Cardiovascular effects of thoracic epidural anaesthesia

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Chapter 8

Biventricular effects of sympathicolysis by high thoracic epidural anaesthesia during dynamic stress

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Submitted

Introduction

Activation of the sympathetic nervous system is considered a key component in cardiovascular homeostasis[1] and mobilization of cardiovascular reserve. As part of an integrated metabolic system, the ability of the heart to augment cardiac output (CO) is the main determinant of enhanced oxygen delivery during stress induced by exercise. Increments in CO are established by sympathetically mediated positive chronotropic and inotropic effects along with metabolically-induced reductions in systemic vascular resistance and enhanced muscle pump function. Thoracic epidural anaesthesia (TEA) reduces sympathetic outflow to the heart and may induce substantial changes in heart rate and ventricular function, depending on the prevailing level of sympathetic tone. We recently demonstrated, using pressure-volume analysis, that TEA impairs right ventricular (RV) function without affecting CO[2]. However, blockade of cardiac sympathetic innervation during exercise may reduce the degree with which the heart accelerates and enhances contraction. As such TEA provides a useful means for study of sympathetic control mechanisms during stress. Previous studies that assessed effects of β-blockers during exercise focused on general hemodynamics and left ventricular function. However, there is evidence that exercise-induced increases in CO lead to a greater load for the RV compared to the LV[3]. The present study therefore was designed to evaluate the biventricular effects of TEA during dynamic ergometric exercise. LV and RV systolic and diastolic function was assessed using pulsed wave tissue Doppler imaging (TDI).

The aims for the study were twofold. First, this study may provide additional insight in the role and effect-size of the cardiac sympathetic nervous system on changes in biventricular function during exercise. Second, the study design using dynamic ergometric exercise may mimic hemodynamic changes and elevations of sympathetic tone as present during surgery and thus may be relevant for clinical applications of TEA. In general, cardiac function has been shown to be an important determinant of outcome in cardiothoracic surgery[4, 5]. From this perspective TEA-induced decreases in cardiac reserve and alterations in circulatory control may potentially counteract the proclaimed beneficial effects in particular patient groups. The observation in several studies that use of TEA in high risk patients is associated with worse cardiovascular outcome seems to support this theory[6, 7]. The mechanisms behind TEA-associated cardiovascular problems are still poorly understood.

Methods

The protocol of this study was reviewed and approved by the Committee on Medical Ethics of the Leiden University Medical Center, reg. no: P14.044, date: 07 Jan 2015 and registered (Nederlands Trial Register, NTR 4880). Between January 2015 and July 2017, patients above 18 years scheduled for thoracic surgery (full lateral thoracotomies or video-assisted thoracoscopic surgery/VATS) under TEA were asked to participate in this study and were enrolled after written informed consent. Patients with contra-indications for TEA, a history of coronary artery disease (CAD), ejection fraction <40%, severe regurgitation or stenosis of a heart valve (grade 3 or 4),

heart rhythm other than sinus rhythm, existence of diabetes mellitus, use of β-blockers or Calcium-antagonists, pregnancy or lactation or participation in a trial on investigational drugs within 3 months prior to the study were excluded.

Study design

The study was performed preoperatively in awake patients in the recovery room. A randomized cross-over design with two study arms was used to eliminate the effect of timing of the tests on treatment effects. An epidural catheter was placed on the day before surgery. Patients performed a supine exercise test on an ergometer at two distinct time points: the day before surgery (test period 1) and immediately before surgery (test period 2). In study arm A, patients received an epidural dose of 6 ml of NaCl 0.9 % (control) in test period 1 and 6 ml of ropivacaine 0.75% (treatment) in test period 2. In study arm B, control and treatment were reversed. Patients were randomized to study arms A or B using a computer-generated randomization list (www.randomization.com)

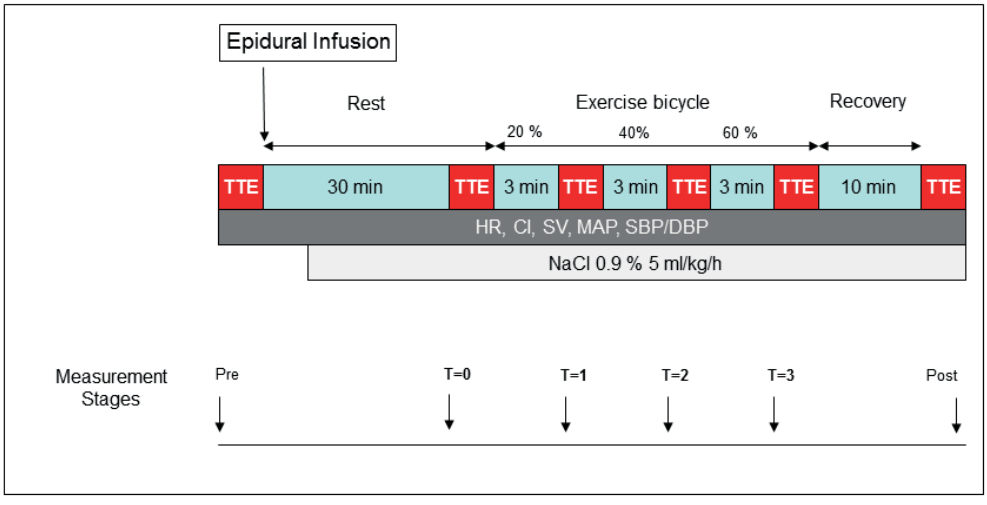


Figure 1. Measurement protocol executed during both test periods (Control and TEA). Hemodynamic and echocardiographic measurements were performed during different measurement stages: Pre (pre-study), immediately before epidural injection of ropivacaine 0.75%/ NaCl 0.9%; T0, 30 minutes after epidural injection of ropivacaine 0.75%/ NaCl 0.9%; T1, after 3 minutes bicycling with 20% of maximal workload; T2, after 3 minutes bicycling with 40% of maximal workload; T3, after 3 minutes bicycling with 60% of maximal workload; Post (post-study), after 10 minutes recovery of exercise test.
TTE, trans thoracic echocardiography; HR, heart rate; CI, cardiac index; SV, stroke volume; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

During both test periods patients performed an incremental supine bicycle exercise test with hemodynamic and echocardiographic measurements at the predefined measurement stages as shown in **Figure 1**.

Intravenous access was established and an infusion of NaCl 0.9% administered at a rate of 5 mL/kg/h starting with the epidural injection of ropivacaine 0.75% or NaCl 0.9%. Investigators were not blinded to epidural study medication during measurements and data acquisition. Evaluation of echocardiographic images and offline calculations were performed by a single investigator who was blinded to treatment group, test period and stages of the exercise protocol.

Premedication and preparations

Patients were allowed to have premedication with midazolam 5.0–7.5 mg orally 45 min before arrival at the recovery room. In case patients received premedication, it was administered before both test periods at equal doses.

Monitoring and general hemodynamics

Heart rate (HR) and oxygen saturation were monitored continuously throughout the study, starting with pre-study measurements before the epidural injection. An arterial line 20 G was inserted after local infiltration with lidocaine 1% in the radial or brachial artery to continuously monitor mean arterial pressure (MAP), systolic blood pressure (SBP), and diastolic blood pressure (DBP) (Edward Lifesciences LLC, Irvine, Ca, USA). In addition, cardiac output (CO) and stroke volume (SV) were monitored using the Vigileo/FloTrac system (software version 4.00; Edwards Lifesciences, Irvine, CA). Systemic vascular resistance was calculated as SVR = 80. MAP/CO, thus neglecting central venous pressure (CVP). SV and CO were indexed to body surface area (SVI, CI). Rate pressure product (RPP) was used as an indicator of myocardial oxygen demand and was calculated as RPP = HR . SBP.

If SBP decreased more than 30% below the pre-anesthetic value or below 90 mmHg following the start of TEA, ephedrine 5 mg IV was given. Bradycardia (heart rate < 40 beats/min) was treated with atropine sulphate, 0.5 mg IV. All monitoring data were automatically recorded in an electronic database (Metavision).

Thoracic epidural procedure

Insertion of the thoracic epidural catheter was performed at the T3-T4 level as described previously[2]. After epidural catheterisation the patient was placed in the supine position on the bicycle and a pre-study TTE exam was performed.

After the pre-study TTE exam, patients received either 6 ml of NaCl 0.9% or 6 ml of ropivacaine 0.75% through their epidural catheter, depending on the study arm. Ropivacaine was first administered as a test dose of 3 ml 0.75% followed within 3 minutes by another 3 ml of ropivacaine in case there was no sign of intrathecal placement of the catheter. On completion

of the measurements, patients returned to the ward. The epidural catheter was continuously flushed using NaCl 0.9% 2 ml/hr via a syringe pump to prevent obstruction.

Treatment schedule

In a previous study we demonstrated that thoracic epidural administration of 8 ml of ropivacaine 0.75% resulted in a rather large extension of sensory blockade[8]. We therefore limited the epidural dose to 6 ml aiming at a level of epidural analgesia sufficient for surgery while avoiding extension of sensory and motor blockade to the legs.

Assessments of analgesia

Analgesia was assessed bilaterally in the anterior axillary line over the chest and in the arms and legs by temperature discrimination using ice blocks. Results from both sides were averaged. All test for analgesic and motor blocks were performed by the same investigator (JW). Motor block of the lower extremities was tested using the Bromage scale (0-3). Motor block of the upper extremities was tested by finger grip (C8/T1), hand flexion (C5/C6), and elbow flexion (ESSAM score)[9]. Maximum sensory and motor blockade was tested 30 minutes after epidural administration of the study component. The following parameters were assessed: highest and lowest dermatomal level of analgesia, maximum numbers of segments blocked and maximum score of motor block (Bromage scale and ESSAM score). Patients were withdrawn from the study in case motor blockade of the legs or a sensory block prevented them from performing the exercise.

Echocardiography

Standard transthoracic (TTE) two-dimensional and M-mode echocardiography, pulsed wave Doppler and tissue Doppler imaging (TDI) examinations were performed with a Vivid 7 ultrasound machine (GE Healthcare, Hoevelaken, The Netherlands) equipped with a multifrequency phased-array transducer. All measurements were acquired from the AP 4CH view and performed by a board-certified echocardiographer.

Echocardiographic images were stored digitally for subsequent off-line analysis with EchoPac software (EchoPAC Dimension version 201; GE Vingmed Ultrasound AS, Horten, Norway). TDI images were acquired at frame rates above 150 Hz. All echocardiographic images were separated and filed according to measurement stage and test period. Subsequently these files were blinded for subject and measurement stage, then coded and digitally stored. The blinded files were presented in random order to the investigator responsible for analysis of echocardiographic data (JW). For each workload, at least three beats at normal sinus rhythm were analyzed and averaged for all outcome variables.

Left Ventricular (LV) function:

Pulsed wave TDI was used to quantify annular velocities of the mitral valve (MV) as peak systolic (MV S') and early and late diastolic mitral velocities at the lateral site of the LV (resp. MV E' and MV A').

In addition, pulsed wave Doppler was used to assess transmitral flow for peak velocity during early filling phase (MV E) and atrial contraction (MV A), the ratio of E to A velocities (MV E/A) and deceleration time (MV E DT).

Right Ventricular (RV) function:
RV systolic function was assessed using Tricuspid Annular Plane Systolic Excursion (TAPSE). Pulsed wave TDI was used to quantify tricuspid valve annular velocity as peak systolic (TV S') and diastolic (TV E' and TV A') velocities at the lateral site.
Pulsed wave Doppler was used to quantify transtricuspid flows as peak velocity during early filling phase (TV E), peak velocity during atrial contraction phase (TV A) and the ratio of E to A (TV E/A).

Exercise test
The exercise test was performed with supine bicycle ergometry on a Cardiowise XRCISE Stress Echo ergometer (Cardiowise, Heilbronn, Germany), with the table inclined to 30-45° and tilted to 20-30° in the left lateral decubitus position. Individual maximal workload was determined using the formula:
Max workload (Watt) = 105 - (2.525xA) + (0.8083xL) + (0.575xW)
(A = age in years, L = length in cm, W = weight in kg)
For female patients the max workload was adjusted to 80% of this calculated value.
Echocardiography (TTE) was performed according to a preset protocol with measurements repeated after 3 minutes of incremental fixed workloads. The pedaling rate was kept constant using patient self-monitoring on a speed display at eye level. The initial workload was 20% of the maximal workload (T1) with subsequent increments towards 40% (T2) and 60% (T3). Patients were prompted to stop bicycling and start the recovery period in case of exhaustion, occurrence of chest pain and/or ST segment abnormalities on the ECG.

Data analysis and sample size
Objectives
Primary endpoints were TDI-based estimates of LV and RV systolic function (MV S' and TV S', respectively). Additional echocardiographic data and hemodynamic data were considered secondary endpoints.

Data analysis
All data are presented as means with range or standard deviation (SD), as appropriate. Outcome parameters were analyzed using a linear mixed effects model (LMM) in order to properly account for repeated measurements. In particular, a random intercepts term was used. To capture the mean progression of each outcome parameter, we used an unstructured mean model with the following covariates: the main effect of exercise (taken as factor), the main effect of TEA, their interaction, and the main effect of period. Based on this model several hypotheses were tested.

First, we tested if the mean profiles were different between TEA and control during the stages T0-T3 (TEA effect). Second, we tested if mean outcome parameters were changed during T0-T3 (Exercise effect). Third, we tested if the mean changes during the exercise levels T1-T3 vs T0 were statistically different between TEA and control (TEA-Exercise interaction).

Normality of the residuals of the fitted models was checked and where appropriate the logarithmic transformation was applied on the relevant outcome parameters. All hypotheses were tested using the F-test or the Multivariate Wald test where appropriate. Results are reported via the corresponding p-values and plots of the fitted mean profiles per group with standard deviation. All analyses were done in R (the R Development Core Team, www.R-project.org) using the packages lme 4[11] and lmerTest (Alexandra Kuznetsova, Per Bruun Brockhoff and Rune Haubo Bojesen Christensen [2016]. lmerTest: Tests in Linear Mixed Effects Models. R package version 2.0-33. https://CRAN.R-project.org/package=lmerTest).

Statistical inference for the primary outcome variables MV S' and TV S' were corrected for multiple testing using the false discovery rate (FDR) method[12]. Other hemodynamic and echocardiographic parameters were not corrected for multiple testing. P values less than 0.05 were considered significant.

Results

Fourteen patients were enrolled in this study. Two of them were not included in the final analysis because of failure of epidural placement (N=1) or vasovagal collapse (N=1) during epidural puncture. Demographics and data regarding neural blockade are presented in **Table 1**. Good-to-fair quality images were obtained in all patients. TDI analysis could not always be completed during highest workload because of suboptimal image quality and/or fusion of E and A waves. However, MV S' and RV S' velocities were obtained at highest workload in 11 (92%) and 12 (100%) patients respectively (T3).

Table 1. Patient characteristics and characteristics of neural blockade 30 minutes after epidural injection

Patient characteristics	N=12
Age (years)	44 (18-68)
Gender (M/F)	7/5
ASA (I/II/III)	10/2/0
Height (cm)	182 (168-196)
Weight (kg)	83 (50-113)
Antihypertensive medication (yes/no)	0/12
Operation side (left/right/median)	6/5/1
Study arm (A/B)	5/7
Neural blockade 30 minutes after epidural administration of Ropivacaine 0.75%	
Highest level of analgesia (dermatome)	C5 (C3-T1)
Lowest level of analgesia (dermatome)	T8 (T6-L1)
Maximum number of spinal segments blocked	12 (9.0-17.5)
Maximum Bromage score (0-3)	0 (0.0-0.0)
Maximum ESSAM score (0-3)	0.3 (0.0-1.0)

Data are presented as mean (range). ASA, American Society of Anesthesiologists; TEA, thoracic epidural anaesthesia.

Conditions

All patients were able to complete the exercise test during control and TEA. The majority of patients reported a high level of fatigue during the maximal exercise level in both conditions, confirming the high intensity of exercise. None of the patients showed signs of coronary ischemia during exercise. The average total exercise time was comparable between the two sessions: control 22 min, TEA 23 min. Individual peak workloads ranged from 50 to 157 Watt. We tested if the TEA effects were different between the two study arms. There was no statistically significant carry-over effect for any of the outcome parameters and thus the period by treatment interaction term was excluded from the LMM.

Measurements

The effects of TEA and exercise on echocardiographic and hemodynamic parameters are presented in **Tables 2-4**. P values indicate statistical significances for TEA effects, exercise effects, and interaction effects between TEA and exercise.

Table 2. The effects of thoracic epidural anaesthesia and exercise on global hemodynamics

	Conditions	Rest	Exercise Stages			Effects		
		T0	T1	T2	T3	TEA	Exercise	Inter-action
Global Hemodynamics								
HR (beats/min)	Control TEA	63 (11) 61 (13)	82 (9) 76 (8)	99 (14) 88 (9)	117 (20) 106 (18)	P=0.001	P<0.001	P=0.205
SBP (mmHg)	Control TEA	149 (18) 129 (22)	163 (24) 139 (27)	174 (28) 150 (28)	183 (28) 161 (25)	P<0.001	P<0.001	P=0.931
DBP (mmHg)	Control TEA	69 (11) 62 (10)	67 (12) 62 (10)	68 (11) 63 (11)	72 (13) 68 (14)	P<0.001	P=0.002	P=0.448
MAP (mmHg)	Control TEA	94 (12) 83 (12)	95 (14) 86 (12)	98 (13) 90 (12)	103 (15) 97 (14)	P<0.001	P<0.001	P=0.417
RPP (mmHg/min.1000)	Control TEA	9.3 (1.7) 7.8 (1.9)	13.4 (2.2) 10.4 (1.9)	17.1 (3.3) 13.0 (2.2)	21.2 (3.9) 16.8 (2.7)	P<0.001	P<0.001	P=0.024
CI (L/min/m^2)	Control TEA	3.4 (0.9) 3.1 (0.7)	4.8 (1.5) 3.8 (0.9)	6.0 (1.9) 4.9 (1.1)	7.6 (2.8) 6.2 (1.2)	P<0.001	P<0.001	P=0.215
SVI (ml/m^2)	Control TEA	54 (11) 52 (13)	59 (18) 50 (10)	60 (14) 54 (12)	64 (17) 57 (12)	P=0.006	P<0.001	P=0.672
SVR (dynes/s/cm^5)	Control TEA	1155 (277) 1093 (222)	847 (259) 905 (193)	696 (209) 752 (164)	586 (181) 630 (113)	P=0.389	P<0.001	P=0.535

Values at rest and during exercise are presented as mean (SD). Effects were determined by a linear mixed effects model (see statistical analysis for details) and presented as P value. T0, 30 minutes after epidural injection of ropivacaine 0.75% / NaCl 0.9%; T1, after 3 minutes bicycling with 20% of maximal workload; T2, after 3 minutes bicycling with 40% of maximal workload; T3, after 3 minutes bicycling with 60% of maximal workload.

TEA, thoracic epidural anaesthesia; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RPP, rate pressure product; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance.

General hemodynamics (Table 2 and Figure 2)

Compared to control, TEA significantly reduced all hemodynamic parameters except SVR. Maximal reductions were -11% for HR, -24% for RPP, -15% for SVI and -21% for CI. During exercise HR, SVI and CI increased (maximal +86%, +19% and +124% versus T0, respectively). MAP, SBP and DBP also increased (+17%, +25% and +10%, respectively) despite significant reductions in SVR (-49%) in both conditions. No significant interactions between TEA and exercise were found, except for RPP (P=0.024).

Table 3. The effects of thoracic epidural anaesthesia and exercise on systolic and diastolic left ventricular function

		Rest	Exercise Stages			Effects		
	Conditions	T0	T1	T2	T3	TEA	Exercise	Interaction
Systolic function								
MV S' (cm/s)	Control	10.8 (2.7)	13.0 (3.3)	16.1 (4.4)	16.9 (5.3)	P=0.025	P<0.001	P=0.302
	TEA	10.6 (2.2)	12.4 (3.5)	13.8 (5.0)	15.7 (5.1)			
Diastolic function								
MV E' (cm/s)	Control	14.0 (4.0)	16.1 (3.3)	17.2 (4.3)	17.9 (4.3)	P=0.470	P<0.001	P=0.956
	TEA	13.4 (4.1)	15.0 (3.3)	16.3 (3.0)	17.4 (4.1)			
MV A' (cm/s)	Control	8.6 (3.3)	10.3 (4.2)	12.7 (3.2)	12.7 (4.2)	P=0.230	P<0.001	P=0.138
	TEA	8.3 (3.6)	10.2 (3.7)	10.3 (4.6)	14.8 (6.3)			
MV E (m/s)	Control	0.76 (0.17)	0.89 (0.14)	0.98 (0.15)	1.09 (0.22)	P=0.836	P<0.001	P=0.724
	TEA	0.76 (0.13)	0.87 (0.11)	0.96 (0.16)	1.13 (0.14)			
MV Dec T (ms)	Control	169 (41)	178 (33)	163 (33)	134 (25)	P=0.056	P<0.001	P=0.035
	TEA	186 (30)	153 (27)	139 (33)	141 (36)			
MV A (m/s)	Control	0.64 (0.19)	0.74 (0.13)	0.81 (0.18)	0.85 (0.24)	P=0.172	P<0.001	P=0.922
	TEA	0.55 (0.18)	0.68 (0.17)	0.72 (0.23)	0.81 (0.25)			
MV E/A	Control	1.3 (0.36)	1.2 (0.35)	1.3 (0.29)	1.3 (0.42)	P=0.039	P=0.159	P=0.701
	TEA	1.5 (0.54)	1.4 (0.33)	1.3 (0.32)	1.6 (0.64)			
MV E/E'	Control	5.6 (1.2)	5.7 (1.0)	6.0 (1.6)	6.0 (1.6)	P=0.233	P<0.001	P=0.744
	TEA	6.0 (1.5)	6.0 (1.2)	6.0 (1.2)	6.7 (1.1)			
MV E'/A'	Control	1.9 (1.0)	1.8 (0.6)	1.5 (0.6)	1.6 (0.8)	P=0.345	P=0.073	P=0.231
	TEA	2.0 (1.2)	1.7 (0.8)	2.0 (1.1)	1.4 (0.7)			

Values at rest and during exercise are presented as mean (SD). Effects were determined by a linear mixed effects model (see statistical analysis for details) and presented as P value. T0, 30 minutes after epidural

injection of ropivacaine 0,75%/ NaCl 0,9%; T1, after 3 minutes bicycling with 20% of maximal workload; T2, after 3 minutes bicycling with 40 % of maximal workload; T3, after 3 minutes bicycling with 60% of maximal workload.

TEA, thoracic epidural anaesthesia; MV S', peak systolic velocity of the mitral annulus; MV E', early diastolic velocity of the mitral annulus; MV A', late diastolic velocity of the mitral annulus; MV E, peak mitral flow velocity during early filling phase; MV Dec T, the time interval required for the E velocity to decline from its peak to the baseline; MV A, peak mitral flow velocity during atrial contraction phase; MV E/A, ratio of E to A; MV E/E', ratio E to E'; MV E'/A', the ratio of E' to A'.

Left Ventricular (LV) function (Table 3 and Figure 3)

Systolic LV function

TEA induced a significant decrease in LV systolic function, reflected by decreases in MV S' (-14%). Exercise resulted in increases in MV S' (maximal +56%).

There were no significant interaction effects between TEA and exercise.

Diastolic LV function

TEA had no effect on MV E',MV A', MV E and MV A, but there was a small increase in MV E/A (P=0.039).

Exercise augmented MV E' (maximal +30%), MV A' (+78%) as well as MV E (+49%) and MV A (+47%). There was a small but significant increase in E/E' (+12%) while MV E/A remained unchanged from resting values.

TEA was associated with a steeper decline in MV E DT (P=0.035) during exercise. No other interactions were found.

Table 4. The effects of thoracic epidural anesthesia and exercise on systolic and diastolic right ventricular function

		Rest	Exercise Stages			Effects		
	Conditions	T0	T1	T2	T3	TEA	Exercise	Interaction
Systolic function								
TV S' (cm/s)	Control	14.3 (1.6)	16.1 (1.7)	20.4 (2.3)	21.5 (2.6)	P<0.001	P<0.001	P=0.086
	TEA	12.3 (1.8)	14.4 (2.1)	16.1 (2.4)	19.0 (2.5)			
TAPSE (cm)	Control	2.7 (0.4)	3.0 (0.4)	3.1 (0.5)	3.2 (0.6)	P=0.097	P<0.001	P=0.719
	TEA	2.5 (0.3)	2.8 (0.2)	3.0 (0.5)	3.1 (0.6)			
Diastolic function								
TV E' (cm/s)	Control	14.9 (2.8)	17.9 (1.7)	21.3 (5.0)	22.5 (6.5)	P=0.390	P<0.001	P=0.736
	TEA	14.8 (1.6)	16.0 (2.1)	20.8 (5.2)	21.5 (6.3)			
TV A' (cm/s)	Control	12.3 (3.6)	14.9 (4.7)	18.3 (5.9)	22.5 (6.0)	P=0.342	P<0.001	P=0.721
	TEA	12.0 (4.2)	14.2 (4.6)	16.1 (4.3)	19.9 (6.2)			
TV E (cm/s)	Control	0.56 (0.09)	0.61 (0.13)	0.73 (0.18)	0.81 (0.15)	P=0.639	P<0.001	P=0.672
	TEA	0.57 (0.12)	0.61 (0.09)	0.80 (0.15)	0.82 (0.26)			
TV Dec T (ms)	Control	222 (68)	169 (68)	138 (33)	128 (44)	P=0.982	P<0.001	P=0.948
	TEA	218 (55)	176 (57)	143 (34)	124 (31)			
TV A (cm/s)	Control	0.37 (0.10)	0.55 (0.11)	0.62 (0.14)	0.77 (0.15)	P=0.005	P<0.001	P=0.330
	TEA	0.33 (0.08)	0.48 (0.15)	0.57 (0.14)	0.61 (0.18)			
TV E/A	Control	1.6 (0.5)	1.2 (0.4)	1.2 (0.3)	1.1 (0.3)	P=0.011	P=0.004	P=0.896
	TEA	1.8 (0.6)	1.4 (0.5)	1.6 (0.6)	1.3 (0.6)			
TV E/E'	Control	3.9 (1.2)	3.4 (0.8)	3.6 (1.0)	4.0 (1.1)	P=0.368	P=0.109	P=0.391
	TEA	3.8 (0.7)	3.9 (0.9)	3.9 (0.7)	3.7 (1.0)			
TV E'/A'	Control	1.4 (0.6)	1.4 (0.8)	1.4 (0.9)	1.0 (0.3)	P=0.891	P=0.230	P=0.787
	TEA	1.4 (0.6)	1.2 (0.4)	1.4 (0.6)	1.1 (0.3)			

Values at rest and during exercise are presented as mean (SD). Effects were determined by a linear mixed effects model (see statistical analysis for details) and presented as P value. T0, 30 minutes after epidural injection of ropivacaine 0.75% / NaCl 0.9%; T1, after 3 minutes bicycling with 20% of maximal workload; T2, after 3 minutes bicycling with 40% of maximal workload; T3, after 3 minutes bicycling with 60% of maximal workload.

TEA, thoracic epidural anesthesia; TV S', peak systolic velocity of the tricuspid annulus; TAPSE, tricuspid annular plane systolic excursion; TV E', early diastolic velocity of the tricuspid annulus; TV A', late diastolic velocity of the tricuspid annulus; TV E, peak tricuspid flow velocity during early filling phase; TV Dec T, the time interval required for the E velocity to decline from its peak to the baseline; TV A, peak tricuspid flow velocity during atrial contraction phase; TV E/A, ratio of E to A; TV E/E', ratio E to E'; TV E'/A', the ratio of E' to A'.

Right Ventricular (RV) function (Table 4 and Figure 4)

Systolic RV function

TEA decreased TV S' (-21%) but did not significantly affect TAPSE.

Exercise significantly increased TV S' (+54%) and TAPSE (+24%).

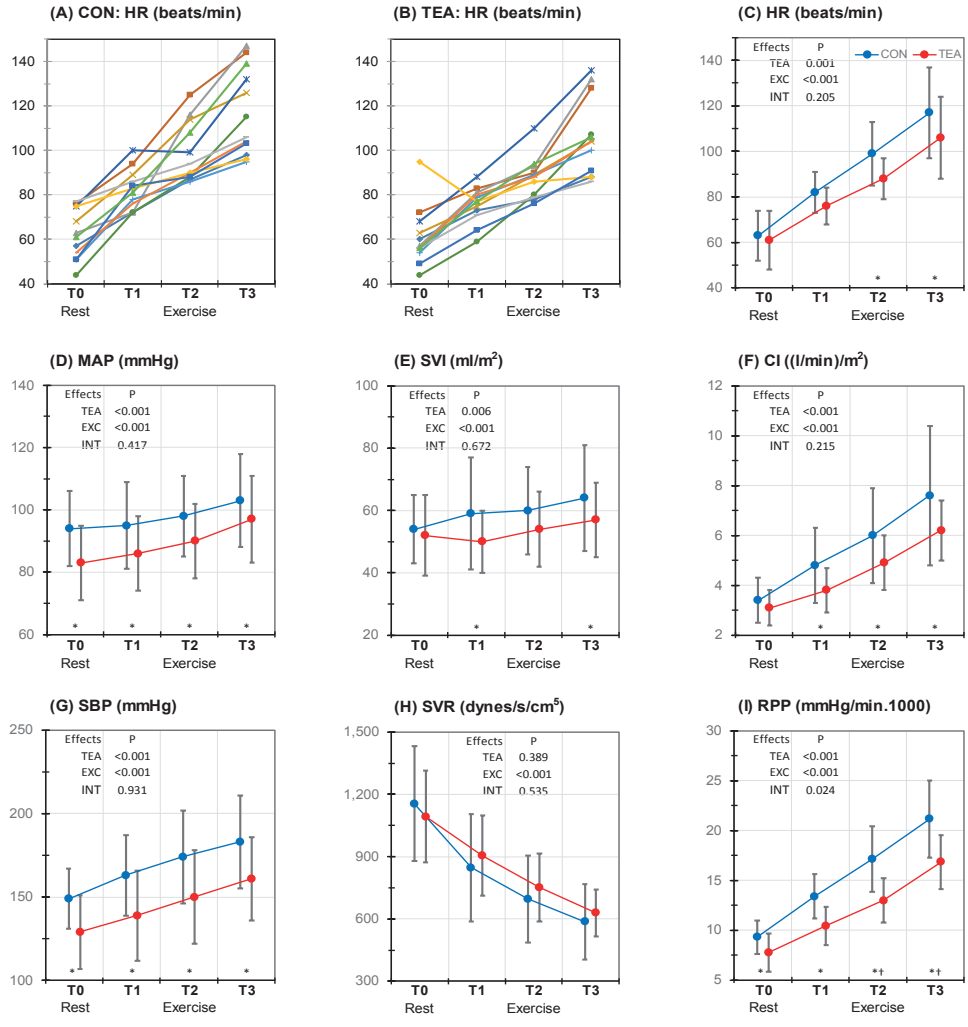
Data suggested an interaction TEA-Exercise effect for TV S', with the effect of TEA being larger at higher levels of exercise. However, after correcting for multiple testing significance was lost (P=0.086).

Diastolic RV function

TEA significantly decreased TV A (–21%) and increased TV E/A (+33%).

Exercise increased TV E' (+51%), TV A' (+83%), TV E (+45%) and TV A (+108 %) and decreased TV E DT (–43%) and TV E/A (–31%). TV E/E' and TV E'/A' were not affected. No interaction TEA-exercise effects were found.

Figure 2. Individual and mean (SD) hemodynamic values at different measurement stages



(Measurement stages, see Figure 1). Spaghetti plot of individual heart rates at control condition (A) and TEA (B); mean values of HR (C), MAP (D), SVI (E), CI (F), SBP (G), SVR (H) and RPP (I) during control (blue symbols) and TEA (red symbols). P values are presented for the overall effects of thoracic epidural anaesthesia (TEA), exercise (EXC) and interaction effects between exercise and TEA (INT). In case of significant overall effects, the specific time points (T0-T3) at which significance was reached are indicated with * for a significant TEA effect and † for a significant TEA-exercise interaction effect.

Discussion

Both ventricles are densely innervated by sympathetic nerves[13, 14]. It seems therefore likely that cardiac sympathetic blockade by TEA reduces biventricular systolic function and attenuates the augmentation of LV as well as RV function during exercise. Our present findings indeed indicate that TEA reduces biventricular systolic function, however exercise-induced augmentation of RV and LV function was largely preserved. Likewise, CI was lowered by TEA which resulted from decreases in both SV and HR, but augmentation during exercise was preserved. Overall, the exercise-induced responses were only minimally influenced by TEA, suggesting that mechanisms other than cardiac sympathetic innervation play a substantial role in the cardiac and circulatory response to exercise.

Exercise has been shown to result in up to 100% increases in the contractile state of the left and right ventricle[10, 15, 16]. Cardiac sympathetic innervation is primarily essential during exercise, stress or dynamic challenges, and not in rest. This is illustrated in cardiac transplant studies where patients with sympathetic reinnervation demonstrated better chronotropic and inotropic responses to exercise and improved exercise performance compared to those without reinnervation. In contrast, cardiac performance during resting conditions did not differ between these groups[17]. In addition, cardiac sympathetic blockade by TEA has also been shown to decrease cardiac norepinephrine spillover following sternotomy whereas there was no effect of TEA on norepinephrine spillover prior to surgical stress[18]. We assessed the effects of TEA during progressive bicycle exercise, which challenges the heart to raise cardiac output to meet the increased O_2 demand. Previous studies show that the elevated sympathetic tone created with bicycle exercise resembles that encountered in the perioperative period; both conditions are reported to lead to 3-4-fold increases in plasma norepinephrine levels[19, 20].

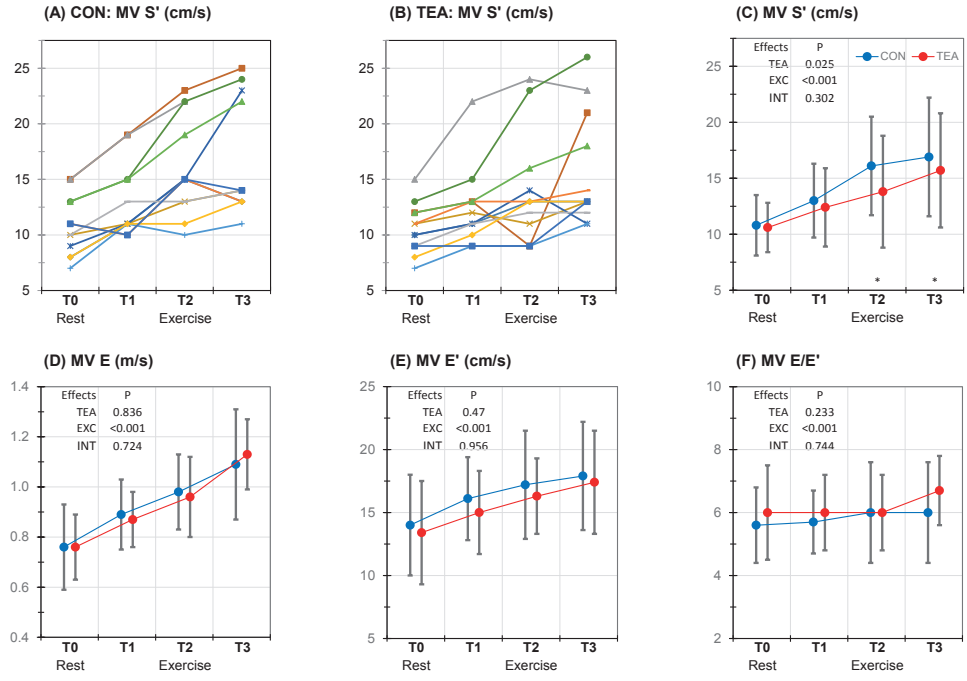


Figure 3. Individual and mean (SD) echocardiographic values for left ventricular function at different measurement stages (Measurement Stages, see Figure 1).

A, spaghetti plot of individual MV S' values at control condition (A) and TEA (B); mean values of MV S' (C), MV E (D), MV E'(E) and MV E/E'(F) during control (blue symbols) and TEA (red symbols). P values are presented for the overall effects of thoracic epidural anaesthesia (TEA), exercise (EXC) and interaction effects between exercise and TEA (INT). In case of significant overall effects, the specific time points (T0-T3) at which significance was reached are indicated with * for a significant TEA effect and † for a significant TEA-exercise interaction effect.

CON, control; MV S', peak systolic velocity of the mitral annulus; MV E, peak mitral flow velocity during early filling phase; MV E', early diastolic velocity of the mitral annulus; MV E/E', ratio E to E'.

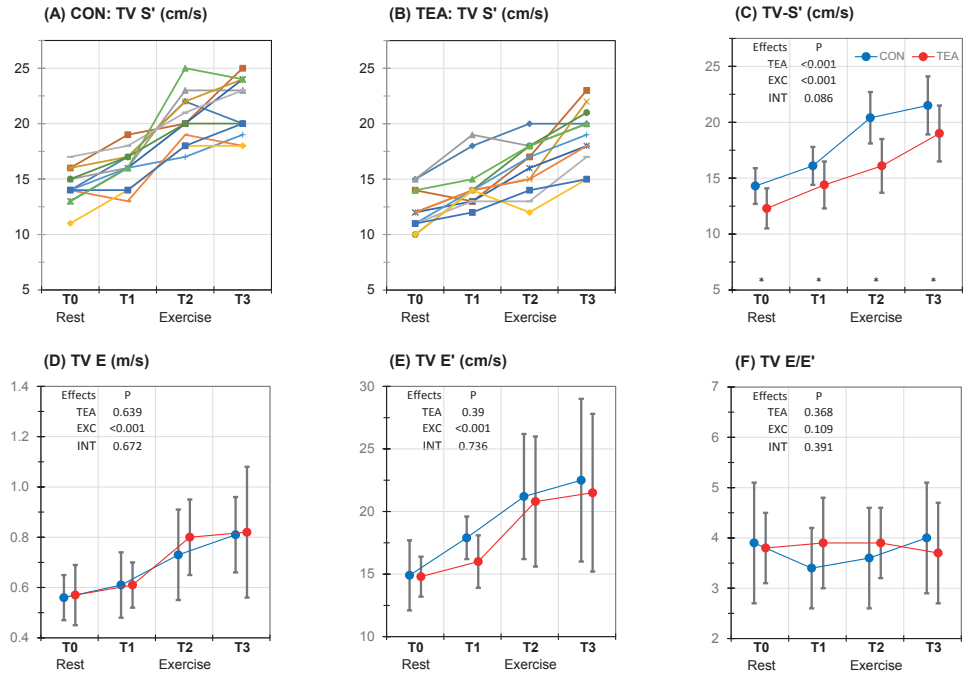


Figure 4. Individual and mean (SD) echocardiographic values for right ventricular function at different measurement stages (Measurement Stages, see Figure 1).

A, spaghetti plot of individual TV S' values at control condition (A) and TEA (B); mean values of TV S' (C), TV E (D), TV E'(E) and TV E/E'(F) during control (blue symbols) and TEA (red symbols). P values are presented for the overall effects of thoracic epidural anaesthesia (TEA), exercise (EXC) and interaction effects between exercise and TEA (INT). In case of significant overall effects, the specific time points (T0-T3) at which significance was reached are indicated with * for a significant TEA effect and † for a significant TEA-exercise interaction effect.

CON, control; TV S', peak systolic velocity of the tricuspid annulus; TV E, peak tricuspid flow velocity during early filling phase; TV E', early diastolic velocity of the tricuspid annulus; TV E/E', ratio E to E'.

In general, TEA may change HR and loading conditions of the heart which affects load dependent echocardiographic variables. To assess the direct effects of TEA on intrinsic cardiac function (contractility) without the confounding effects of loading conditions is cumbersome. Pressure-volume analysis using conductance catheters is the gold standard to obtain load-independent indices of cardiac function, however it is a rather invasive and technically challenging technique. We used TDI, which allows for quantitative assessment of systolic and diastolic LV and RV function by measuring velocities of the mitral and the tricuspid annulus. Longitudinal myocardial velocities correlate with ejection fraction[21-23], cardiac function indices

obtained by conductance catheters [23] and τ, the time constant of isovolumic relaxation[24]. TDI was demonstrated to be a robust and reproducible measure of cardiac function during exercise[10,15,16]. Supine exercise testing was chosen over treadmill or handgrip exercise because potential motor blockade of the arms by TEA prevents safe or reliable use of the latter. Studies report that TDI yields relatively load independent parameters of cardiac function[25,26], but TDI has also been shown to be preload dependent[27,28]. This is relevant because neural blockade by TEA may result in venodilatation and pooling of blood in the splanchnic vascular beds[29]. In our study TV E, MV E, TV E/E', MV E/E' and SVR (**Figures 2, 3 and 4**) were not significantly influenced by TEA, suggesting only limited influences on loading conditions. In addition, exercise results in marked increases in venous return by contractions of skeletal muscles making the effect, if any, of TEA on venous return probably small. Afterload, as indexed by SVR (**Figure 2**), was not affected by TEA which may have been the result of compensatory vasoconstriction in the neural segments not blocked by TEA[30]. Another explanation might be that the exercise-induced decreases in SVR were too large for TEA to have any additional effect on SVR. Thus, loading conditions appeared to be comparable between control and TEA measurements.

In line with the present findings, previous studies demonstrated decreased LV function following neural blockade by TEA[31,32]. We previously reported decreased resting RV isovolumetric acceleration (IVA) in patients following induction of TEA[33]. In addition we demonstrated that TEA reduced RV contractility 2 using pressure-volume analysis.

To our knowledge no previous studies assessed TEA effects on biventricular function during exercise stress. Two previous studies examined the circulatory effects of TEA during bicycle exercise and reported limited effects of TEA on HR, CO, MAP and oxygen extraction during exercise[34,35]. One of these studies also assessed LV function, however, only at rest[35].

There are however studies assessing cardiovascular effects of β-blockers during exercise which might serve as framework to evaluate our findings. Acute treatment with β-blockers during exercise caused a reduction in HR, SV and CO which was compensated for by increases in O2-extraction. End-diastolic dimensions increased after administration of β-blockade, indicating use of the Frank-Starling mechanism as a compensatory mechanism for the decreases in myocardial contractility[36-38]. β-blockers have also been reported to significantly decrease exercise endurance, with decreases up to 40%[36,39]. In the present study exercise endurance, although not measured, appeared unchanged after TEA with all patients being able to execute the exercise protocol. The reported 15-25% reductions in HR, SV and CO elicited by β-blockers are comparable to those observed in our study[36-40]. Another resemblance is the preserved ability to increase heart rate and cardiac output during exercise. Moreover, our study indicates that both LV and RV systolic function are slightly depressed by TEA but maintain their ability to improve with exercise without significant interaction TEA-exercise effects. Only the augmentation of RV systolic function assessed by TV S' tended to be somewhat less after TEA. Regarding LV function,

our findings are in concordance with a previous β–blocker study using LV dP/dt[37]. Previous studies assessing effects of β–blockers on RV function during exercise are to our knowledge not available.

A partial explanation for our findings may be that sympathetic blockade by TEA was not complete. The degree of sympathetic blockade achieved seems to vary and TEA probably induces reductions in sympathetic neural transmission rather than complete blockade[41, 42]. Despite this limitation, our findings, like the mentioned β-blocker studies, indicate that sympathetic cardiac innervation is only one of multiple control mechanisms in the cardiovascular response to exercise and other mechanisms must be involved. A potential mechanism may be the increased venous return during exercise as a result of muscle contractions and systemic venoconstriction by increased sympathetic tone[43]. Increases in preload would increase CO via the Frank-Starling mechanism. However, the marked increases in TDI-derived indices of cardiac function during exercise observed in our study are much larger than would be expected merely on basis of increases in preload[44]. In addition, reduced afterload by metabolically induced reductions in SVR during exercise facilitates systolic ejection and increases systolic performance[26, 45]. Interestingly, SVR was not significantly reduced by TEA in our study and no significant TEA-exercise interaction was found.

Also catecholamine release from the adrenal glands during exercise may explain the maintained augmentation of HR, CI and TDI parameters in the presence of TEA. The adrenal medulla receives its sympathetic innervation from preganglionic fibers from spinal segments T6 through L2. The mean lower border of analgesia in our patients was spinal level T8 (T6-L1) (**Table 1**), implying no or only partial blockade of sympathetic innervation to the adrenal medulla in our patients.

We cannot exclude the confounding effects of HR on cardiac systolic function. HR during exercise was lowered by TEA, which via a phenomenon known as the force-frequency relationship may have resulted in decreased cardiac systolic function[46]. However, TEA resulted in relatively small reductions of HR. In addition, a previous study demonstrated that the effect of a β-blocker on myocardial systolic performance was independent of alterations in heart frequency[40].

The effects of TEA on systolic ejection parameters appeared more pronounced for the RV than the LV, which might be explained by differential effects of exercise on the pulmonary and systemic circulation. Excessive raise of pulmonary and systemic arterial pressure by enhanced CO during exercise is prevented by decreases in pulmonary and systemic vascular resistance, respectively. Via recruitment and distension of pulmonary vessels[47] the pulmonary vascular resistance can be reduced approximately 30%[48], but the decrease in systemic vascular resistance can be much more pronounced[49] and may partly mask the decrease in LV systolic function. Increases in left atrial pressures during exercise[50, 51] may further contribute to elevated RV pressures during exercise. Therefore the hemodynamic load on the RV increases more during exercise than on

the LV[3], consistent with increases in the PAP/MAP ratio during exercise reported in a study by Ottesen and colleagues[34]. For the RV to maintain SV while afterload increases it has to use volumetric autoregulation (Frank-Starling) or raise its inotropic state. Enhanced inotropic state may result from homeometric autoregulation (Anrep effect) or increases in sympathetic tone[52]. Although RV function during exercise is pivotal in order to maintain or raise CO when faced with increased afterload and wall stress, augmentation of RV function may be less compared to LV function[53]. Thus, interactions between cardiac sympathetic blockade by TEA and exercise would be expected to be more pronounced for the RV than the LV.

With regard to application of TEA during surgery the results of this study are reassuring and demonstrate that use of TEA in patients with normal cardiovascular function attenuates ventricular function but does not abolish mobilization of cardiovascular reserve. It is however important to realize that in this study PVR and SVR were lowered as a result of exercise, facilitating ejection, which might be the opposite during surgery. Patients at risk for or with raised RV afterload may be more susceptible to the TEA-induced reductions in cardiac reserve which needs to be explored in future studies.

There are several potential limitations in our study. We chose this randomized cross-over design with two study arms to increase the statistical power, allowing a relatively small patient sample. The design also aimed to eliminate the effect of timing of the tests on treatment effects: because of the large time interval between the two test periods we assumed no carryover effects related to infusion of local anaesthetics or the repeated exercise test. This was confirmed statistically for all outcomes analyzed. Despite this, the sample size was relatively small which may have limited the power to detect TEA-exercise interaction effects.

Dynamic exercise was used to mimic stress during surgery. However, exercise is typically associated with decreases in SVR, where surgical stress is more likely to increase afterload of the RV or LV.

We used pulsed wave TDI with high sampling frequency (> 150 Hz) to obtain reliable myocardial velocities during exercise. However, frame rate may remain too low to measure peak velocities at high HR. Also Doppler flow measurements may suffer from underestimation by misalignment with high velocity as well. Consequently systematic underestimation of peak velocities with increasing workload may have occurred.

The adrenal glands receive sympathetic innervation from preganglionic sympathetic neurons in spinal segments T6-L2[54]. Therefore there might have been only partial blockade of sympathetic outflow to the adrenal medulla. We did not measure levels of circulating epinephrine which might have given information on the association between adrenal medullary activity[54] and rise of HR, CI and cardiac systolic parameters during exercise. We did not measure norepinephrine

plasma concentrations, which would have provided a reflection of overall sympathetic activation, but no indication on the dominant source of release during exercise[55]. However, norepinephrine concentration needs to increase to levels above 1800 ng/L (8 fold increase from baseline) to elicit a hemodynamic effect[56]. Bicycle ergometry (100 watt for 10 min) has been shown to result in a 3-4 fold increase in plasma norepinephrine concentration to approximately 1000 ng/L and only vigorous exercise yielded values above 1800 ng/L[57]. Epinephrine rises 3-4 fold with exercise and might stimulate β-receptors of the heart[58]. Therefor adrenal medullary activity might be an explanatory mechanism for the sustained augmentations in cardiac function despite sympathetic blockade to the heart by TEA.

Conclusion

Cardiac sympatheticolysis reduced LV and RV systolic function without affecting diastolic biventricular function. Augmentation of LV and RV function during exercise was preserved. Thus, besides cardiac sympathetic stimulation other important mechanisms are involved in the regulation of cardiac function during exercise leading to preserved homeostatic adaptation via enhanced cardiac function and heart rate.

With regard to application of TEA during surgery the results are reassuring. However, all patients in this study were cardiovascular healthy. Patients with cardiopulmonary disease may have exaggerated workload of the RV during exercise stress and therefor may be more vulnerable to TEA-induced reductions in cardiac reserve. Moreover, during or after surgery afterload of the RV or LV may be increased and cardiovascular effects of TEA might be more pronounced in these circumstances.

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