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Influence of high thoracic epidural anesthesia on left ventricular contractility assessed using the end-systolic pressure-length relationship

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The effect of high thoracic epidural anesthesia (TEA) on left ventricular contractility was studied in a prospective clinical trial. Forty-eight patients with ASA physical status 1 and 2 and without cardiovascular disease were included in the study. Thirty-six patients scheduled for elective upper abdominal surgery were randomly assigned to Group 1 (TEA, bupivacaine 0.25%, n = 12), Group 2 (TEA, bupivacaine 0.5%, n = 12) or to Group 3 (control without TEA, n = 12). TEA induced a sensory block which extended over all cardiac segments. In order to assess the effect of systemically absorbed bupivacaine, we studied a separate group of patients who received lumbar epidural anesthesia without involvement of the cardiac segments: Group 4 (LEA, bupivacaine 0.5%, n = 10). Left ventricular contractility was assessed using the end-systolic pressure-length relationship. Left ventricular dimensions were measured by transesophageal echocardiography. All hemodynamic measurements were performed under general anesthesia. There was no significant difference in systolic or diastolic arterial pressure, heart rate, left ventricular end-systolic and end-diastolic cross-sectional areas and left ventricular wall stress between the four groups. Left ventricular maximum elastance as a measure of left ventricular contractility was significantly ($P < 0.001$) reduced in Groups 1 and 2 [8.1 ($\pm$3.5) and 9.6 ($\pm$4.4) kPa · cm^{-1}, respectively] as compared to Groups 3 and 4 [18.4 ($\pm$8.8) and 17.7 ($\pm$7.7) kPa · cm^{-1}, respectively]. No significant difference could be demonstrated between Groups 1 and 2 or between Groups 3 and 4. It is concluded that high TEA severely alters left ventricular contractility even in subjects without pre-existing cardiac disease.

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High thoracic epidural anesthesia (TEA) has recently been proposed for therapeutic use in patients with coronary artery disease (1–4). The use of high TEA in this group of patients raises the question whether this technique has an effect on global left ventricular function. Although this has been the subject of several experimental (5–7) and clinical studies (8–12), there is still controversy about the effect of high thoracic epidural block on left ventricular contractility, which is variously reported to be unaltered (5, 12), reduced (6–8, 10, 11) or even improved (3, 4, 9). Besides differences in study design or population, one reason for these discrepancies may be the varying extent of vasomotor blockade leading to different cardiac loading conditions. As a measure of ventricular performance isovolumetric and ejection phase indices like dp/dt_{max} (5–7, 9), stroke volume (10, 12), systolic time intervals (11) or ejection fractions (4) have been used. All these parameters are known to be highly dependent on cardiac loading conditions (13).

At present, there is no report on the assessment of left ventricular contractility under high TEA using the end-systolic pressure-volume (or -length) relationship (ESPVR and ESPLR, respectively), which is believed to be relatively insensitive to alterations in cardiac loading (14). The aim of the current investigation was to assess left ventricular contractility in subjects with normal left ventricular function using ESPLR. Since bupivacaine is commonly used in either 0.5% or 0.25% concentration, both concentrations were used in our study in separate groups. In order to consider the systemic action of absorbed bupivacaine, we included a group of patients receiving lumbar epidural anesthesia (LEA) without involvement of cardiac segments.

MATERIAL AND METHODS

Patients

After approval by the ethics committee of our university and informed written consent, 48 patients (ASA physical status 1 or 2) of either sex were included in the study. All patients were scheduled for elective

abdominal surgery: duodenum-preserving resection of the pancreatic head (n = 18), cholecystectomy (n = 6), cholecystojejunostomy (n = 3), liver tumor resection (n = 2), Whipple's pancreaticoduodenectomy (n = 3), resection of the sigmoid (n = 7), cholecystectomy + nephrectomy (n = 1), hemicolectomy (n = 3), partial resection of the pancreas (n = 3) and cystojejunostomy of a pancreas cyst (n = 2). Exclusion criteria were any kind of cardiocirculatory disorder, contraindications against epidural anesthesia and contraindications against transesophageal echocardiography such as gastric or esophageal pathology. Two of the 48 subjects were excluded during the course of the trial because the echocardiographic recordings were of insufficient quality.

Thirty-six of the patients scheduled for upper abdominal surgery were randomly assigned to Group 1 (TEA with bupivacaine 0.25%, n = 12), Group 2 (TEA with bupivacaine 0.5%, n = 12) or Group 3 (control group without epidural anesthesia, n = 12). Another ten patients scheduled for lower abdominal surgery were assigned to Group 4 (LEA with bupivacaine 0.5%). The assignment to Group 4 was not done at random since the epidural catheter of patients participating in our study was used for postoperative analgesia and we found it unethical to provide patients scheduled for lower abdominal surgery with thoracic catheters and *vice versa*. Demographic data are presented in Table 1.

Experimental protocol

The patients of Groups 1, 2 and 4 received their epidural catheter on the evening before surgery. The epidural space was punctured using the loss-of-resistance technique and the median approach. The site of insertion was the mid to lower thoracic region (Groups 1 and 2) and the lumbar region (Group 3), respectively.

All measurements were performed on the day of the operation under general anesthesia and prior to surgery. All patients were premedicated with dipotassium clorazepate 20 mg p.o. given 2 h prior to the measurements. On arrival in the operating theatre, intravenous cannulas, a radial artery catheter and ECG leads were placed. Epidural anesthesia was established giving increments of 3 to 5 ml of plain bupivacaine 0.25% (Group 1) and 0.5% (Groups 2 and 4), respectively, until the extension of the block, evaluated by pin-prick, exceeded the cardiac segments (Groups 1 and 2). Data about the puncture site, the extension of the block, the dosage and volume of bupivacaine are presented in Table 1.

During administration of the local anesthetic 10 $ml \cdot kg^{-1}$ of a 6% hydroxyethyl starch solution was infused in order to compensate for peripheral vasodilation. This volume augmentation was not performed in the control group. Once the desired extent of the block was established, general anesthesia was induced using midazolam (0.1 $mg \cdot kg^{-1}$) and fentanyl (5 $\mu g \cdot kg^{-1}$). Neuromuscular blockade was performed with vecuronium (0.1 $mg \cdot kg^{-1}$). The trachea was intubated and respiration controlled by intermittent positive pressure ventilation. The respiratory rate was 10 min^{-1}, using 40% oxygen in nitrous oxide. Tidal volume, and thereby minute volume, was adjusted to produce normocapnea (P_Eco_2 4.6–6.0 kPa, Capnometer Hewlett-Packard®). The measurements started 10 min after the induction of general anesthesia with the patient in a supine position and without any surgical stimulation.

Hemodynamic measurements and calculations

The transesophageal echocardiographic registrations were performed using a 3400R Varian® with a 3.5 MHz transducer (Diasonics® Inc., Milpitas, CA, USA). The esophageal probe was advanced to a position where left ventricular cross-sectional registrations at mid-papillary muscle level could be obtained (15). Real-time two dimensional as well as M-mode registrations were recorded on videotape together with the arterial pressure curve, ECG and capnographic curve.

The following parameters were measured on the echocardiographic recordings: left ventricular end-systolic and end-diastolic cross-sectional area (LVESA and LVEDA, respectively), left ventricular end-systolic and end-diastolic diameter (LVESD and LVEDD, respectively) and left ventricular end-systolic and end-diastolic wall thickness (LVSWT and LVDWT, respectively). For calculating ESPLR, the systolic arterial pressure (SAP) was transiently decreased by central venous bolus injections of nitroglycerine (NTG). In order to induce a drop of systolic pressure of 20–25 mmHg (2.7–3.3 kPa), we administered a NTG bolus dose of 0.5–1 $\mu g \cdot kg^{-1}$.

All data were analyzed offline using an electronic evaluation device (Cardio 200®, Kontron Instruments GmbH, Stuttgard, FRG). The measurements were restricted to the expiratory phase of the respiratory cycle. The endocardial and pericardial line were identified according to the leading edge method (16). End-diastole was indicated by the peak of the R-wave. End-systole was defined as the smallest systolic endocardial area and diameter, respectively. The observers analyzing the echocardiographic data were blinded to the group. Interobserver variability was assessed prior to a series of investigations and has been reported in an earlier publication (17).

The following parameters were calculated from the data measured:
Fractional area change (FAC) = (LVEDA − LVESA)/LVEDA 100% (18).
End-systolic wall stress (ESWS) = 0.334 SAP LVESD/LVSWT (1 + LVSWT/LVESD) 10^3 dyn cm^{-2} (19).

According to Thys and coworkers (20), we calculated peak systolic wall stress by including the diastolic ventricular dimensions in the original equation, assuming that no significant changes occur in these dimensions between end-diastole and the time at which peak systolic wall stress is developed:
Peak-systolic wall stress (PSWS) = 0.334 SAP LVEDD/LVDWT(1 + LVDWT/LVEDD) 10^3 dyn cm^{-2}

The inotropic state of the left ventricle was assessed using the maximal elastance (E_{max}) of the end-systolic pressure-length relationship according to the method described by Suga and Sagawa (21–23). During the nitroglycerine-induced decrease in arterial pressure, end-systolic pressure/end-systolic diameter values were obtained and subjected to linear regression analysis. Only those values were included that were measured before any change in heart rate occurred as a result of decreasing arterial pressure.

Statistical analysis

All numerical data about the patients' characteristics and extradural anesthesia as well as the hemodynamic data were analyzed using analysis of variance (ANOVA), followed by Scheffé's test. All data are given as arithmetic means (± s.d.) with the exception of data on the extent of the sensory block and the puncture site that are presented as median (range). Statistical significance was assumed with $P < 0.05$.

RESULTS

The four groups were comparable with respect to their age, height, weight and body surface area. The extent of the sensory block was equal in Groups 1 and 2. In all patients receiving TEA, the sensory block exceeded Th_1 and thus completely covered the cardiac segments. There was no significant difference in the amount of bupivacaine given in Groups 2 and 4. As expected, the bupivacaine dose was lower in Group 1 compared to Groups 2 and 4 (Table 1).

All hemodynamic data are summarized in Table 2. Systolic, diastolic and thus also mean arterial pressure were not significantly altered during either thoracic or

Table 1

Demographic and anesthetic data. Age, height, weight and body surface area (BSA) are given as arithmetic means (± s.d.). The data about epidural anesthesia include volume and dose of administered bupivacaine, given as mean (± s.d.), the segmental location of the puncture site and the upper and lower level of sensory block presented as median {range}.

					Epidural anesthesia				
						Sensory block		Bupivacaine	
	Age (years)	Height (cm)	Weight (kg)	BSA (m^2)	Puncture site (segm.)	Upper level (segm.)	Lower level (segm.)	Volume (ml)	Dosis (mg)
Group 1 TEA bupivacaine 0.25% n = 12	54 (± 12)	169 (± 12)	70 (± 19)	1.79 (± 0.27)	$Th_{9/10}$ {$Th_{8/9}$–$Th_{10/11}$}	Th_1 {C_6–Th_1}	L_3 {Th_{12}–L_4}	19.7 (± 4.0)	49.1 (± 10.1)***
Group 2 TEA bupivacaine 0.5% n = 12	49 (± 10)	172 (± 7)	69 (± 10)	1.80 (± 0.14)	$Th_{9/10}$ {$Th_{7/8}$–Th_{10-11}}	Th_1 {C_7–Th_1}	L_2 {Th_{11}–L_3}	17.7 (± 3.5)	88.7 (± 17.7)
Group 3 control n = 12	44 (± 14)	168 (± 8)	65 (± 8)	1.73 (± 0.13)	----	----	----	----	----
Group 4 LEA bupivacaine 0.5% n = 10	50 (± 7)	167 (± 6)	71 (± 18)	1.77 (± 0.23)	$L_{3/4}$ {$L_{2/3}$–$L_{4/5}$}	Th_{12} {Th_8–L_1}	S_5 {L_5–S_5}	18.6 (± 4.6)	93.0 (± 22.9)

*** indicates $P < 0.001$ compared to Group 2 and 4.

Table 2

Hemodynamic data. Systolic, diastolic and mean arterial pressure (SAP, DAP and MAP, respectively), heart rate (HR), end-diastolic and end-systolic left ventricular area (EDA and ESA, respectively), fractional area change (FAC), end-systolic and peak-systolic wall stress (ESWS and PSWS, respectively) and the maximal elastance of the left ventricle (E_{max}(ESPLR) of the four groups. All data are given as arithmetic means (± s.d.).

	SAP (mmHg) (kPa)	DAP (mmHg) (kPa)	MAP (mmHg) (kPa)	HR (min^{-1})	EDA (cm^2)	ESA (cm^2)	FAC (%)	ESWS (10^3 dynes cm^{-2})	PSWS	E_{max}(ESPLR) (mmHg mm^{-1}) (kPa cm^{-2})
Group 1 TEA bupivacaine 0.25% n = 12	111 (± 15) 14.8 (± 2.0)	63 (± 10) 8.4 (± 1.3)	79 (± 10) 10.5 (± 1.3)	64 (± 13)	21.1 (± 6.7)	9.9 (± 4.3)	54 (± 9)	60.1 (± 18.5)	131.7 (± 22.2)	6.1 (± 2.6)*** 8.1 (± 3.5)
Group 2 TEA bupivacaine 0.5% n = 12	113 (± 14) 15.1 (± 1.9)	64 (± 9) 8.5 (± 1.2)	80 (± 10) 10.7 (± 1.3)	65 (± 10)	22.2 (6.2)	9.7 (± 2.8)	56 (± 6)	49.3 (± 10.0)	116.7 (± 38.3)	7.2 (± 3.3)*** 9.6 (± 4.4)
Group 3 control n = 12	115 (± 12) 15.3 (± 1.6)	65 (± 6) 8.7 (± 0.8)	82 (± 7) 10.9 (± 0.9)	77 (± 13)	20.2 (± 5.2)	9.7 (± 3.0)	53 (± 6)	58.6 (± 19.0)	133.5 (± 45.5)	13.8 (± 6.6) 18.4 (± 8.8)
Group 4 LEA bupivacaine 0.5% n = 10	113 (± 13) 15.1 (± 1.7)	66 (± 9) 8.8 (± 1.2)	81 (± 10) 10.8 (± 1.3)	62 (± 12)	20.6 (± 6.1)	9.7 (± 2.9)	54 (± 6)	63.2 (± 12.7)	135.7 (± 23.7)	13.3 (± 5.8) 17.7 (± 7.7)

*** indicates $P < 0.001$ compared to Group 3 (control) and compared to Group 4 (LEA).

lumbar epidural anesthesia. The heart rate tended to be somewhat lower during thoracic and lumbar epidural anesthesia as compared to the control group; however, the level of significance was not reached. Left ventricular end-diastolic and end-systolic areas were similar in all four groups, leading to comparable values for the fractional area change. No significant difference could be demonstrated between the values for end-systolic and peak-systolic wall stress calculated in the four groups. Left ventricular contractility, measured as maximal elastance (E_{max}) of the ESPLR, was approximately halved during thoracic epidural anesthesia, without any difference between the two bupivacaine concentrations. This reduction was highly significant in comparison to the control and the lumbar epidural group ($P=0.0002$). There was no difference in the E_{max} value between Groups 3 and 4 (Fig. 1).

No complications resulted from the study, and in all patients receiving epidural anesthesia the epidural catheter was used intraoperatively in combination with general anesthesia, and also provided the route for postoperative analgesia.

DISCUSSION

The major finding of this study was that left ventricular contractility, measured as the maximal elastance of the left ventricle, was grossly reduced during high thoracic epidural anesthesia, but that this did not occur when the same amount of bupivacaine was injected into the lumbar epidural space. This negative inotropic effect was not dependent on the concentration of bupivacaine administered, indicating that a similar degree of sympathetic blockade was achieved with bupivacaine 0.25% and bupivacaine 0.5%. The patients receiving either thoracic or lumbar epidural anesthesia showed a remarkable degree of hemodynamic stability, with no alteration in systolic or diastolic arterial pressure and only insignificant cardiac slowing. The indices of left ventricular preload were not reduced with either form of epidural anesthesia. Without performing intravascular volume expansion (as was done in the epidural groups), we might have seen a reduction in left ventricular preload as a result of peripheral vasodilation and reduced systemic venous return (24, 25), in spite of some compensatory vasoconstriction that may have occurred in segments not affected by the block (9, 25, 26).

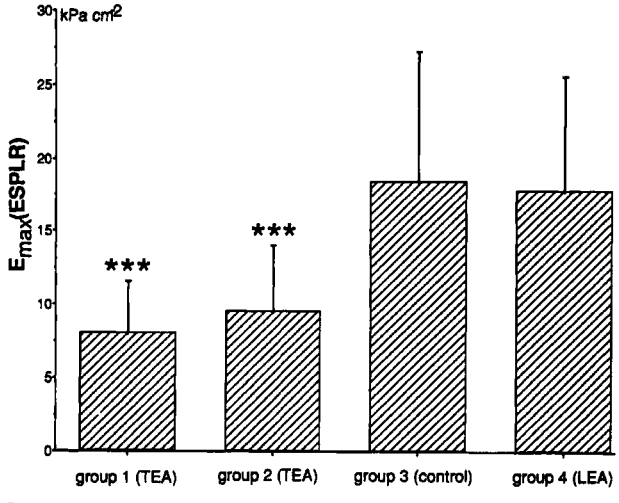

Fig. 1. Arithmetic means (± s.d.) of the maximal elastance (E_{max}) of the left ventricle. ***indicates $P<0.001$ versus Group 3 (control) and versus Group 4 (lumbar epidural anesthesia).

Surprisingly, left ventricular afterload measured as end-systolic and peak-systolic wall stress was not significantly affected by lumbar or thoracic epidural anesthesia. We are not aware of any study using wall stress as a measure of left ventricular afterload in subjects receiving epidural anesthesia. However, one must keep in mind that the true invasively measured peak systolic wall stress occurs towards the end of the first third of systole and is probably overestimated in our approximation of peak-systolic wall stress (27). This uncertainty must be considered when interpreting the effect of epidural block on FAC which appeared not to be altered by either TEA or LEA. In face of an unchanged pre- and afterload and a reduced contractility, a constant FAC is difficult to interpret and may require the inclusion of systolic time indices which were not measured in our study.

An improvement in left ventricular performance during high thoracic epidural anesthesia has been reported by two groups (3, 4, 9). Kock and coworkers found an improvement in left ventricular global and regional function during stress-induced myocardial ischemia in patients with coronary artery disease under TEA plus β-blocker compared to the same patients under β-blocker alone (4). It is remarkable that they did not find any effect of high TEA on central hemodynamics, when applied to patients treated with β-blockers and without ischemic attack (3). It is difficult to compare the experimental setting and study population of their study to that of our investigation, but since the mean systolic pressure measured during exercise was reduced from 197 to 160 mmHg (26.3 and 21.3 kPa, respectively) under TEA, one may speculate that the increased ejection fraction seen with TEA might, at least in part, have been the result of a reduced left ventricular afterload. Bonica and coworkers studied the hemodynamic effects of different levels of epidural anesthesia in healthy volunteers (9). They reported the unexpected results of an increase in cardiac output when they extended the block over the

cardiac segments. They speculated that this might have been the result of a stimulating effect of absorbed lidocaine on the cardiovascular system, due either to central nervous stimulation or to potentiation of endogenous catecholamines.

The reduction in left ventricular contractility found in our study during TEA could have been caused by two separate mechanisms. Firstly by the blockade of cardiac sympathetic fibers and secondly by the systemic action of absorbed local anesthetic. The effect of absorbed local anesthetic on ventricular inotropic state is twofold. It is well known that bupivacaine may have a direct depressant effect on the myocardium (11). On the other hand, it potentially elicits some stimulating effects on the circulation, most likely via central activation (9, 28, 29). In order to consider the effect of absorbed local anesthetic we included a group who received a dose of bupivacaine equal to that of the Group 2 patients into the lumbar epidural space. In both groups, plasma concentrations of local anaesthetic would be expected to be comparable (30). The upper level of the sensory block in the LEA group ranged from Th_8 to L_1. So it is unlikely that the block induced by LEA involved the cardiac segments (26). We therefore conclude that the negative inotropic effects seen with high thoracic epidural anesthesia in our study are mainly due to sympathetic denervation of the heart. This denervation is evident even at the lower concentration of bupivacaine.

We used the slope (E_{max}) of the end-systolic pressure length relationship (ESPLR) as a measure of left ventricular contractility since it is believed to be relatively insensitive to left ventricular loading conditions (14, 21–23). This load independency represents the major advantage over the traditional ejection phase and isovolumetric phase indices of contractility (13). There have been several studies on intact animals (31, 32) and on humans (33–35) that confirmed the initial results from Suga and Sagava (14, 21–23). However, the concept of E_{max} as a measure of left ventricular contractility has recently been the subject of some criticism (36, 37). Crottogini and coworkers proposed a new index combining the changes of E_{max} and of the volume axis intercept: the area beneath the ESPVR-line between defined volume limits (36). However, this method (i.e. the definition of volume- or diameter-limits) has not yet been validated for interindividual comparisons, so that it did not appear applicable in our experimental setting.

In this study we chose to use transesophageal echocardiography (TEE) to determine left ventricular dimensions because it is superior to external echocardiography with respect to the quality and reproducibility of the recordings (38). Performing TEE on conscious patients is unpleasant and might cause adrenergic as well as vagal reactions. We therefore performed our measurements under general anesthesia. That may well have lowered the baseline levels of heart rate and arterial pressure, and may thereby have influenced other derived parameters.

Individual cardiovascular response to different levels of sympathetic blockade varies widely, depending on the degree of sympathetic tone prior to the block (9). Obviously, even in healthy subjects under general anesthesia and without any surgical stimulation, a relevant degree of sympathetic influence on the heart seems to be present, the blockade of which leads to significant alteration in ventricular performance. Using high TEA in patients with impaired global ventricular function and increased sympathetic tone could therefore have deleterious effects.

In summary, we found left ventricular contractility to be grossly reduced with high thoracic epidural anesthesia. Since this negative inotropic effect could not be demonstrated with the same dose of bupivacaine when administered into the lumbar epidural space, it is likely that this reduction in contractility is mainly the result of sympathetic denervation of the heart. Whether these results are valid for patients with compromised ventricular function and how β-blocker therapy alters the effects of epidural block in these patients remain to be investigated.

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