patients managed with continuous TEA, indirect observations supported the supposition that anaesthetic blockade included the preganglionic cardiac sympathetic nerves that escape from the spinal cord between T1 and T4. Median sensory block extended from T1 to T5–T9 and sympathetic block was expected to exceed the dermatomal borders of somatic sensory block.[25] The tachycardic and hypertensive responses were blunted after operation; given the low dose of bupivacaine (0.125%), it was unlikely that systemic depressive haemodynamic effects resulted from reabsorbed local anaesthetics.[26] Finally, the LF/HF ratio of HRV was decreased and cardiac acceleration in response to hypotension was slightly obtunded.

In all the patients, TEA provided satisfactory analgesia with no increased risk of haemodynamic disturbances and no alteration in α-adrenergic pressure response. However, the hypotensive response to NTG was exaggerated shortly after recovery from anaesthesia and was associated with a diminished tachycardic response. The greater extent of segmental anaesthetic block (from T1 to T9), including sympathetic nerves to the heart and the adrenal medulla, possibly accounted for transiently impaired cardiovascular adaptation as a result of cardiac denervation, impaired release of catecholamines from the adrenal medulla and less effective compensatory vasoconstriction in unblocked segments.

In contrast with the PCA group, in the TEA group physiological periodic fluctuations of RR interval mediated by the autonomic nervous system recovered partially over the 2 days after surgery. The persistent decrease in LF/HF ratio confirms a TEA-induced shift in sympathovagal balance towards vagal predominance or sympathetic inhibition, or both. Several studies have shown that TEA reduces sympathetic tone and the endocrine response to thoracic surgery, as indicated by reduced HR, deactivation of the renin–angiotensin–aldosterone system and decreased circulatory concentrations of catecholamines, neuropeptide Y, β-endorphins and cortisol.[27–29] Interestingly, the increased release of vasopressin that has been shown to stabilize blood pressure after high TEA may also potentiate cardiovascular reflexes.[30 31] Accordingly, preservation of the functional integrity of α- and β-adrenergic receptors and resetting of the sympathovagal balance probably contributed to postoperative haemodynamic homeostasis, with restoration of beat-to-beat HR oscillations in TEA-treated patients as a result of modulation of the neuroendocrine and metabolic stress response.

We selected patients with no cardiovascular diseases recovering from uncomplicated lung resection and assessed both HRV and baroreflex sensitivity during short time periods (~30 min) in awake resting conditions, for 2 days after surgery. Besides surgical stress, cardiac autonomic control was also influenced by other perioperative factors (e.g. hypoxaemia, pulmonary hypertension, right heart distension, circadian rhythm, sleep pattern and physical rehabilitation) that were not evaluated. Moreover, the duration of postoperative impairment in HRV among PCA-treated patients and the effect of thoracic epidural

blockade on the recovery profile of cardiac autonomic regulation in patients with cardiovascular risk factors are not known.

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