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Cardiovascular effects of thoracic epidural anaesthesia

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Section III

Central neural blockade

Chapter 5

Upper thoracic epidural anaesthesia with ropivacaine: effects of age on neural blockade and cardiovascular parameters

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Introduction

Thoracic epidural anaesthesia (TEA) combined with general anaesthesia (GA) is common practice for lung surgery. To our knowledge there are no data describing the spread of neural blockade after a loading dose of local anaesthetic at the T3-T4 level[1]. In elderly patients compared to younger ones, lumbar epidural anaesthesia resulted in increased levels of analgesia often associated with hypotension and bradycardia[2-5]. However, limited data is available about the effect of age on the quality of neural blockade and hemodynamic changes following thoracic epidural anaesthesia.

After thoracic epidural administration of a fixed dose of a local anaesthetic solution more segments are blocked in the elderly compared with younger patients[6]. Another study showed that elderly patients require a lower dose of a local anaesthetic solution to block the same number of segments. Furthermore there is a greater incidence of hemodynamic instability with increasing age[7]. However in both studies the epidural injection site was at a low thoracic region (T6-T10), which might not be the appropriate injection site for patient scheduled for a surgical procedure of the lung because the upper border of sensory blockade might not be high enough. Thoracic epidural anaesthesia is associated with an attenuation of the sympathetic tone due to blockade of the sympathetic nerves which may result in hemodynamic instability. Since increasing age is associated with decreased cardiac reserves, structural changes in the arterioles and changes in the autonomic nervous system, thoracic epidural anaesthesia may be associated with impaired cardiovascular responses in the elderly. The primary objective of this study was to confirm or refute the hypothesis that age increases the maximum number of spinal segments blocked after thoracic epidural administration of a fixed dose of ropivacaine. In addition other variables of analgesia and motor blockade and changes in HR, MAP, SV and CI were studied.

Methods

The protocol of this study was reviewed and approved by the Committee on Medical Ethics of the Leiden University Medical Centre, reg. no: P09060, date 6 July 2009. The study was approved by the Centrale Commissie Mensgebonden Onderzoek (CCMO), as Competent Authority for the review of clinical trials in the Netherlands, NL27041.058.09.

Between August 2009 and April 2011, patients scheduled for pulmonary surgery (full lateral thoracotomies or pleurodesis by video-assisted thoracoscopic surgery/VATS) under thoracic epidural anaesthesia were asked to participate, and gave their consent, and were included in this open, observational, single-center study. Patients were enrolled in one of three age groups (young age group: 18-45 years, middle age group: 46-65, older age group: 66 years and older) after written informed consent was obtained from all patients after full explanation of the study. After finishing the last measurements for this study all patients underwent pulmonary surgery under thoracic epidural anaesthesia and general anaesthesia. Patients were regarded as having hypertension as shown if they had been diagnosed with hypertension in their medical record

and were being treated with anti-hypertensive drugs. Patients who had a history of known hypersensitivity to amide local anaesthetics, infection of the skin in the area of the epidural site, a history of neuromuscular diseases and a history of bleeding diathesis were excluded from the study. Patients who weighed more than 110 kg or were shorter than 150 cm were also excluded. In addition, pregnant women were excluded as well. The groups were not matched with regard to antihypertensive or anti-arrhythmic medication in order to have a population sample that resembles clinical reality, which implies "natural confounding" of age and use of medication. Patients fasted from midnight before surgery. Antihypertensive medication was continued 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 epidural anaesthesia. A 14-gauge intravenous (i.v.) catheter was placed in the arm for administration of fluids and medication. A colloid (Voluven®, Hydroxyethyl starch 130/0.4, Fresenius Kabi, Bad Homburg, Germany.) infusion was administered at a rate of 10 mL/kg over a 40-min period beginning 10 min before the epidural injection of ropivacaine to maintain preload[8].

Epidural puncture was performed with the patient in the sitting position at the T3-T4 interspace, using the paramedian approach. The interspace was identified by examination and palpation of the spine, counting upward from the inferior angle of the scapula, which was assumed to correspond with T7 and counting downward from the vertebra prominens which was assumed to correspond with C7[9]. After local infiltration of the skin with lidocaine 1% the epidural space was identified using the hanging drop technique with an 18 gauge Tuohy needle with the bevel pointing cephalad. A 20-gauge lateral eye catheter was introduced 5 cm into the epidural space in the cephalad direction. In case of signs of intravascular puncture during epidural needle or catheter placement or signs of dural puncture from the epidural needle or catheter, patients were excluded from the study. After catheter insertion patients received 8 ml ropivacaine 0.75% through the catheter with an injection rate of 1 ml per 10 seconds. After epidural catheterization the patient was placed in the supine position for the entire study period.

To avoid inter-operator variability analgesic- and motor blocks were performed by one investigator (JW). Analgesia was assessed bilaterally in the anterior axillary line, arms and legs by pinprick using a short- bevelled 25-gauge needle and by temperature discrimination using ice cubes. Analgesia was defined as the inability to detect a sharp pinprick and the inability to recognize the temperature of the ice-cube. Results from both sides were averaged. Motor block of the lower extremities was tested on both sides 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), with a maximum score of 3[10]. Assessments were made every 5 min during the first 30 min. Analgesia of dermatomes T3 and T4 was tested every minute until onset of sensory blockade.

The following parameters were investigated:

Time to initial onset of analgesia at the T3-T4 dermatomes
Time to initial onset of motor blockade
Time until maximum cephalad spread of analgesia
Time until maximum caudal spread of analgesia
Highest dermatomal level of analgesia
Lowest dermatomal level of analgesia
Maximum numbers of segments blocked
Maximum score of motor block (Bromage scale and ESSAM score)

An arterial line 20 G was inserted prior to induction of thoracic epidural anaesthesia and after local infiltration with lidocaine 1% in the radial artery to monitor arterial blood pressure (Edward Lifesciences LLC, Irvine, CA, USA). With the FloTrac/Vigileo™ system (software version 1.01; Edwards Lifesciences, Irvine, CA) cardiac index and stroke volume were measured by analysis of the arterial pulse wave. Mean arterial pressures (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP) and cardiac index (CI) were measured continuously during the study. Heart rate (HR) was monitored continuously from the electrocardiogram.

Data were recorded at 5-min intervals during the first half hour after induction of thoracic epidural anaesthesia. Baseline values were the baseline values measured at the starting point of epidural injection. If the systolic blood pressure decreased more than 30% below the baseline value or to less than 90 mm Hg, ephedrine 5 mg was given IV. Bradycardia (heart rate < 55 beats/min) was treated with atropine sulphate, 0.25-0.5 mg IV.
Regarding baseline characteristics frequencies or group percentages were compared using the overall χ^2- test when data were categorical and one way ANOVA when data were continuous. The distribution of analgesia and motor blockade data, and the values of the hemodynamic variables were tested for normality using the Kolmogorov-Smirnov test. We used least significant difference (LSD) for correction of multiple testing, taking into account the dependent nature of the various outcome variables. One way ANOVA was used to compare the means of continuous variables between the age groups. The relationship between age and total amount of spinal segments blocked by TEA was evaluated using linear regression analysis. P-values equal to or less than 0.05 were considered as the minimum level of significance.
A sample size of 30 patients was calculated to provide 90 % power to detect a slope coefficient of 0.10 of maximal number of spinal segments blocked after TEA versus age, assuming a standard deviation of 3 in the outcome variable based on a previous study with ropivacaine [11]. In order to ensure sufficient variation in age we enrolled patients in age categories which also allowed comparisons among the age categories. All statistics were calculated using the software package SPSS Statistics 17.0 (SPSS Inc, Chicago, IL). Graphs were made using SigmaPlot 11.0 (Systat Software Inc, San Jose, CA).

Table 1. Demographic data and characteristics of patients

	Young Age Group (18-45 years) (*n* = 10)	Middle Age Group (46-65 years) (*n* = 10)	Older Age Group (66 years and older) (*n* = 11)	Total (*n* = 31)
Age (years)	33(3)	57 (2)	74 (1)	55 (18)
Gender (M/F)	6/4	6/4	6/5	18/13
ASA (I/II/III)*	7/3/0	2/7/1	2/6/3	11/16/4
Height (cm)	177 (6.8)	176 (12.1)	174 (7.7)	176 (8.9)
Weight (kg) 71	71 (13.2)	85 (16.8)	74 (10.2)	77 (14.4)
Hypertension (y/n)**	0/10	2/8	8/3	10/21
Anti-arrhythmic (y/n)***	0/10	0/10	6/5	6/25

* Overall comparisons, χ^2 [2] = 9.6; p=0.047

** Overall comparisons, χ^2 [2] =13.7; p=0.001

*** Overall comparisons, χ^2 [2] =13.5; p=0.001

Results

Forty-two patients were asked to participate, thirty-five patients gave their written informed consent and were included in this study. Four patients were excluded because placement of an epidural catheter technically failed. All catheters were placed in the T3-T4 interspace. Demographic data and characteristics of the groups are presented in **Table 1**. The three age groups did not differ in the ratio of men to women, height or weight. In the young age group most patients had an ASA 1 classification, whereas in the middle and older age groups more patients were classified as ASA II or ASA III (overall χ^2 test, p=0.047).

In the young age group there were no patients, in the middle age group two and in the older age group eight patients with pre-existing hypertension (overall χ^2 test, p=0.001).

Table 2. Characteristics of neural blockade

	Young Age Group (18-45 years) (*n* = 10)	Middle Age Group (46-65 years) (*n* = 10)	Older Age Group (66 years and older) (*n* = 11)
Variables of analgesia			
Epidural approach (Paramedian/Median)	8/2	10/0	11/0
Time to initial onset of analgesia at dermatome level T3-T4 (min)	4.2(1.3)	4.3 (2.3)	6.5 (7.2)
Time to maximum cephalad spread by pin prick (min)	22.3 (6.3)	21.0 (5.4)	18.9 (5.6)
Time to maximum cephalad spread by ice cube (min)	20.3 (7.8)	21.8 (4.7)	19.3 (5.0)
Time to maximum caudal spread by pin prick (min)	24.5 (4.0)	25.3 (2.8)	23.1 (6.0)
Time to maximum caudal spread by ice cube (min)	25.8 (3.9)	27.0 (2.6)	24.1 (6.8)
Upper level of analgesia by pin prick (dermatome)	C4 (C2 – T1)	C5 (C3 – T2)	C6 (C2 – T4)
Upper level of analgesia by ice cube (dermatome)	C4 (C2 – C7)	C4 (C2 – T2)	C4 (C2 – T4)
Lower level of analgesia pin prick (dermatome)	L1 (T8 – L3)*	L3 (T11 – S1)*	L3 (T11 – S1)*
Lower level of analgesia ice cube (dermatome)	L1 (T10 – L5)**	L4 (T11 – S1)	L3 (T12 – S1)**
Variables of motor blockade			
Time to initial onset of motor blockade (ESSAM)	18.3 (5.6)	21.3 (3.8)	18.0 (7.4)
Maximum ESSAM score	0.9 (0.8)	0.6 (0.7)	0.5 (0.8)
Maximum Bromage score	0.0 (0.0)	0.0 (0.0)	0.0 (0.3)

Data presented as mean (SD) or mean (range).

* Differences between the young and middle age group (P=0.014), and the young and older age group (P=0.045).

** Difference between group the young and older age group (P=0.029).

Six patients in the older age group were treated with an anti-arrhythmic drug (five patients using β- blockade and one using flecainide (Tambocor®), whereas none of the patients in the young and middle age group were using an anti-arrhythmic drug (overall χ^2 test, p=0.009). Values of the parameters of analgesia and motor blockade are shown in **Table 2**. In two patients the epidural catheter was placed by the median approach instead of a paramedian approach because of technical difficulties. There was no statistically significant regression of the total number of segments blocked on age, the slope of the regression line being 0.054 (p=0.218) (**Figure 1**). The maximum number of spinal segments blocked in all patients was 18.2 (SD 4.3). No differences between groups were observed for time to initial onset of analgesia at dermatome level T3-T4, time to maximum cephalad spread (by pinprick or ice), time to maximum caudal spread (by pinprick or ice) and maximum cephalad spread (by pinprick or ice). The maximum caudal extension of analgesia was different between the groups, being higher in the young age group compared to the middle – and older age group. The differences were significant between the young and middle age group (pinprick p=0.014) and between the young and older age group (pinprick p=0.045, ice p=0.029).

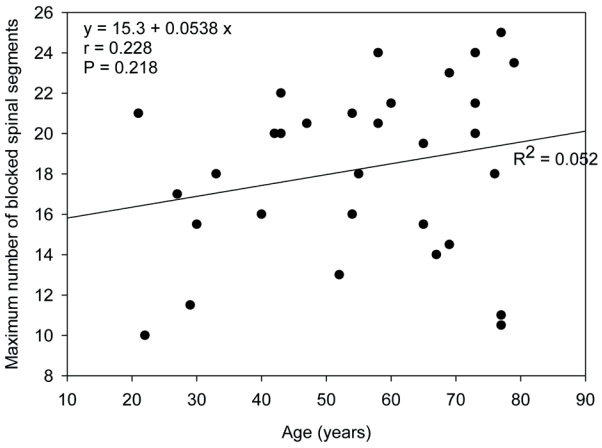

Figure 1. Relationship between maximum number of dermatomes blocked and age after thoracic epidural administration of 8 ml ropivacaine 0.75%.

In a mixed model evaluating the effect of age group and time on cephalad and caudad borders, and patient as a random factor, only time was a significant predictor and age group was not (**Figure 2**). Approximately half of the patients (15/31) did have some degree of motor blockade of the upper extremities (ESSAM score), with one patient having a maximal ESSAM score. There was no difference between age groups for time to initial onset of motor blockade, maximum ESSAM score and maximum Bromage score. Only two patients (older group) had a Bromage score of 1.

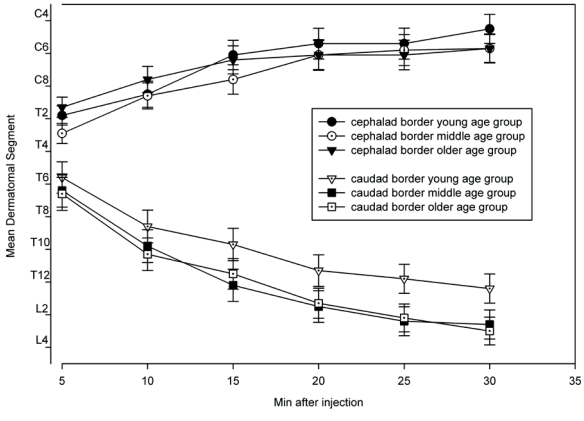

Figure 2. Mean cephalad and caudad borders of the three age groups every 5 minutes after thoracic epidural administration of ropivacaine.

Hemodynamic data are shown in table 3. There was a significant maximal decrease of HR (6.0 ± 5.9, p<0.001), MAP (16.1 ± 15.6, p<0.001), CI (0.55 ± 0.49, p<0.001) and SV (9.6 ± 14.6, p=0.001) after TEA for the total group. Mean values for baseline heart rate and time to maximal decrease of heart rate were not different between the age groups. Maximal decrease of heart rate did differ between the young and middle age group (p=0.03) and the young and older age group (p=0.01) (**Figure 3**). Five patients became bradycardic (HR < 55/min-1) during a 30-minute period after TEA, but age did not make a significant difference in the incidence of bradycardia. No significant differences between the age groups were found for all data of MAP and stroke volume. In total, ten patients developed hypotension during a 30-minute period after TEA but the incidence of hypotension did not differ between the age groups. Two patients required atropine 0.5 mg and ephedrine 5 mg to correct bradycardia and hypotension, two patients required 5 mg ephedrine and two patients required two times 5 mg ephedrine to correct hypotension (**Table 3**). Excluding these patients from post treatment analysis resulted in a more significant difference in maximal decrease of heart rate between the groups (young 11.3 ± 5.5 vs. middle 3.0 ± 4.7, p=0.001 and young 11.3 ± 5.5 vs. older 3.4 ± 3.4, p=0.002). Other hemodynamic data were minimally affected with exclusion of these patients, and therefore were included for analysis.

The baseline values of cardiac index did differ between the young and older age group (p=0.007), the mean difference being 0.9 $L.m^{-2}.min^{-1}$. Time to minimum value of cardiac index and maximal decrease did not differ between groups.

Table 3. Hemodynamic data

	Young Age Group (18-45 years) (*n* = 10)	Middle Age Group (46-65 years) (*n* = 10)	Older Age Group (66 years and older) (*n* = 11)
Administration of			
Atropine	1	1	0
Ephedrine	1	2	3
Heart rate			
Reference value (beats.min-1)	72.7 (9.3)	73.8 (19.2)	69.5 (9.0)
Time to minimum value (min)	16.0 (8.1)	15.5 (8.6)	16.8 (7.2)
Maximal decrease (beats.min-1)	10.0 (6.6)*	4.6 (5.5)*	3.7 (3.8)*
Number of patients with bradycardia	3	1	1
MAP			
Reference value (mmHg)	84.4 (15.8)	91.1 (14.3)	96.2 (16.6)
Time to minimum value (min)	19.0 (7.0)	19.5 (6.4)	16.8 (7.5)
Maximal decrease (mm Hg)	11.8 (8.9)	13.9 (17.4)	22.1 (18.0)
Number of patients with hypotension	2	3	5
Cardiac index			
Reference value (L.m-2.min-1)	3.8 (1.0)**	3.3 (0.7)	2.9 (0.4)**
Time to minimum value (min)	14.5 (6.4)	13.5 (7.5)	16.4 (7.8)
Maximal decrease (L.m-2.min-1)	0.6 (0.7)	0.5 (0,5)	0.5 (0.3)
Stroke volume			
Reference value (mL)	96.8 (29.0)	91.4 (21.6)	89.6 (21.7)
Time to minimum value (min)	12.0 (8.2)	13.0 (8.2)	16.0 (8.8)
Maximal decrease (mL)	7.6 (21.6)	8.3 (8.8)	12.9 (11.0)

Data presented as mean (SD) or n.

* Differences between the young and middle age group (p=0.033), and the young and older age group (p=0.013).

** Difference between the young and older age (p=0.007).

Discussion

This study demonstrated that the amount of segments blocked following thoracic epidural administration of a fixed loading dose of ropivacaine is large. In addition there is a large variability in the spread of analgesia within the age groups. We were not able to confirm our hypothesis that age influences the total amount of segments blocked after TEA. All hemodynamic parameters decreased following epidural anesthesia, but only decrease in HR was influenced by age.

The effect of age on the level of analgesia and the number of dermatomes anaesthetised during thoracic epidural anesthesia in the present study does not agree with other reports that have evaluated the effect of age on the spread of thoracic epidural anaesthesia[6, 7]. Discrepancies may be based on differences in the mode of administration, the site of injection at the thoracic spine, and volume and concentration of the local anaesthetic[12, 13]. However the assumption of a slope coefficient of 0.10, underlying the power calculation, may have been too strong.
Hirabayashi and colleagues[6] reported a 40% reduction in dose requirement in the elderly compared with the young adults after administration of a fixed volume of a local anesthetic agent at the T9-T10 interspace. In their study the local anesthetic solution was injected through the needle whereas in the present study the solution was administered through a catheter. This difference is relevant because injection through a catheter compared to injection through the needle has been shown to result in greater extension of analgesic spread[14].

Another study[7] found a decrease in segmental dose requirements as well. In addition more hemodynamic changes were observed in the elderly after epidural injection of 5 or 9 ml lidocaine 2% through an epidural catheter at the T6 to T10 level. Their study was designed however to constitute a safe test dose and the analgesic blockade observed was clearly not sufficient for surgical analgesia. Another difference between our study and above mentioned studies is the level of epidural puncture. In the present study the puncture site was at the T3-T4 interspace whereas in the above mentioned studies injection took place at a lower interspace (T6-T10). To our knowledge there are no data describing the spread of neural blockade and the effect of age after a loading dose at the T3-T4 level. Radiological studies have shown a positive correlation between age and longitudinal spread of contrast in the thoracic epidural space[15, 16]. It is possible that radio-opaque material and local anesthetic do not spread in an identical manner.

The upper level of analgesia was not different between age groups in our study, but there was a small difference in the lower level of analgesia. In lumbar epidural anaesthesia it is well documented that age influences the clinical profile[2-5]. In older patients the spread of analgesia is more extensive, and the onset time of analgesia is faster at the caudal segments. In addition an enhanced intensity of motor blockade is shown with advancing age. Anatomical features and possible pharmacodynamic changes may best explain these alterations, rather than variation in the pharmacokinetics changes in the elderly[17]. Progressive sclerotic closure of the lateral intervertebral foramina, gradual degeneration of the central and peripheral nervous systems

and degeneration of the epidural fat may all promote the greater longitudinal spread of injected solutions following lumbar epidural administration in elderly patients[12, 18, 19].

Discrepancies between the observations in the spread of analgesia in the present study and the lumbar epidural studies may be based on the differences in shape of the thoracic and lumbar epidural space, differences in vertebral column height and differences in local distribution of the local anesthetic at the site of action. Furthermore there is a considerable variability in the spread of analgesia between persons of the same age. Motor blockade of the upper extremities was tested using the ESSAM score. The ESSAM score has been designed by Abd Alrazek and colleagues[10] to test three arm movements consisting of four grades (0-3). Paralysis of the arms proceeds paralysis of the diaphragm and may be associated with respiratory problems due to cephalad extension of neural blockade. In the present study half of all patients had some degree of motor blockade of one or both arms, but none of them experienced respiratory problems. Increasing age did not influence motor blockade. Only two patients in the older age group had decreased motor function of the lower extremities with a Bromage score of 1. In the present study the HR, MAP, CI and SV in all patients decreased significantly after TEA. When looking at the hemodynamic effects per age group there is one significant difference between the age groups. The decrease in HR after TEA is more pronounced in the young compared to the middle - and older age group. In contrast to our study, a previous study[7] showed that HR reduction after TEA was also age related, but seemed to be more pronounced in the elderly group, which is the opposite of our results. Another study demonstrated a more pronounced reduction in HR after beta-blockade in the young men compared with the older men[20].

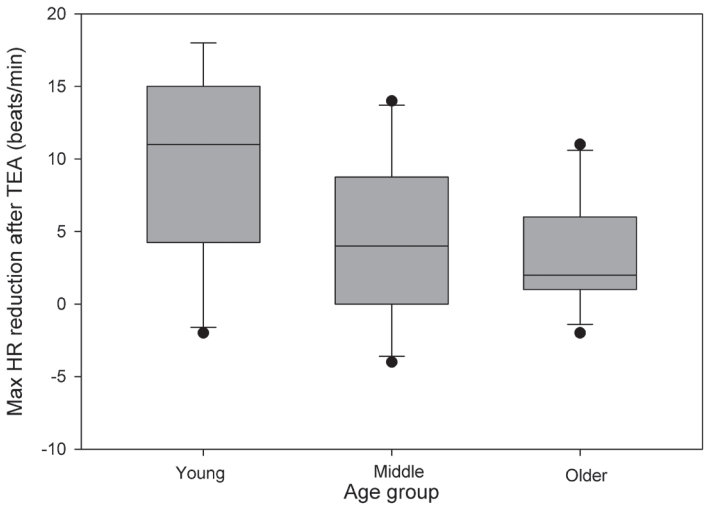

Fig 3. Maximum reduction of Heart Rate (HR) after TEA in the three age groups presented as boxplots. Mean heart rate reduction was different between the young and middle group and between the young and older group (p=0.03 and p=0.01 respectively).

The observed decreases in heart rate are likely to be influenced by the fact that 6 out of 11 patients were using anti-arrhythmic drugs in the older group. In the young and middle age group however, there were no patients using anti-arrhythmic drugs and the decrease in heart rate after TEA between these groups was significantly different. We can't exclude a possible influence of oral premedication with midazolam on pre-existing sympathetic tone. However, all patients were very much awake at the start of hemodynamic measurements and in addition oral dosage of midazolam was adjusted to age. On the other hand, denying patients premedication with midazolam could result in anxiety resulting in increased sympathetic tone. So there might be an influence of age on the decrease of HR after TEA. Changes of autonomic control with accompanying aging might explain these age related differences. In the normal ageing process increased sympathetic tone in combination with decreased parasympathetic tone and blunted cardiovagal baroreflex sensitivity are acknowledged physiologic changes[21]. Explanations remain difficult because age related changes of autonomic control of the heart are complex and remain to be clarified.

The reference value for Cardiac Index (CI) was significantly lower in the older compared to the young age group. The effect of age on resting cardiac function has been shown to differ depending on the selection of the study population[22]. Several studies have found a decrease of cardiac output with increasing age[23-25]. The Baltimore study however excluded patients with CAD and found no effect of age on cardiac output or cardiac index[26]. In the present study we did not exclude patients with cardiovascular disease, which makes our results corresponding with the above mentioned studies. Limitation in our study is that cardiac index and stroke volume were measured with pulse wave analysis by FloTrac/Vigileo™. A limitation of this system is the substantial degree of error in measuring absolute values of cardiac output and trending of cardiac output compared to measurements done with a pulmonary artery catheter[27].

In studying the effects of TEA on cardiovascular parameters we were not able to demonstrate that increasing age plays a significant role, except for maximum reduction of heart rate by TEA. Considering the structural changes of the heart and the changes in autonomic function with increasing age we expected to see differences between the groups regarding hemodynamic effects of TEA. Some hemodynamic parameters varied between the age groups but not significantly, possibly because of the large spread in values.

In summary, we showed that in the population we studied no correlation was found in the number of segments blocked and increasing age after an epidural loading dose (8 ml) of ropivacaine 0.75% at the T3- T4 level. Only caudad spread of analgesia increased with advancing age. One of the complicating factors when studying age effects is the great interindividual variation in the ageing process. These data also indicated the great variability in the cephalad spread and effect of age of a given epidural dose of ropivacaine in any patient[28]. Hemodynamic effects of TEA did not differ significantly between the age groups, yet increasing age might play a role in the amount of reduction in heart rate after TEA.

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