Cardiovascular effects of thoracic epidural anaesthesia
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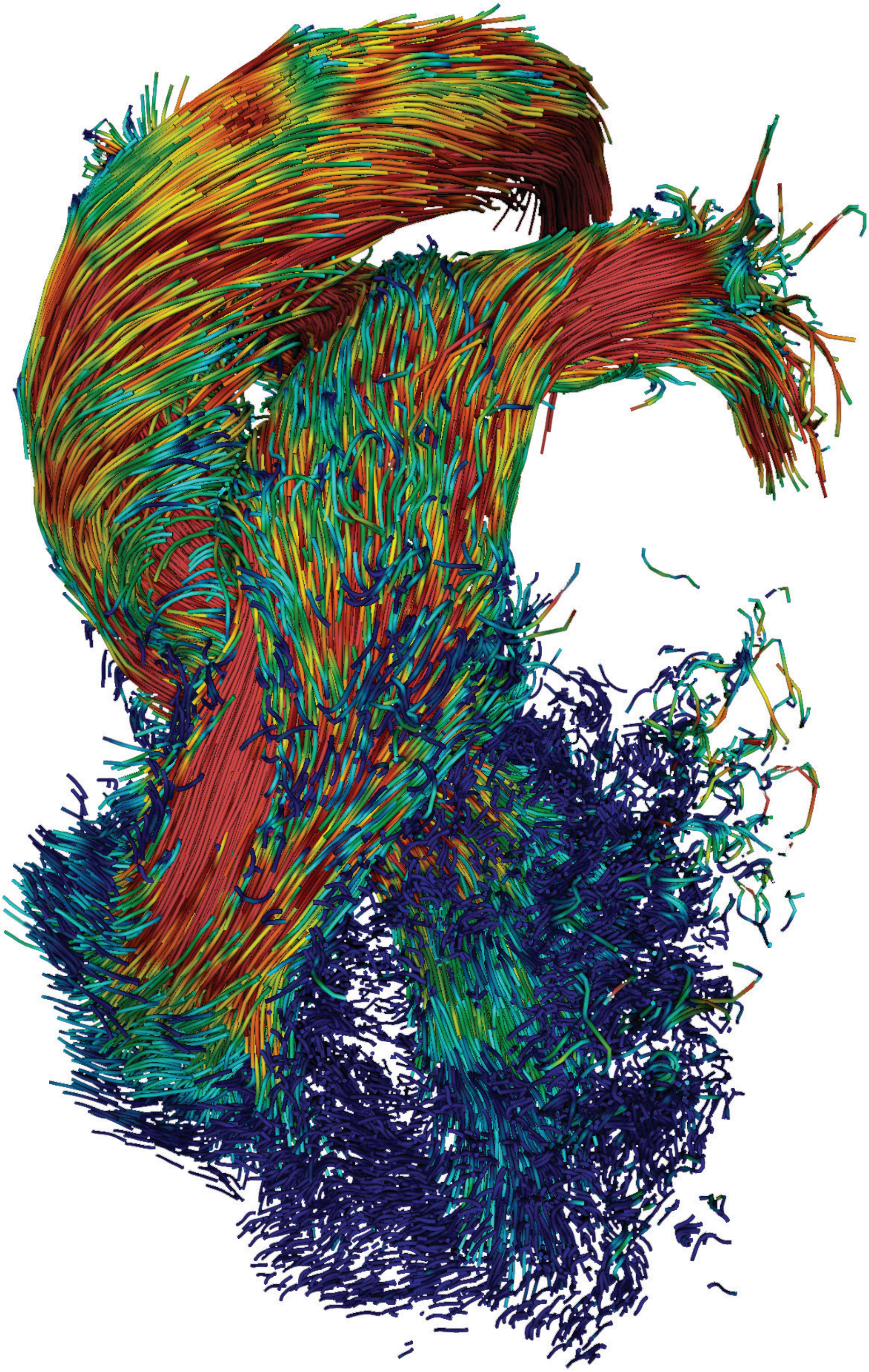

Section IV

Thoracic epidural anaesthesia: effects on cardiac performance

Chapter 7

Thoracic epidural anaesthesia reduces right ventricular systolic function with maintained ventricular-pulmonary coupling

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Introduction

Thoracic epidural anaesthesia (TEA) is considered to be the gold standard anaesthetic approach in lung surgery and also widely applied in patients undergoing cardiac surgery. TEA provides excellent analgesia, decreases postoperative pulmonary complications[1, 2] and may have a positive effect on the immune and the coagulation system[3, 4]. Furthermore, experimental studies have shown that TEA provides cardiac protection from ischemia-reperfusion injury[5] and partly normalizes the myocardial blood flow response to sympathetic stimulation[6]. Especially in the elderly population these risk reductions are highly relevant.

However, blockade of the cardiac sympathetic fibers by TEA may affect right ventricular (RV) function and interfere with the coupling between the RV function and right ventricular afterload. A possible negative effect of TEA on the regulation of RV contractility could be highly relevant in surgical patients, particularly those with already depressed RV function and in conditions of pulmonary hypertension. Experimental studies have shown that increased afterload leads to enhanced RV systolic function which enables the right ventricle to maintain stroke volume without having to involve the Frank-Starling mechanism[7-9]. This mechanism is referred to as homeometric autoregulation[10] and is believed to be an intrinsic myocardial mechanism triggered by stretch of the myocardium leading to a cascade of signaling events finally resulting a transient increase of $Ca2+$ transient amplitude and increase in myocardial force[11] .

There is limited information on the effects of TEA on RV function. Recently, Wink et al. evaluated the effects of TEA on RV function in humans, but results were inconclusive[12]. Recent animal studies[13,14] demonstrated that in pigs TEA did not decrease baseline contractility of the RV but strongly inhibited the positive inotropic response of the right ventricle to acute pulmonary hypertension, suggesting an important role for sympathetic nervous system. If this phenomenon is confirmed in humans, it is highly relevant for daily practice in cardiothoracic surgery because pulmonary hypertension is frequently encountered and RV function is an important determinant of early and late outcome.

Therefore, we investigated the effects of TEA on RV function in patients subjected to lung resection surgery. RV function was assessed by invasive pressure-volume loop analysis using combined pressure- conductance catheters [15,16]. This approach enables quantification of intrinsic RV function independent of loading conditions. Baseline RV function and the response of RV function to increased afterload, induced by temporary, partial clamping of the pulmonary artery, was tested before and after induction of TEA.

Methods

The protocol of this study was reviewed and approved by the Committee on Medical Ethics of the Leiden University Medical Center, reg. no: P10.225, date: 11 Feb 2011 and registered (Nederlands Trial Register, NTR 2844). Between January 2012 and December 2014, patients above 18 years scheduled for lung resection under thoracic epidural and general anaesthesia were asked to participate in this study and were enrolled after written informed consent. Patients with contra-indications for thoracic epidural, a history of lung resection surgery, pregnancy or lactation or participation in a trial on investigational drugs within 3 months prior to the study were excluded. Further exclusion criteria were occurrence of an allergic reaction to the local anaesthetic, signs of dural puncture, signs of intrathecal or intravascular injection of lidocaine, technical failure of epidural catheter placement or unilateral or no analgesic block after epidural injection of a test dose lidocaine.

Epidural procedure

The epidural catheter was inserted and tested for correct positioning the day before surgery to avoid possible influence of the epidural test dose on measurements during surgery. After skin infiltration with lidocaine 1.0 % a 18-gauge Tuohy needle was introduced, at the T3-4 interspace using a paramedian approach with the patient in the sitting position. The epidural space was identified using the hanging drop technique. An 20-gauge lateral eye catheter was introduced 5 cm into the epidural space in the cephalad direction. After catheter insertion a test dose of 3 ml Lidocaine 2% was given through the catheter. Analgesia was assessed bilaterally in the anterior axillary line and arms by temperature discrimination using ice blocks 15 minutes after epidural injection of lidocaine. Results from both sides were averaged. The following parameters were measured: time to initial onset of analgesia at the T3-T4 dermatomes, highest and lowest level of analgesia after 15 minutes and the maximum number of spinal segments blocked after 15 minutes. Following measurements patients returned to the ward with a syringe pump infusing 2 ml.hr^{-1} NaCl 0.9 % through the epidural catheter to prevent closure of the catheter.

General anaesthesia

On the day of surgery patients were premedicated with midazolam 7.5 mg (if < 65 yr) or 5 mg (if > 65 yr) orally, 45 min before induction of anaesthesia. A 14-gauge intravenous (IV) catheter was placed in the arm for the administration of fluids and medication. Anaesthesia was induced and maintained with propofol, remifentanil and rocuronium. Dosage of propofol and remifentanil was adjusted as necessary to achieve a bispectral index (BIS) between 40 and 60. Muscle relaxation was monitored using a TOF (train of four) watch, and rocuronium was infused to achieve maximally one twitch with a TOF watch. Starting at induction of anaesthesia an electrolyte solution (NaCl 0.9%) was administered at a rate of 5 ml.kg^{-1}.hr^{-1} and maintained until the end of this study. Patients were intubated with a double lumen tube. Single lung ventilation was started after lateral thoracotomy and maintained during measurements.

Monitoring

Electrocardiogram, heart rate (HR), noninvasive blood pressure (NIBP) and oxygen saturation were monitored starting at induction of anaesthesia. A TOF watch was used to monitor muscle relaxation. After local infiltration of the skin with lidocaine 1% a 20 G arterial line was inserted in the radial artery to continuously monitor mean arterial pressures (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP). In addition continuous cardiac output (CO) was monitored with the LiDCOplus hemodynamic monitor (software version 3.02; LiDCO Ltd, Cambridge U.K.), which analyses and processes the arterial pressure signal obtained from a primary blood pressure monitor (PulseCO™). Initial calibration was performed using the calculated average of five consecutive thermodilution CO values from the pulmonary artery catheter with bolus injections equally distributed over the ventilatory cycle (coefficient of variation < 5.0%)[17, 18]. Venous access for the insertion of central lines was obtained under guidance of ultrasound. Hypotension (decrease in systolic blood pressure > 30% below the pre-anaesthetic value or to less than 90 mmHg) was treated with phenylephrine 100 µg IV. Bradycardia (heart rate < 50 beats.min-1) was treated with atropine sulphate, 0.25-0.5 mg IV.

A Swan-Ganz pacing Pulmonary Artery Catheter (PAC) (Edwards Lifesciences LLC, Irvine, Ca, USA) was inserted via the internal jugular vein for CO measurements. The electrodes integrated into the PAC were used for atrial pacing to obtain a constant fixed heart rate during all measurements. In addition, the PAC was used to perform hypertonic saline (10%, 5 ml) injections required for calibration of the pressure- volume catheter[19].

A 7 French pressure-volume catheter (CA-71103-PL, CD Leycom, Zoetermeer, The Netherlands) was positioned into the right ventricle via the internal jugular vein under guidance of trans esophageal echo (TEE) and online pressure-volume signals. Display of pressure-volume loops, beat-to-beat in real time (250 samples.s^{-1}) was obtained after connection to an intracardiac function monitor (Inca©, CD Leycom, Zoetermeer, The Netherlands). Data were used to assess RV function and hemodynamics and ventricular- pulmonary coupling[16, 20] using custom-made software (Circlab).

Surgical procedure

Via a lateral thoracotomy, the right or left pulmonary artery was encircled with retraction tape (Mersilene retraction tape 4 mm by Ethicon, Johnson & Johnson, CA, USA) to facilitate temporarily increased afterload by unilateral pulmonary artery occlusion. This encircling was done either inside the pericardium or directly outside the pericardium, depending on the anatomy of the pulmonary artery. Occlusion of the artery was achieved by using this retraction tape as a tourniquet or with a vascular clamp. Because the occlusion periods were short (approximately 5 minutes), usage of heparin to prevent blood cloths in the pulmonary artery was unnecessary.

Measurements protocol

Measurements were performed before (referred to as baseline) and during clamping of the pulmonary artery, sequentially before (control) and after induction of TEA. Measurements started after isolation of either the right or left pulmonary artery, and confirmation of hemodynamic steady state, normoxia and normocapnia. Right atrial pacing was performed at 10 beats.

min^{-1} above spontaneous heart rate (HR) to obtain the same constant heart rate in control and blocked (TEA) conditions. RV function was assessed by pressure-volume loops. To avoid respiratory influences, pressure- volume measurements were performed with the ventilation suspended at end expiration. After baseline measurements, conditions of stable increased RV afterload were created by temporarily clamping of the right or left pulmonary artery. Pressure-volume measurements were repeated during stable increased afterload. After completion of measurements, clamping of the left or right pulmonary artery was discontinued.

Subsequently, sensory blockade was induced by administration of 9 ml of lidocaine 2% through the epidural catheter. After waiting 15 min minutes to achieve maximal sensory blockade and confirmation of stable hemodynamics, normoxia and normocapnia, the hemodynamic measurements were repeated as described above. After completion of all study measurements, surgery was continued.

Data acquisition and analysis

General hemodynamics was monitored with the LiDCOplus hemodynamic monitor after initial calibration with the averaged CO value of five consecutive bolus CO measurements measured with pulmonary artery catheter. RV function was determined from RV pressure-loops. The RV conductance data were calibrated as previously described. Slope factor alpha was determined by matching with thermodilution-derived CO and parallel conductance was determined by hypertonic saline injections[19]. Pressure–volume signals acquired during steady state yielded heart rate (HR), end-diastolic and end-systolic volume (EDV, ESV), stroke volume (SV), ejection fraction (EF), cardiac output (CO), end-diastolic and end-systolic pressure (EDP, ESP), stroke work (SW), peak rate of ventricular pressure increase (dP/dtMAX), peak rate of ventricular pressure decrease (dP/dtMIN), and isovolumic relaxation time constant Tau (τ). The end-systolic and end- diastolic pressure-volume relations (ESPVR, EDPVR) were determined using single-beat approaches 21 and provided load-independent indices of systolic and diastolic RV function. Systolic RV function was quantified by the slope (Ees) and the volume intercept at 25 mmHg (ESV_{25}) of the ESPVR. Diastolic RV function was quantified by the slope (stiffness, Eed) and intercept at 7 mmHg (EDV_7) of the EDPVR. Right ventricular afterload was determined by effective arterial elastance Ea, calculated as ESP/SV. Ventricular- pulmonary coupling was quantified as Ees/Ea[16, 20]. CO and MAP from the LiDCOplus hemodynamic monitor (software version 3.02;LiDCO Ltd, Cambridge U.K.) and right ventricular end-diastolic pressure as a measure for central venous pressure (CVP) were used to calculate the systemic vascular resistance as SVR = 80.(MAP-CVP)/CO.

Statistical analysis and sample size.

The main statistical aim was to detect possible, physiologically relevant differences in RV function and ventricular-pulmonary coupling between control and TEA. In this regard, a ~20-30% change in hemodynamic indices was considered physiologically relevant. Our protocol determines within-subject changes between conditions. Previous studies indicated typically a

20% within-group variability (defined as standard deviation divided by mean: σ/μ) for the main hemodynamic indices. This within-group variability was used as a conservative estimate for the expected within-subject variability in the present study. Consequently, the effect size (defined as the mean differences between conditions divides by standard deviation: ES = $(\mu1 - \mu0)/\sigma$) is > 1. The required sample size was calculated as $n = (Z^{\alpha/2} + Z_{\beta})^2 / ES^2$. Thus, to determine differences >20% with type I error <5% ($Z_{\alpha/2} = 1.960$) and type II error <10% ($Z_{\beta} = 1.282$), power analysis yields a sample size of approximately 10.

Data are presented as mean (SD) or mean (range). All statistical computations were done using R (the R Development Core Team, www.R-project.org) and the R-package for Linear and Nonlinear Mixed Effects Models (NLME) (Pinheiro J, Bates D, DebRoy S, Sarkar D and R Core Team (2015). R package version 3.1- 122, http://CRAN.R-project.org/package=nlme). All indices were fitted with a linear mixed effects model (model A) using TEA and pulmonary artery clamping as fixed effects and the subject as random effect. In addition, we applied a linear mixed model (model B) using not only the effects mentioned above, but also a possible interaction between the two fixed effects (TEA x pulmonary clamping). For each index we compared these two models using the Bayesian Information Criterion (BIC), and reported the model with the lowest BIC, hence the absence of interaction p-values for some of the outcomes. Visual inspection of Q- Q plots of the standardized residuals showed one outlier. A sensitivity analysis was performed excluding the outlier, showing similar results with P values becoming more significant. After checking that the outlier was not due to measurement error we decided to retain the observation in our analysis. P values less than 0.05 were considered significant.

Table 1. Patient characteristics and characteristics of neural blockade 15 minutes after epidural test dose

Patient characteristics	N=10
Age (years)	60 (50-69)
Gender (M/F)	4/6
ASA (I/II/III)	5/5/0
Height (cm)	169 (156-189)
Weight (kg)	79 (59-128)
Diabetes (yes/no)	1/9
B-blocker (yes/no)	2/8
Antihypertensive medication (yes/no)	2/8
B-blocker	1/9
ACE blockers	1/9
Calcium antagonist	1/9
Operation side (left/right)	4/6
Epidural test dose	
Lidocaine 2%, epidural	60 mg
Time to initial onset of analgesia at the T3-T4 dermatomes (minutes)	3.0 (1.5 – 5.0)
Highest level of analgesia (dermatome)	T2 (C8 – T3)
Lowest level of analgesia (dermatome)	T6 (T1 – L1)
Maximum number of spinal segments blocked	6 (3 – 11)
Baseline hemodynamic and respiratory variables	
HR (beats min -1)	
Control	88 (11)
TEA	88 (11)
PaO2 (kPa)	
Control	16.0 (9.3)
TEA	17.1 (13.2)
PaCO2 (kPa)	
Control	5.8 (1.0)
TEA	5.9 (1.4)

Data are presented as mean (SD) or mean (range). ASA indicates American Society of Anesthesiologists; HR, heart rate; and TEA, thoracic epidural anaesthesia.

Results

15 patients gave their informed consent and were enrolled in this study. Five of these patients were not included in the final analysis because of failure of epidural placement (n=1), unusual high upper border of sensory block after epidural test dose (n=1), hemodynamic instability requiring inotropic support (n=1), surgical failure to isolate the pulmonary artery (n=1) and insufficient quality of PV-loops (n=1).

Conditions and interventions

Patients were normoxic and normocapnic at control and TEA conditions with comparable PO2 and PCO2 values (**Table 1**). Heart rate was kept at the same constant level by atrial pacing (**Table 1**). PA clamping resulted in a significant ~30% increase in ESP, both at control (27.5±4.5 to 37.5±7.2 mmHg, 36% increase) and TEA (24.5±2.6 to 32.3±5.4 mmHg, 32% increase). Figure 1 shows a representative example (patient #4) combining 5 seconds of continuous signals from all four conditions obtained by the pressure-volume catheter (RV volume, pressure, dP/dt, ECG, and pressure-volume-loops).

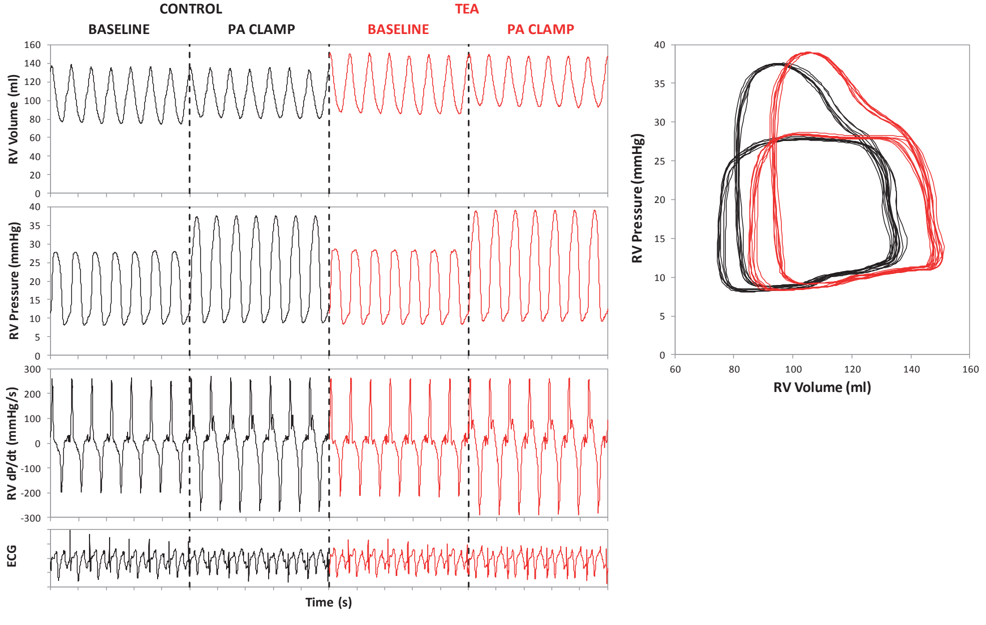

Figure 1. Representative (patient #4) pressure-volume signals obtained during 5 s in all 4 conditions.
The control conditions (baseline and pulmonary artery [PA] clamping) are shown in black, corresponding TEA conditions in red. Right ventricular (RV) volume, pressure, dP/dt, and ECG were recorded from the pressure-volume catheter. dP/dt indicates rate of ventricular pressure increase; PA, pulmonary artery; RV, right ventricle; and TEA, thoracic epidural anaesthesia.

Table2. The effects of thoracic epidural anaesthesia and clamping of the pulmonary artery on systolic and diastolic right ventricular function

	Condition	Baseline mean (SD)	PA clamp mean (SD)	TEA effect P (95 % CI)	PA clamp effect P (95 % CI)	TEA - PA clamp interaction P (95 % CI)
SYSTOLIC FUNCTION						
SW (ml.mmHg)	Control	1553 (619)	1967 (1069)	-292 (-535 to -49) P=0.0203	414 (171 to 657) P=0.0017	-224 (-568 to 120) NS
	TEA	1260 (595)	1451 (662)			
SW/EDV (mmHg)	Control	12.6 (3.8)	15.4 (5.7)	-3.6 (-5.3 to -2.0) P=0.0001	2.8 (1.2 to 4.5) P=0.0018	-1.5 (-3.9 to 0.9) NS
	TEA	8.9 (2.3)	10.2 (3.3)			
Ees (mmHg.ml-1)	Control	0.30 (0.08)	0.33 (0.09)	-0.025 (-0.049 to -0.001) P=0.0443	0.034 (0.010 to 0.058) P=0.0079)	n/a
	TEA	0.27 (0.11)	0.31 (0.11)			
ESV25 (ml)	Control	57 (22)	30 (24)	25.5 (13.0 to 38.0) P=0.0003	-26.6 (-39.2 to -14.1) P=0.0002	6.5 (-11.2 to 24.3) NS
	TEA	82 (29)	62 (29)			
dP/dt_{max} (mmHg. sec-1)	Control	367 (105)	401 (137)	-88 (-126 to -50) P=0.0001	34 (-4 to 71) P=0.0794	-22 (-75 to 32) NS
	TEA	279 (65)	291 (75)			
dP/dt_{max}/EDV ($mmHg.sec^{-1}.ml^{-1}$)	Control	3.13 (1.39)	3.37 (1.62)	-1.08 (-1.36 to -0.81) P< 0.001	0.14 (-0.14 to 0.42) NS	n/a
	TEA	2.15 (0.85)	2.19 (0.87)			
ESV (ml)	Control	65 (17)	70 (17)	14.1 (4.3 to 23.9) P=0.0066	5.3 (-4.5 to 15.1) NS	3.9 (-10.0 to 17.8) NS
	TEA	79 (28)	88 (34)			
ESP (mmHg)	Control	27.5 (4.5)	37.5 (7.2)	-3.0 (-5.6 to -0.5) P=0.0229	10.0 (7.4 to 12.6) P<0.0001	-2.1 (-5.8 to 1.5) NS
	TEA	24.5 (2.6)	24.5 (2.6)			
EF (%)	Control	48.3 (6.7)	44.3 (7.9)	-3.7 (-7.1 to -0.2) P=0.0370	-4.0 (-7.5 to -0.6) P=0.0236	-1.1 (-6.0 to 3.7) NS
	TEA	44.6 (8.0)	39.5 (7.8)			
DIASTOLIC FUNCTION						
τ (msec)	Control	60.1 (8.7)	76.9 (14.2)	5.0 (-4.5 to 14.5) NS	16.8 (7.3 to 26.3) P=0.0012	-3.6 (-17.0 to 9.9) NS
	TEA	65.1 (15.9)	78.3 (20.1)			
dP/dtmin (mmHg. sec-1)	Control	-240 (63)	-330 (87)	36 (10 to 62) P=0.0092	-90 (-116 to -64) P<0.0001	29 (-9 to 66) NS
	TEA	-204 (43)	-266 (53)			
dP/dt_{min}/EDV ($mmHg.sec^{-1}.ml^{-1}$)	Control	-1.96 (0.43)	-2.71 (0.87)	0.60 (0.41 to 0.80) P<0.0001	-0.60 (-0.80 to -0.40) P<0.0001	n/a
	TEA	-1.51 (0.34)	-1.96 (0.51)			
EDV (ml)	Control	125 (29.1)	127 (35.4)	15.9 (5.7 to 26.1) P=0.0035	2.5 (-7.7 to 12.7) NS	-0.5 (-14.9 to 13.9) NS
	TEA	140 (43.3)	142 (43.3)			
EDP (mmHg)	Control	9.6 (3.3)	10.0 (3.3)	-1.16 (-1.78 to -0.54) P=0.0007	0.54 (-0.08 to 1.16) P=0.0830	n/a
	TEA	8.3 (2.4)	9.0 (2.2)			
Eed (mmHg.ml-1)	Control	0.05 (0.03)	0.06 (0.03)	-0.010 (-0.019 to 0.000) P=0.0415	0.006 (0.004 to 0.015) NS	n/a
	TEA	0.04 (0.02)	0.05 (0.03)			

EDV7 (ml)	Control	89 (96)	61 (107)	21.9 (-11.4 to 55.2) NS	-27.8 (-61.1 to 5.5) P=0.0983	-0.9 (-48.0 to 46.2) NS
	TEA	111 (115)	82 (95)			
GENERAL						
Ea (mmHg.ml-1)	Control	0.49 (0.15)	0.75 (0.28)	-0.094 (-0.155 to -0.033) P=0.0037	0.225 (0.164 to 0.286) P< 0.001	n/a
	TEA	0.43 (0.12)	0.63 (0.17)			
Coupling Ees/Ea	Control	0.64 (0.21)	0.48 (0.15)	0.002 (-0.061 to 0.065) NS	-0.153 (-0.216 to -0.090) P<0.0001	n/a
	TEA	0.64 (0.17)	0.49 (0.12)			

Values at Baseline and PA clamp are presented as mean (SD). Effects were determined by a linear mixed effects model (see Statistical analysis for details) and presented as mean (95% confidence interval). P-values of the effects are presented in full when P<0.1 and as NS (non-significant) when P>0.1.Interaction of TEA and PA clamp effects was tested for all indices, but the interaction did not reach significance for any of the indices. For those outcome variables where the model fit did not improve by adding the interaction term , results from the model without interaction term are presented and n/a is shown in the last column.

RV, right ventricle; TEA, thoracic epidural anesthesia; PA, pulmonary artery; SW, stroke work; SW/EDV, stroke work divided by end-diastolic volume; Ees, the slope of the end-systolic pressure-volume relationship; ESV_{25}, volume intercept of end-systolic pressure-volume relation, quantified at pressure 25 mmHg; dP/dtmax, peak rate of RV pressure increase; dP/dtmax/EDV, peak rate of RV pressure increase divided by end-diastolic volume; ESV, end-systolic volume; ESP, end-systolic pressure; EF, ejection fraction; τ (tau), time constant of ventricular relaxation; dP/dtmin, peak rate of ventricular pressure decrease; dP/dt_{min}/EDV, peak rate of ventricular pressure decrease divided by end-diastolic volume; EDV, end-diastolic volume; EDP, end-diastolic pressure; Eed, slope of the end-diastolic pressure-volume relation; EDV_7, volume intercept of end-diastolic pressure-volume relation, quantified at pressure 7 mmHg; Ea, effective arterial elastance; Ees/Ea, ventricular-pulmonary coupling ratio.

Effects of TEA

RV systolic function significantly decreased after TEA. The increase in ESV25 and the decrease in Ees reflect a rightward shift and more shallow slope of the ESPVR, both indicating a decrease in intrinsic RV contractile state (**Table 2 and Figure 2**). The decreased systolic function is further supported by significant reductions in ESP, EF, SW, SW/EDV, dP/dtMAX and (dP/dtMAX)/EDV (**Table 2 and Figure 3**). CO and SV remained unchanged after TEA. Stable systemic hemodynamics are indicated by unchanged MAP and SVR (**Table 3**), and pulmonary flow was maintained by a reduction in Ea which compensated for the reduced RV and PA systolic pressure. RV SV was maintained despite the increase in RV ESV by a compensatory increase in RV EDV. The decrease in RV EDP indicates that this increase in EDV did not result from altered loading, but from improved diastolic RV function. The intrinsic myocardial effect is evidenced by the reduced stiffness Eed and increased volume intercept of the EDPVR (EDV7).

The significant reductions in dP/dtMIN and (dP/dtMIN)/EDV after TEA indicate limitations in early active relaxation which are consistent with the decreased systolic function[22, 23]. Prolongation of Tau was not significant and too limited to cause incomplete relaxation at the present heart rates[24].

Effects of PA clamping

Unilateral clamping of the pulmonary artery resulted in an increased afterload as expected, evidenced by a ~50% increase in Ea. During clamping, CO decreased slightly and SV did not decrease significantly, with both EDV and ESV remaining virtually unchanged, despite the significantly higher ESP. These effects indicating effective homeometric autoregulation were all very similar at control and during TEA: statistical analysis indicates that for none of these indices an interactive effect was present.

The homeometric autoregulation, i.e. maintained RV volumes despite altered loading, is enabled by an increase in intrinsic systolic RV function in response to the increased afterload. The ESPVR is shifted leftward (decrease in ESV$_{25}$) and steeper (increase in Ees) after clamping (**Figure 4**). The same positive inotropic effect is also reflected by changes in SW and SW/EDV. The effects on pre-ejection indices dP/dtMAX and (dP/dtMAX) /EDV were less pronounced. The EDPVR is virtually unchanged after clamping, indicating no clear changes in intrinsic diastolic function. dP/dtMIN and (dP/dtMIN) / EDV significantly improved with clamping which may suggest improved active relaxation, but presumably largely reflects the load- dependency of these parameter (since ESP increased about 50%). In contrast however, Tau was significantly prolonged which cannot be explained by load-dependency of this parameter[25].

Effects of TEA and PA clamp on ventricular-pulmonary coupling

Theoretically, optimal mechanical RV-pulmonary coupling corresponds to an ratio Ees/Ea equal to 1[26]. In present study Ees/Ea was 0.64±0.21 in control and with TEA the coupling ratio remained unchanged (0.64±0.17) since both Ees and Ea decreased by the same extent (**Table 2 and Figure 5**). Thus TEA did not affect ventricular-pulmonary coupling. With PA clamping Ea increased more than Ees, thus the ventricular-arterial coupling significantly decreased despite the significant improvements in contractile performance of the RV. This afterload-induced reduction in coupling was virtually identical in control and TEA, thus TEA apparently did not influence this mechanism (**Figure 5**).

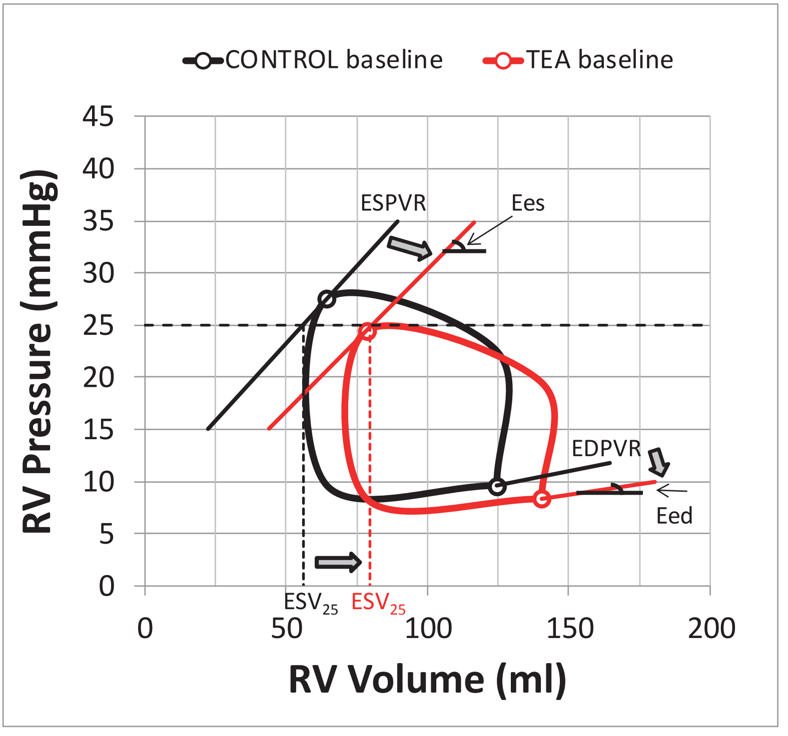

Figure 2. Schematic RV pressure-volume loops based on mean end-diastolic and end-systolic pressures and volumes at baseline (black loop) and after induction of TEA (red loop). The increase in ESV25 and the rightward shift and shallower slope of the ESPVR after TEA indicate a decreased contractile performance. EDPVR indicates end-diastolic pressure-volume relationship; ESPVR, end-systolic pressure-volume relationship; ESV25, volume intercept of ESPVR at 25 mm Hg; RV, right ventricle; and TEA, thoracic epidural anaesthesia.

Discussion

It is well established that right ventricular function is an important determinant of early and late outcome in cardiothoracic surgery and RV dysfunction and post exercise deterioration of RV pump function have been demonstrated after pulmonary surgery[27, 28].
Furthermore, perioperative RV function is highly clinically relevant and may be challenged particularly since poor RV function and increased pulmonary artery pressures are frequently encountered in cardiothoracic surgery patients. TEA is widely applied in cardiac, lung and upper abdominal surgery as well as in chest trauma, but the impact of TEA on RV function is not well established In this context we studied three aspects of RV function: baseline contractile function, the ability of the RV to respond to increased afterload via homeometric autoregulation, and ventricular-pulmonary coupling.

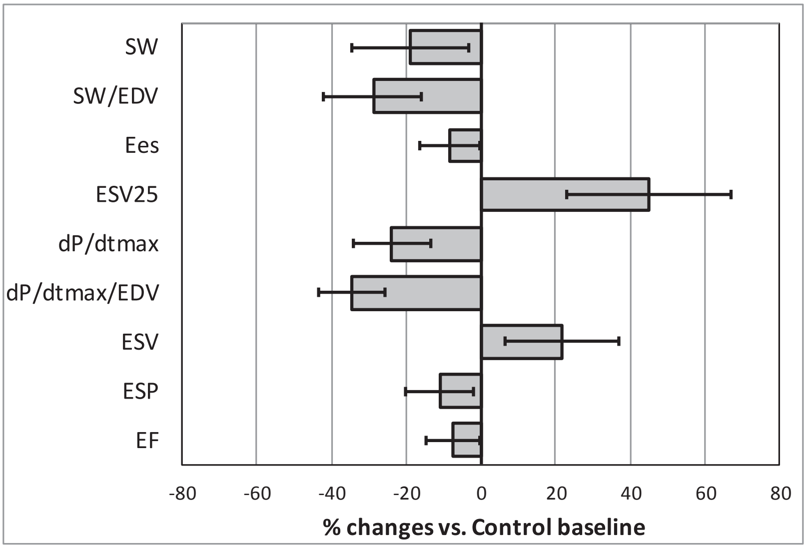

Figure 3. TEA effects on RV systolic function indices presented as % changes versus control baseline. Error bars indicate the 95% confidence interval (CI). All effects were statistically significant (**see Table 2**), indicating decreased systolic RV function after TEA. dP/dtmax indicates peak rate of ventricular pressure increase; dP/dtmax/EDV, peak rate of ventricular pressure increase divided by enddiastolic volume; Ees, the slope of the end-systolic pressurevolume relationship; EF, ejection fraction; ESP, end- systolic pressure; ESV, end-systolic volume; ESV25, volume intercept of end-systolic pressure-volume relation; SW, stroke work; SW/EDV, stroke work divided by end-diastolic volume; and TEA, thoracic epidural anaesthesia.

Both the LV and the RV are densely innervated by sympathetic fibers[29 30], which either directly innervate the myocardium or synapse with intrinsic cardiac ganglia[31], but studies directly assessing TEA effects on ventricular function are scarce. With regard to LV performance conflicting results with either decreased[13, 32, 33], unaltered[12] or even improved systolic function[34] have been reported. Experimental animal studies[13, 14] found no significant change in RV systolic and diastolic function after TEA, but reported important negative effects of TEA on right ventricular-pulmonary coupling[13, 14]. In general, the interpretation of these studies is complicated by heart rate changes and the vascular effects of TEA altering loading conditions.We recently reported decreases in RV isovolumetric acceleration (IVA) in patients undergoing TEA, but changes in loading conditions prevented clear conclusions regarding effects of TEA on RV contractility[12].

Table 3. The effects of thoracic epidural anesthesia and clamping of the pulmonary artery on general hemodynamics

	Condition	Baseline mean (SD)	PA clamp mean (SD)	TEA effect P (95% CI)	PA clamp effect P (95% CI)	TEA - PA clamp interaction P (95% CI)
HEMODYNAMICS						
RV SV (ml)	Control	60.1 (16.3)	57.2 (22.6)	1.8 (-3.7 to 7.4) NS	-2.8 (-8.4 to 2.8) NS	-4.4 (-12.3 to 3.5) NS
	TEA	61.9 (20.3)	54.7 (13.0)			
CO ($l.min^{-1}$)	Control	5.2 (1.2)	5.0 (1.7)	0.00 (-0.33 to 0.32) NS	-0.43 (-0.76 to -0.10) P=0.0119	n/a
	TEA	5.4 (1.6)	4.8 (1.0)			
MAP (mmHg)	Control	78.1 (10.7)	75.4 (12.9)	1.1 (-6.2 to 8.4) NS	-2.7 (-10.0 to 4.6) NS	3.7 (-6.6 to 14.0) NS
	TEA	79.2 (13.6)	80.2 (14.2)			
M_{sys}PAP (mmHg)	Control	25.6 (4.8)	32.1 (5.7)	-3.4 (-4.8 to -2.0)	6.0 (4.6 to 7.4)	n/a
	TEA	22.7 (2.8)	28.1 (4.6)	P <0.0001	P <0.0001	
SVR ($dynes.s.cm^{-5}$)	Control	1111 (409)	1112 (481)	29 (-139 to 198) NS	2 (-167 to 170) NS	22 (-217 to 260) NS
	TEA	1140 (369)	1163 (426)			
PVR ($dynes.s.cm^{-5}$)	Control	245 (78)	377 (108)	-48 (-88 to -8) P=0.0209	132 (92 to 172) P<0.0001	-17 (-74 to 40) NS
	TEA	197 (54)	312 (79)			

Values at Baseline and PA clamp are presented as mean (SD). Effects were determined by a linear mixed effects model (see Statistical analysis for details) and presented as mean (95% confidence interval). P-values of the effects are presented in full when P<0.1 and as NS (non-significant) when P>0.1. Interaction of TEA and PA clamp effects was tested for all indices, but the interaction did not reach significance for any of the indices. For those outcome variables where the model fit did not improve by adding the interaction term, results from the model without interaction term are presented and n/a is shown in the last column. TEA, thoracic epidural anaesthesia; PA, pulmonary artery; RV, right ventricle; SV, stroke volume; CO, cardiac output; MAP, mean arterial pressure; MSYSPAP, mean systolic pulmonary artery pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

We therefore used fixed rate pacing and employed pressure-volume loop analyses, to obtain load- independent indices of intrinsic RV function, to investigate the effects of TEA in patients scheduled for lung surgery[16, 35, 36]. We have chosen to use a fixed heart rate during the entire protocol to exclude confounding HR effects on intrinsic cardiac function, a phenomenon that is referred to as the force- frequency relationship. This mechanism leading to enhanced function at higher HR was recently demonstrated in the human RV[37]. Furthermore we specifically manipulated RV afterload to study two additional aspects via which TEA may affect

hemodynamics; RV homeometric autoregulation and ventricular-pulmonary coupling.
In brief, our study demonstrated that cardiac sympathetic blockade with TEA decreases baseline contractility of the RV but does not affect homeometric autoregulation and ventricular-arterial coupling.
The impairment of RV systolic function in our study was evidenced by changes of the slope and intercept of the ESPVR and also reflected by a 25-30% reduction in stroke work (**Figure 3**). This finding may be clinically highly relevant since RV systolic function is an important determinant of outcome in cardiothoracic surgery as mentioned before. Via concomitant improvements in RV diastolic function and decreases in Ea, TEA did not decrease CO in our study. It should be noted that RV function was relatively normal in our patient group, but TEA might be detrimental in patients with already diminished RV function or pulmonary hypertension.

RV function can also be assessed by challenging the RV with increased afterload. The first physiologic response of the ventricle to increased afterload is dilatation (raising end diastolic volume) to maintain stroke volume via the Frank-Starling mechanism. A secondary mechanism, referred to as homeometric autoregulation (or Anrep[11], or Slow Force Response [38]), is initiated by stretch of the myocardium leading to an increase in contractility enabling the RV to maintain stroke volume[7-9]. The underlying mechanisms are complex, comprising various signaling pathways and are only partly elucidated[38]. To our knowledge, the present study is the first in vivo human study demonstrating a positive inotropic response of the RV to acutely increased afterload. Moreover, this effect was evident with and without TEA, despite the decreases in baseline contractility after TEA. Both with and without TEA, SV was maintained and CO only slightly reduced after clamping of the PA without increasing EDV.

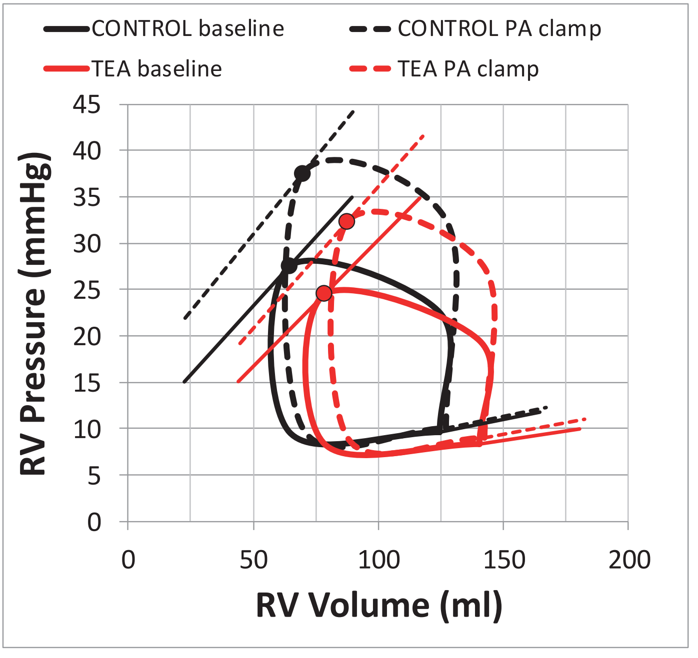

Figure 4. Schematic RV pressure-volume loops based on mean end-diastolic and end-systolic pressures and volumes. Black loops represent the control conditions, solid at baseline and dashed during PA clamp. The red loops represent the same conditions during TEA. The figure illustrates that homeometric autoregulation was maintained after TEA. ESPVR, end-systolic pressure-volume relationship; EDPVR, end-diastolic pressure-volume relationship; RV, right ventricle; PA, pulmonary artery; TEA, thoracic epidural anaesthesia.

We also studied ventricular-pulmonary coupling. RV pressure volume loops allow for the determination of Ees, a load independent parameter of myocardial contractility, and of Ea, a measure of total RV afterload. The ratio Ees/Ea is known as the ventricular-pulmonary coupling. Theoretically, matching of Ees and Ea, thus Ees/Ea = 1[26], allows for the maximal SW, whereas myocardial efficiency, defined as the ratio of SW to myocardial oxygen consumption per beat, is optimal at Ees/Ea = 2[39, 40]. However there is a broad range for Ees/Ea of approximately 0.5 to 2.0 in which SW is still close to optimal (<5% decrease), and the same applies to efficiency which remains close to optimal for Ees/Ea values from 1.0 to 3.0[41].
In awake human subjects and in animal studies, RV Ees/Ea values were found to be around 1.5 to 2.0[42-44]. In our study the coupling ratio was 0.64 which seems suboptimal, presumably resulting from relatively low Ees and high Ea values. Most anaesthetics, including propofol, are known to have myocardial depressant effects[45], which possibly explains the relatively low values of Ees in our patients compared to the values in awake humans[42]. The relatively high Ea values in our patients might be the result of one lung ventilation (OLV) and associated hypoxic pulmonary vasoconstriction. Because ageing effects like arterial and ventricular stiffening might influence Ees and Ea, age differences between study populations could also be relevant.

Interestingly, TEA did not alter ventricular arterial coupling because Ees and Ea were reduced to the same extend and thus Ees/Ea was maintained. In contrast, pulmonary artery clamping resulted in a reduced ventricular-pulmonary coupling. Clamping typically increased Ea by 50%, but since Ees increased only by about 10%, Ees/Ea dropped significantly. Thus, despite the homeometric autoregulation, the increased afterload condition was associated with decreased ventricular-pulmonary coupling. Statistical analysis indicated that there was no significant interactive (TEA x clamping) effect, thus the effect of clamping on ventricular-pulmonary coupling was the same with and without TEA

These results are partly in contrast with the above mentioned animal studies[13, 14], where TEA did not affect baseline RV contractility but inhibited the positive inotropic response of the RV to acute pulmonary hypertension and reduced ventricular-pulmonary coupling. Species related differences in sympathetic innervation of the RV[46] and sympathetic tone may explain these conflicting results. Methodological differences in anaesthetic management, surgical approach and the technique used to increase RV afterload may also contribute to the distinct findings. Data regarding involvement of the autonomic nervous system in homeometric autoregulation have been conflicting. For the LV the positive inotropic response to increased afterload was not abolished by sympathetic and parasympathetic denervation in dogs[47]. For the RV however, experimental studies both in dogs and pigs, have suggested a role for the autonomic nervous system in modulating the inotropic response of the ventricle to high afterload[13, 14, 48, 49]. Interestingly, we observed rather high baselines values of Ea in the pulmonary circulation of our patients. This was most likely related to the presence of hypoxic vasoconstriction in the non-dependent lung during one lung ventilation[50]. It is therefore possible that the negative inotropic effect of TEA observed in our patients compares to the negative inotropic effects reported in animals subjected to increased afterload. Most importantly, the common finding in our human data, and those previously reported in animals is that TEA-induced sympatholysis may reduce RV contractile performance. We assume that the magnitude of this effect may vary depending on the prevailing hemodynamic conditions and sympathetic tone. Our patients were paced at constant heart rate to allow a more accurate assessment of ventricular contractility. We acknowledge that this intervention may have attenuated the full effect of TEA on global cardiac performance as it excluded the potential reduction in heart rate after sympatholysis and thus the cardiodepressant effects could have been more profound without pacing.

Our study has other potential limitations. We used a study design in which each subject served as its own control rather than a placebo-controlled design. The important statistical advantage (in addition to ethical and economic considerations) is offset by a potentially confounding spill-over effect. However, since the effects of clamping and TEA where generally opposite, a spill-over effect would tend to mask rather than confound the observed significant findings.

The power analysis of this study was based on the comparison between TEA and control and yielded a sample size of 10 patients. The relatively small sample size may have limited the power to detect a possible interaction between TEA and pulmonary clamping

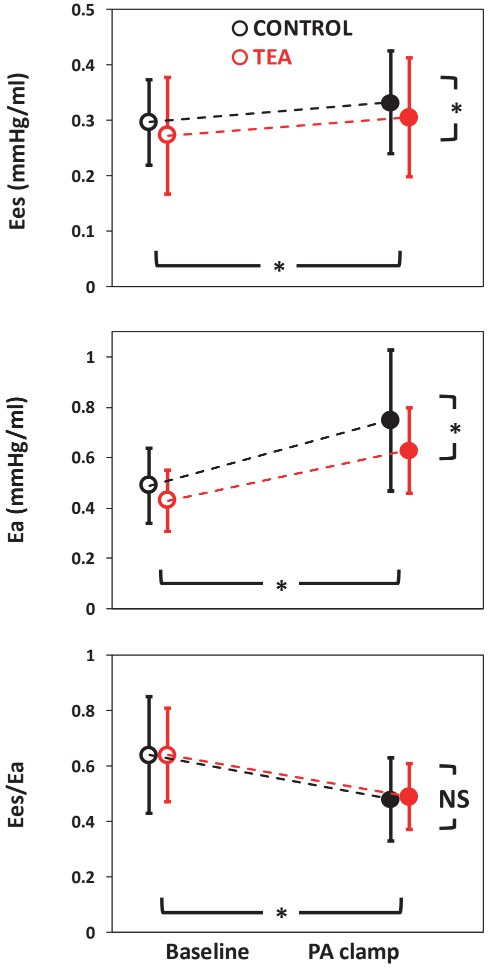

Figure 5. The effects of TEA and PA clamp on Ees, Ea and Ees/Ea . Black symbols indicate the control condition, red symbols TEA. The PA clamp effects (horizontal brackets) were significant for all three parameters, the TEA effects (vertical brackets) were significant for Ees and for Ea, but not for Ees/Ea. The parallel dashed lines illustrate that the PA clamp effect was similar at control and TEA, as evidenced by the absence of interaction between the PA clamp effect and the TEA effect in the statistical analysis. TEA, thoracic epidural anaesthesia; PA, pulmonary artery; Ees, slope of the end-systolic pressure-volume relationship; Ea, effective arterial elastance; Ees/Ea, ventricular-pulmonary coupling ratio;. Values are presented as mean ± SD. *, significant; NS, non- significant. For detailed statistics, see Table 3.

Two patients were using antihypertensive drugs (beta-blocker and calcium antagonist, and ACE inhibitor) which were not discontinued for the study, and could have influenced the measurements. Separate analysis did not identify this subgroup as outliers.

We were not able to measure the analgesic spread of TEA during the study measurements because patients were anaesthetized. However, correct positioning of the epidural catheter was verified the day before surgery to exclude the possible influence of the epidural test dose. In addition to adequate analgesic blockade after the epidural test dose (**Table 1**), all patients had proficient postoperative pain relief from analgesic blockade confirming proper positioning of the epidural catheter. We used an epidural loading dose of 9 ml of lidocaine 2% based on the results of an earlier study[51], to effectively block all cardiac sympathetic fibres (T1-T5). Maximum blockade was expected to be achieved approximately 15 min after epidural injection[51]. The extent of analgesic blockade after this rather large initial loading was not confined to selective blockade of the cardiac sympathetic innervation and will certainly have comprised a large number of dermatomes. TEA with blockade of the low thoracic region (T6-L1) results in an extensive sympathetic block with expected decreases in pre- and afterload as a result of increase venous capacitance. However MAP and SVR remained unchanged probably because the infusion of propofol and remifentanil could be lowered after TEA while maintaining a BIS between 40 and 60[52]. Consequently, none of the patients were given atropine and/or phenylephrine during measurements. The lower dose of propofol and remifentanil with subsequently less cardiodepressive effect after induction of TEA, would imply that the negative inotropic effects of TEA observed in this study are an underestimation of the actual effect.

In this study the pressure-volume catheter was inserted via the jugular vein, entering the RV via the tricuspid valve. Previous experimental and theoretical studies have shown that with this approach RV volume changes in the outflow tract are picked up with relatively lower sensitivity and a straight catheter position from pulmonary artery towards the apex would be more ideal[53]. However that would require catheter placement with open thorax and apical or pulmonary artery puncture which was not considered ethical in this human study. We therefore used a percutaneous approach via the tricuspid valve using echo- guidance and careful inspection of the pressure and volume tracings to optimize the catheter position. Occasionally a single volume segment showed an out-of-phase signal reflecting a position in the right atrium and was removed from the total volume signal. The thermodilution-based calibration corrected for underestimation of total stroke volume related to partial sensing of the outflow tract.

In conclusion, our data are the first to demonstrate a direct negative inotropic effect of TEA on RV contractility in humans. The decrease in RV contractility was well tolerated in our patients as TEA concomitantly lowered RV afterload and preserved homeometric autoregulation and ventricular-pulmonary coupling. However, a potential reduction in the contractile reserve of the RV could be important to consider in patients with preexisting or pending RV dysfunction as well as pulmonary hypertension.

Reference List

1. Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC Angelillo IF, Mosteller F. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta- analyses of randomized, controlled trials. Anesth Analg 1998;86:598-612.
2. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Jr., Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 2003;290:2455-2463.
3. Kozian A, Schilling T, Hachenberg T. Non-analgetic effects of thoracic epidural anaesthesia. Curr Opin Anaesthesiol 2005;18:29-34.
4. Waurick R, Van Aken H. Update in thoracic epidural anaesthesia. Best Pract Res Clin Anaesthesiol 2005;19:201-213.
5. Davis RF, DeBoer LW, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. Anesth Analg 1986;65:711-717.
6. Nygard E, Kofoed KF, Freiberg J, Holm S, Aldershvile J, Eliasen K, Kelbaek H. Effects of high thoracic epidural analgesia on myocardial blood flow in patients with ischemic heart disease. Circulation 2005;111:2165-2170.
7. de Vroomen M, Cardozo RH, Steendijk P, van Bel F, Baan J. Improved contractile performance of right ventricle in response to increased RV afterload in newborn lamb. Am J Physiol Heart Circ Physiol 2000;278:H100-H105.
8. Wauthy P, Pagnamenta A, Vassalli F, Naeije R, Brimioulle S. Right ventricular adaptation to pulmonary hypertension: an interspecies comparison. Am J Physiol Heart Circ Physiol 2004;286:H1441-H1447.
9. Hon JK, Steendijk P, Khan H, Wong K, Yacoub M. Acute effects of pulmonary artery banding in sheep on right ventricle pressure-volume relations: relevance to the arterial switch operation. Acta Physiol Scand 2001;172:97-106.
10. Sarnoff SJ, Mitchell JH, Gilmore JP, Remensnyder JP. Homeometric autoregulation in the heart. Circ Res 1960;8:1077-1091.
11. Cingolani HE, Perez NG, Cingolani OH, Ennis IL. The Anrep effect: 100 years later. Am J Physiol Heart Circ Physiol 2013;304:H175-H182.
12. Wink J, Veering BT, Aarts LP, Wouters PF. Effect of increasing age on the haemodynamic response to thoracic epidural anaesthesia: an observational study. Eur J Anaesthesiol 2014;31:597-605.
13. Rex S, Missant C, Segers P, Wouters PF. Thoracic epidural anesthesia impairs the hemodynamic response to acute pulmonary hypertension by deteriorating right ventricular-pulmonary arterial coupling. Crit Care Med 2007;35:222-229.
14. Missant C, Claus P, Rex S, Wouters PF. Differential effects of lumbar and thoracic epidural anaesthesia on the haemodynamic response to acute right ventricular pressure overload. Br J Anaesth 2010;104:143-149.
15. Hein M, Roehl AB, Baumert JH, Rossaint R, Steendijk P. Continuous right ventricular volumetry by fast-response thermodilution during right ventricular ischemia: head-to-head

comparison with conductance catheter measurements. Crit Care Med 2009;37:2962-2967.
16. Steendijk P. Right ventricular function and failure: methods, models, and mechanisms. Crit Care Med 2004;32:1087-1089.
17. Linton R, Band D, O'Brien T, Jonas M, Leach R. Lithium dilution cardiac output measurement: a comparison with thermodilution. Crit Care Med 1997;25:1796-1800.
18. Jansen JR. The thermodilution method for the clinical assessment of cardiac output. Intensive Care Med 1995;21:691-697.
19. Steendijk P, Staal E, Jukema JW, Baan J. Hypertonic saline method accurately determines parallel conductance for dual-field conductance catheter. Am J Physiol Heart Circ Physiol 2001;281:H755- H763.
20. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 2005;289:H501-H512.
21. ten Brinke EA, Klautz RJ, Verwey HF, van der Wall EE, Dion RA, Steendijk P. Single-beat estimation of the left ventricular end-systolic pressure-volume relationship in patients with heart failure. Acta Physiol (Oxf) 2010;198:37-46.
22. De Hert SG, Gillebert TC, Ten Broecke PW, Mertens E, Rodrigus IE, Moulijn AC. Contraction-relaxation coupling and impaired left ventricular performance in coronary surgery patients. Anesthesiology 1999;90:748-757.
23. Gaasch WH, Blaustein AS, Andrias CW, Donahue RP, Avitall B. Myocardial relaxation. II. Hemodynamic determinants of rate of left ventricular isovolumic pressure decline. Am J Physiol 1980;239:H1-H6.
24. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953-1959.
25. Leeuwenburgh BP, Steendijk P, Helbing WA, Baan J. Indexes of diastolic RV function: load dependence and changes after chronic RV pressure overload in lambs. Am J Physiol Heart Circ Physiol 2002;282:H1350-H1358.
26. Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. Circ Res 1985;56:586-595.
27. Reed CE, Dorman BH, Spinale FG. Mechanisms of right ventricular dysfunction after pulmonary resection. Ann Thorac Surg 1996;62:225-231.
28. Okada M, Ota T, Okada M, Matsuda H, Okada K, Ishii N. Right ventricular dysfunction after major pulmonary resection. J Thorac Cardiovasc Surg 1994;108:503-511.
29. Momose M, Tyndale-Hines L, Bengel FM, Schwaiger M. How heterogeneous is the cardiac autonomic innervation? Basic Res Cardiol 2001;96:539-546.
30. Ito M, Zipes DP. Efferent sympathetic and vagal innervation of the canine right ventricle. Circulation 1994;90:1459-1468.
31. Kapa S, Venkatachalam KL, Asirvatham SJ. The autonomic nervous system in cardiac electrophysiology: an elegant interaction and emerging concepts. Cardiol Rev 2010;18:275-2784.

32. Goertz AW, Seeling W, Heinrich H, Lindner KH, Schirmer U. Influence of high thoracic epidural anesthesia on left ventricular contractility assessed using the end-systolic pressure-length relationship. Acta Anaesthesiol Scand 1993;37:38-44.
33. Wattwil M, Sundberg A, Arvill A, Lennquist C. Circulatory changes during high thoracic epidural anaesthesia--influence of sympathetic block and of systemic effect of the local anaesthetic. Acta Anaesthesiol Scand 1985;29:849-855.
34. Kock M, Blomberg S, Emanuelsson H, Lomsky M, Stromblad SO, Ricksten SE. Thoracic epidural anesthesia improves global and regional left ventricular function during stress-induced myocardial ischemia in patients with coronary artery disease. Anesth Analg 1990;71:625-630.
35. Bleeker GB, Steendijk P, Holman ER, Yu CM, Breithardt OA, Kaandorp TA, Schalij MJ, van der Wall EE, Nihoyannopoulos P, Bax JJ. Assessing right ventricular function: the role of echocardiography and complementary technologies. Heart 2006;92 Suppl 1:i19-i26.
36. White PA, Redington AN. Right ventricular volume measurement: can conductance do it better? Physiol Meas 2000;21:R23-R41.
37. Hsu S, Houston BA, Tampakakis E, Bacher AC, Rhodes PS, Mathai SC, Damico RL, Kolb TM, Hummers LK, Shah AA, McMahan Z, Corona-Villalobos CP, Zimmerman SL, Wigley FM, Hassoun PM, Kass DA, Tedford RJ. Right ventricular functional reserve in pulmonary arterial hypertension. Circulation 2016;133:2413-2422.
38. Kockskamper J, von Lewinski D, Khafaga M, Elgner A, Grimm M, Eschenhagen T, Gottlieb PA, Sachs F, Pieske P. The slow force response to stretch in atrial and ventricular myocardium from human heart: functional relevance and subcellular mechanisms. Prog Biophys Mol Biol 2008;97:250- 267.
39. Suga H, Igarashi Y, Yamada O, Goto Y. Mechanical efficiency of the left ventricle as a function of preload, afterload, and contractility. Heart Vessels 1985;1:3-8.
40. Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. Am J Physiol 1986;250:R1021-R1027.
41. Kass DA, Kelly RP. Ventriculo-arterial coupling: concepts, assumptions, and applications. Ann Biomed Eng 1992;20:41-62.
42. Spruijt OA, de Man FS, Groepenhoff H, Oosterveer F, Westerhof N, Vonk-Noordergraag A, Bogaard HJ. The effects of exercise on right ventricular contractility and right ventricular-arterial coupling in pulmonary hypertension. Am J Respir Crit Care Med 2015;191:1050-1057.
43. Fourie PR, Coetzee AR, Bolliger CT. Pulmonary artery compliance: its role in right ventricular-arterial coupling. Cardiovasc Res 1992;26:839-844.
44. Kuehne T, Yilmaz S, Steendijk P, Moore P, Groenink M, Saaed M, Weber O, Higgins CB, Ewert P, Fleck E, Nagel E, Schulze-Neick I, Lange P. Magnetic resonance imaging analysis of right ventricular pressure-volume loops: in vivo validation and clinical application in patients with pulmonary hypertension. Circulation 2004;110:2010-2016.

45. Royse CF, Liew DF, Wright CE, Royse AG, Angus JA. Persistent depression of contractility and vasodilation with propofol but not with sevoflurane or desflurane in rabbits. Anesthesiology 2008;108:87-93.
46. Wallis D, Watson AH, Mo N. Cardiac neurones of autonomic ganglia. Microsc Res Tech 1996;35:69- 79.
47. Schipper IB, Steendijk P, Klautz RJ, van der Velde ET, Baan J. Cardiac sympathetic denervation does not change the load dependence of the left ventricular end-systolic pressure/volume relationship in dogs. Pflugers Arch 1993;425:426-433.
48. Brimioulle S, Wauthy P, Ewalenko P, Rondelet B, Vermeulen F, Kerbaul F, Naeije R. Single-beat estimation of right ventricular end-systolic pressure-volume relationship. Am J Physiol Heart Circ Physiol 2003;284:H1625-H1630.
49. Szabo G, Sebening C, Hagl C, Tochtermann U, Vahl CF, Hagl S. Right ventricular function after brain death: response to an increased afterload. Eur J Cardiothorac Surg 1998;13:449-458.
50. Talbot NP, Balanos GM, Dorrington KL, Robbins PA. Two temporal components within the human pulmonary vascular response to approximately 2 h of isocapnic hypoxia. J Appl Physiol 2005;98:1125- 1139.
51. Holman SJ, Bosco RR, Kao TC, Mazzilli MA, Dietrich KJ, Rolain RA, Stevens RA. What constitutes an effective but safe initial dose of lidocaine to test a thoracic epidural catheter? Anesth Analg 2001;93:749-754.
52. Senturk M, Gucyetmez B, Ozkan-Seyhan T, Karadeniz M, Dincer S, Akpir D, Sengul T, Denkel T. Comparison of the effects of thoracic and lumbar epidural anaesthesia on induction and maintenance doses of propofol during total i.v. anaesthesia. Br J Anaesth 2008;101:255-260.
53. Woodard JC, Bertram CD, Gow BS. Detecting right ventricular volume changes using the conductance catheter. Pacing Clin.