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Cardiovascular effects of thoracic epidural anaesthesia

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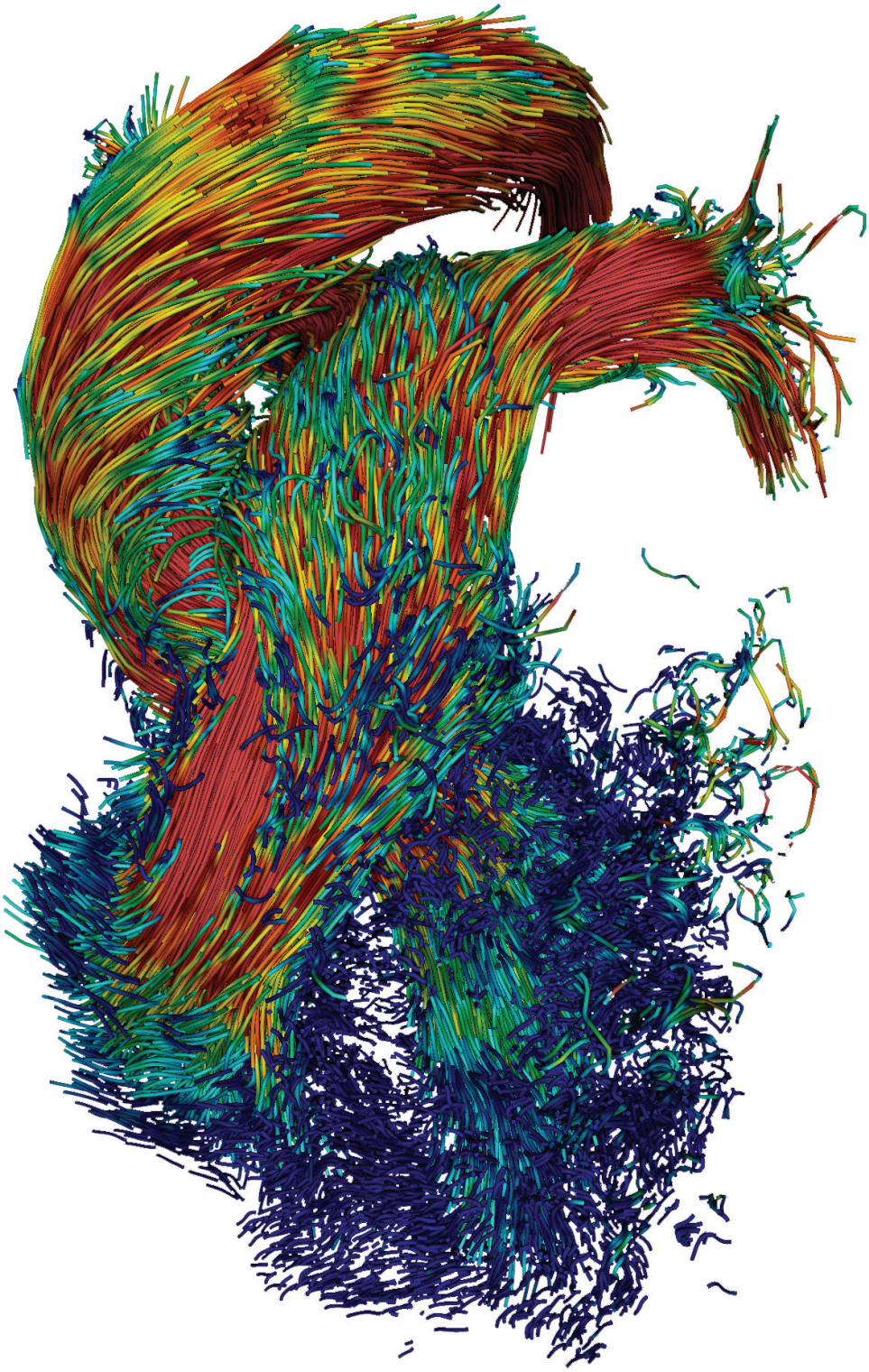

Section I

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Chapter 1

Thoracic epidural neural blockade

Epidural anaesthesia results in sensory and motor blockade but also implies blockade of sympathetic outflow resulting in cardiovascular changes. This section will focus on neural blockade after TEA. Anatomy of the epidural space will be briefly discussed as it is of importance in understanding variations in analgesic spread after epidural anaesthesia.

1.1 Anatomy of the (thoracic) epidural space

The epidural space extends from the foramen magnum to the sacral hiatus. Anteriorly the epidural space is bounded by the dura mater, laterally by the pedicles and intervertebral foramina, and posteriorly by the ligamentum flavum (**Figure 1**). The epidural space is mostly empty: it is a potential space rather than a true cavity[1].

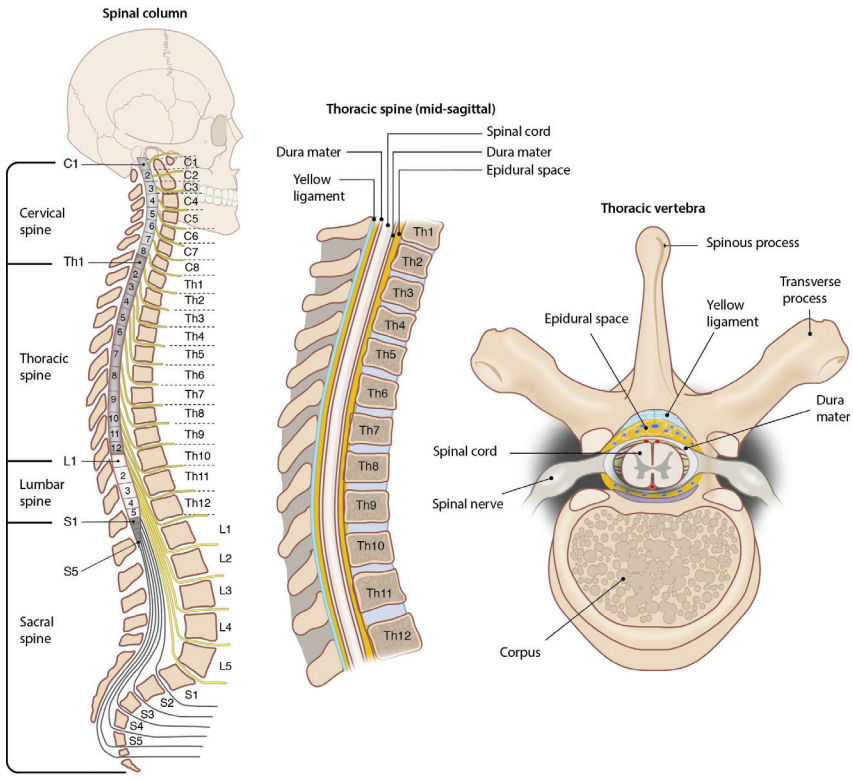

Figure 1. Anatomy of the thoracic spine

The epidural space is discontinuous, giving rise to compartments within the epidural space. Longitudinally and circumferentially the epidural space is not continuous and separated by zones where the dura is in contact with the spinal canal wall[1]. Despite the compartimentization of epidural space, fluids are allowed to pass these compartments freely making the epidural space a functional continuum[2].

Contents of the epidural space:

- Fat
- Veins
- Arteries
- Spinal nerves
- Epidural lymphatics

There are anatomical differences between the lumbar and the thoracic epidural region. The epidural space becomes smaller from lumbar to cervical, ranging from 5 to 6 mm at L2 to 2.5 to 3 mm at T6 and to 1 to 1.5 mm at the level of C5[3]. The size and shape of the thoracic vertebral column is different from that of the lumbar vertebral column. The lumbar curve is convex anteriorly and the thoracic curve is convex posteriorly and the thoracic vertebrae are smaller than the lumbar vertebrae. In addition epiduroscopy[4] and MRI[5] demonstrated that the thoracic epidural space contains less fatty and fibrous tissue and has increased patency of the extradural space after injection of air compared to the lumbar epidural space.

1.1.1 Effects of ageing on epidural space

Structural changes of the epidural space might influence the distribution of local anesthetics and extension of neural blockade. With advancing age anatomical change occurs in the epidural space. Epiduroscopy showed that with advancing age the lumbar epidural space becomes more patent and the amount of fatty tissue diminishes[6], which might promote more longitudinal spread of local anesthetics in the elderly. It seems fair to assume that these age-associated changes of the epidural space apply to the thoracic epidural space as well.

Compared to the young, there is partially sealing of the intervertebral foramina of the thoracic spine in the elderly, because of structural changes of the tissue around the intervertebral foramina[5]. With advancing age the diameter of the myelinated fibers in the dorsal and ventral nerve roots becomes smaller and the number of myelinated fibers decreases[7]. Weakening of the connective tissue sheets covering the nerves with advancing age, makes more penetrable by local anesthetics[7]. Furthermore, increasing age is accompanied with a greater permeability of the dura[8].

1.2 Sensory blockade

One of the primary aims of epidural blockade is to prevent the conduction of nociceptive impulses from the surgical field to the brain. The skin and other organs host a rich diversity in different receptors and nerve endings responsible for sensations like touch and proprioception but also nociception. Activation of nociceptive receptors by noxious stimuli results in impulses that are conducted by specific fiber types within peripheral nerves. The impulses conducted through these fibers reach the spinal column by way of the dorsal spinal roots[9]. Conduction of the impulses to the brain will generate perception of pain.

Sensory blockade after epidural administration of local anesthetics might differ between the thoracic level and lumbar level. Differences in shape and contents 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 may explain these regional characteristics. Furthermore, there is a considerable variability in the spread of analgesia between persons of the same age.

In clinical practice spread of analgesic blockade after TEA has been demonstrated to depend on the insertion site of the epidural injection. At the low thoracic level analgesic spread was more cranial whereas spread of analgesic blockade at high thoracic level was more caudal[10]. Differences in epidural pressure at the different epidural regions might contribute to this typical pattern of spread of sensory blockade[11]. The amount of spinal segments blocked appears to depend on the total amount of local anesthetic administered[10].

1.2.1 Assessment of sensory blockade

The spinal nerves leave the spinal cord through the intervertebral foramina, where each spinal segment supplies a specific region of the skin, muscle (myotomes) or bone (osteotomes). Assessment of sensory or analgesic blockade is by testing for loss of sensory discrimination (pin prick) or by temperature discrimination (ice). In our studies we used both pinprick and ice as stimuli for assessing sensory blockade. Assessment of sensory blockade in our studies has been performed at each dermatome on both sides of the body according to a dermatomal chart.

1.2.2 Influence of age on sensory blockade

The effect of age on extradural dose requirements have been investigated numerously in lumbar epidural anesthesia, however results are conflicting[12-23].

Studies investigating the effects of age and dose requirements in thoracic epidural anesthesia are scarce. Though the number of studies is limited, they all demonstrated a positive correlation between age and spread of blockade following thoracic epidural administration of a local anesthetic solution. A study by Hirabayashi and colleagues[24] concluded that the extradural dose requirement decreased with increasing age (r = -0,7), the requirement in the elderly (60-79 year) being about 40% smaller than that in the young adults (20-39 year) (**Figure 2**). Another study by Holman et al[25] found smaller segmental dose requirements and greater incidence of hemodynamic instability in the elderly group (56-86 year) vs the younger group (18-51 year). Their study was designed to constitute a safe test dose for TEA and analgesic blockade was not appropriate for surgery.

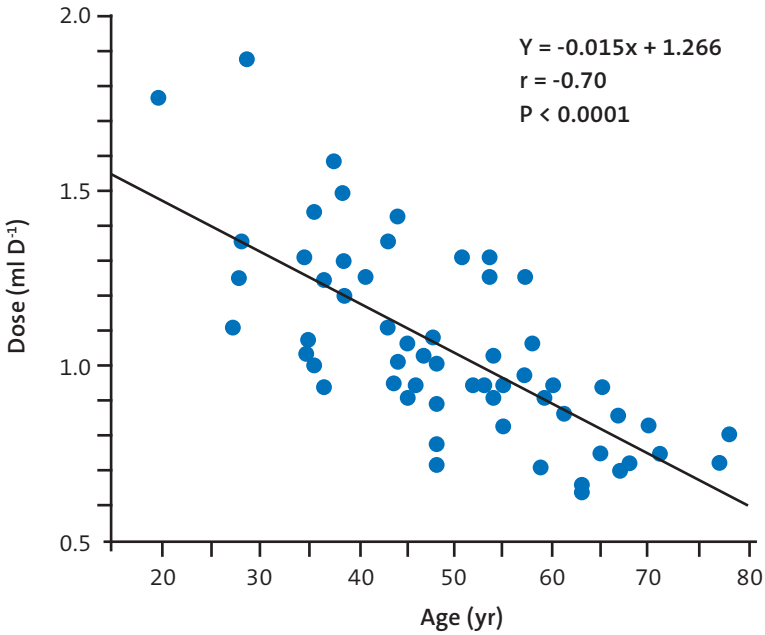

Figure 2. Relationship between age and extradural dose requirement in thoracic extradural anesthesia. From Y. Hirabayashi and R Shimizu, effect of age on extradural dose requirement in thoracic extradural anaesthesia, British Journal of Anaesthesia 1993; 71: 445.

Radiological studies have shown a positive correlation between age and longitudinal spread of contrast in the thoracic epidural space[26, 27]. However, spread of radio-opaque material might differ from spread of local anesthetics.

1.3 Sympathetic blockade

Sympathetic blockade will be discussed more extensively since it responsible for the cardiovascular effects associated with TEA and the main focus of this thesis. Thoracic epidural anesthesia results in blockade of sympathetic outflow to heart (T1-T5) and vessels (T6-T10) which is responsible for the hemodynamic changes after induction of TEA. Blockade of preganglionic sympathetic innervation to the heart (T1-T5) may lead to changes in heart rate, conduction velocities, inotropic state and lusitropic state.

Blockade of preganglionic sympathetic innervation to splanchnic organs (T6-L1) may result in arterial dilatation, venodilatation with sequestration of blood in capacitance vessels, decreases in preload and inhibited sympathetic outflow to the adrenal glands with diminished secretions of catecholamines[28, 29]. The concept that epidural anaesthesia results in a complete block of sympathetic nerve activity of at least the same extent as sensory block has been questioned. Some studies indicate that the level of sympathetic block associated with epidural anesthesia

may be lower than the level of sensory block and more incomplete in terms of quality of block[30, 31]. On the other hand several studies concluded that the level of sympathetic block exceeds the level of sensory block by at least two dermatomes[32, 33]. Differences in methods to evaluate the effect of epidural anesthesia on sympathetic outflow to the thoracic and abdominal organs as well as the trunk may contribute to these controversies. Since it has not been established whether the efferent sympathetic nerves are distributed segmentally, the methods used until now do not indicate a clearly discernible boundary between the blocked and unblocked dermatome.

1.3.1 Assessment of sympathetic blockade

Skin Sympathetic Activity (SSA), e.g. abolition of sweating or sympathogalvanic response is the standard tests of complete interruption of the sympathetic nerve pathways[34]. Muscle Sympathetic Nerve Activity (MSNA) by microneurgraphy is the only technique available that directly measures sympathetic neuronal activity[35]. However one has to bear in mind that both SSA and MSNA measure local sympathetic activity which does not necessarily reflect cardiac sympathetic activity. Clinical application of this technique is limited because it is a rather invasive. Sympathetic innervation of the heart may be assessed by analysis of the power spectrum of heart rate (HR) oscillations[36]. Changes in HR over time depend on parasympathetic and sympathetic input.

Fourier analysis of HR data yields power spectra with high frequency and low frequency oscillations. Some authors claim that the low frequency domain represents cardiac sympathetic drive[37, 38,] however this is disputed by others[39, 40].
The low frequency domain measures end-organ response and is influenced by multiple factors including cardiac sympathetic innervation[41]. Because the validity of heart rate variability as a tool of measuring sympathetic activity is uncertain, we did not use this technique in our studies and excluded studies using this technique in our review article (Chapter 4). Cardiac noradrenaline spillover reflects sympathetic nerve firing to the heart and is a more direct way of assessing cardiac sympathetic innervation[41]. However, administration of isotopes and its invasive character prevent its use as a clinical marker of sympathetic innervation.

Assuming that temperature increase of the foot as measured by infrared telethermometry reflect diminished sympathetic outflow, upper thoracic segmental epidural anesthesia can result in a widespread diminution of sympathetic outflow extending to and including the most caudal part of the sympathetic system beyond sensory blockade[30]. However direct measurements of sympathetic nerve activities by muscle and skin sympathetic nerve activity demonstrated that upper thoracic epidural anesthesia is not associated with blockade of sympathetic nerve activity to the legs[42]. Despite high levels of epidural blockade (above T5) weak galvanic skin responses to arousal could still be elicited in the foot, indicating incomplete sympathetic blockade[32]. A possible approach to investigate the intensity of a sympathetic block is to measure catecholamine response. Epidural anesthesia with a sensory level to T1 did not produce

complete sympathectomy irrespective of the local anesthetic used since plasma concentrations of catecholamines were nearly unchanged[43]. Blockade of preganglionic sympathetic fibers innervating the adrenal medulla and innervating peripheral sympathetic fibers appeared to be incomplete, even during quite extensive epidural anesthesia to C8. Only analgesic blockade at the C8 level significantly decreased norepinephrine levels[44]. The degree of sympathetic blockade achieved after epidural injection of a local anesthetic seems to vary and epidural anesthesia probably induces reductions in sympathetic neural transmission rather than complete blockade.

In conclusion assessment of sympathetic blockade remains difficult and reliable tests are invasive and time consuming.

1.4 Sympathetic nervous system and aging (Figure 3)

Aging is associated with changes in the human sympathetic nervous system. One of the aging associated changes is a diminished responsiveness to ß-receptor stimulation[45-47] which seems to be related to multiple mechanisms such as downregulation of ß-receptors, decreased agonist binding of beta 1-receptors and abnormal post-synaptic ß-adrenergic signaling[46]. Studies demonstrating decreased cardiovascular response to ß-adrenergic antagonist infusion with aging and a comparable hemodynamic profile between ß-blocked younger subjects and older unblocked subjects support these mechanisms[48, 49]. Despite these aging-associated functional changes, resting heart rates, end-diastolic and end-systolic volumes, cardiac output and myocardial contraction are similar in older and younger healthy subjects[50, 51].

Effects of aging are most evident during exercise or other forms of ß-adrenergic sympathetic stimulation. In elderly patients the cardiovascular response to ß-adrenergic sympathetic stimulation during hypotension, stress or exercise is diminished with decreases in chronotropic and inotropic response. Maximal exercise heart rate and ejection fraction decline whereas maximal exercise end-systolic volume increases[50]. Despite the diminished chronotropic and inotropic response after ß-adrenergic stimulation in elderly subjects, cardiac output remains unchanged by volumetric adaptation (cardiac dilatation, Frank-Starling mechanism) as a compensatory mechanism[50].

Although systolic function is preserved with aging, changes in diastolic cardiac function occur with advancing age. There is an age-associated reduction in early diastolic filling and an increase in late diastolic filing of the LV[52, 53]. This pattern of reversement of predominant early diastolic flow with increasing age is mainly due to an increase in the isovolumic relaxation time[54]. Normally ß-adrenergic stimulation, e.g. during exercise, increases the rate of isovolumic relaxation creating a “suction” effect which enables faster ventricular filling.This mechanism ensures adequate filling of the ventricles during exercise without elevating filling pressures. However, diminished ß –receptor responsiveness and structural changes of the heart result in a decline of early ventricular filling which is also present during maximal exercise. Since elderly

patients dependent on volumetric adaptation to maintain cardiac output during exercise, decline of early ventricular filling with advancing age endangers maintenance of cardiac output during exercise. These changes in diastolic function may lead to lead to elevated cardiac filling pressures and insufficient cardiac reserve during ß –receptor stimulation[54].

The deficits in sympathetic modulation of cardiac function with aging are accompanied by elevated plasma concentrations of norepinephrine[55, 56], which suggest that sympathetic nervous system activity increases with aging. This may be a compensatory response to a decrease in cardiac ß-receptor density and diminished ß- receptor responsiveness with advancing age[54]. Also the response of the sympathetic nervous system to different stressors seem to be stronger with aging resulting in greater increases in plasma levels of norepinephrine[47, 57]. The rise in norepinephrine results partly from increased norepinephrine spillover to plasma, especially from the heart[56, 58].

1.4.1 Aging effects in the cardiovascular response to sympathetic blockade by TEA (Figure 3)

Besides the aforementioned changes in the autonomic nervous system aging is also accompanied by structural changes of the heart and vasculature. Stiffening of connective tissue results in decreased compliance of arteries, veins and ventricular myocardium. Arterial stiffening leads to systolic hypertension, increases pressure wave velocity and reflection of pressure waves at end-systole resulting in increased afterload of the heart and consequently hypertrophy of the myocardium[59]. Myocardial hypertrophy and stiffening impair ventricular relaxation and decrease myocardial compliance which makes the heart more susceptible to volumetric changes. Venous stiffening reduces the ability of the venous system to maintain central volume and pressures when faced with volume changes or distributional changes.

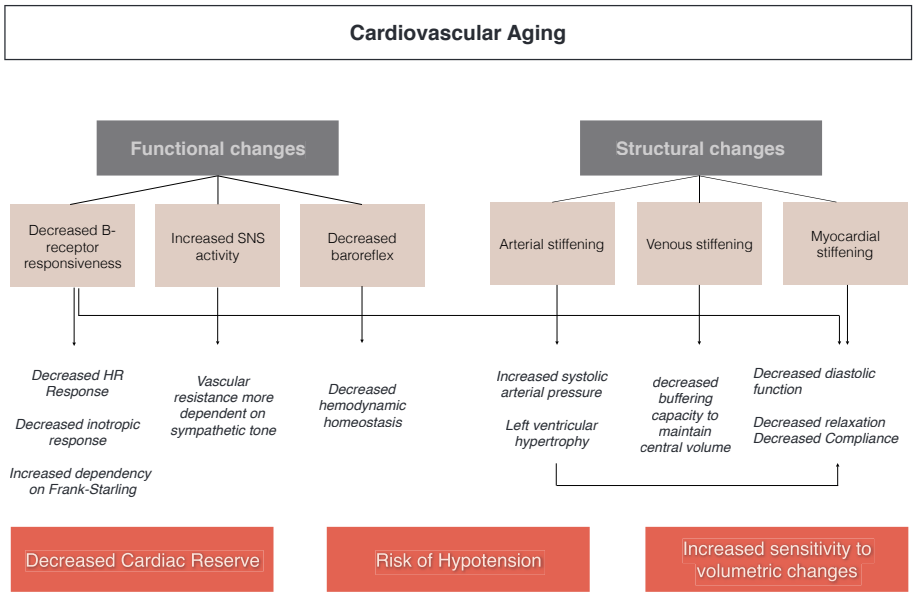

Figure 3. Cardiovascular aging and implications for thoracic epidural anesthesia.

These structural changes combined with decreased ß-adrenergic responsiveness, decreased chronotropic and inotropic response during hypotension, exercise and infusion of inotropes result in increased dependency on the Frank-Starling mechanism and ventricular filling. Consequently, in the elderly cardiac output during stress or exercise primarily depends on maintaining or increasing end-diastolic volumes. The limited chronotropic and inotropic response to ß-adrenergic stimulation in the elderly results in a 25% fall in cardiac output during exercise and leads to a reduction in cardiac reserve[48]. The negative inotropic and chronotropic effects of TEA make the elderly heart even more dependent on cardiac filling pressures to generate sufficient cardiac output. Indeed increasing age is associated with a greater sensitivity of the cardiovascular system to volumetric changes[51]. Therefore, TEA-induced reductions in preload will have more effect on cardiac performance in the elderly patients compared to younger patients. The decreased compliance and relaxation of the myocardium put the elderly at risk for fluid overloading. Volume loading of the heart in the elderly will compared to that in the young heart more rapidly raise filling pressures to levels causing symptoms of congestive heart failure. Rapid volume loading to compensate for the relative hypovolemia caused by venodilatation following induction of TEA should be done with caution in the elderly. Also redistribution of fluids after regression of neural blockade by TEA constitutes a risk of fluid overloading in the elderly. In addition, increases in resting sympathetic activity and age-related baroreflex dysfunction[60, 61] make the elderly more susceptible to hypotension following sympathetic blockade by TEA. This is clinically highly relevant since elderly patients with cardiovascular disease are at increased risk for hypotension induced ischemia[62].

1.5 Motor blockade

Epidural anesthesia induces segmental block of the spinal nerves including motor block and can be assessed with reference to specific myotomes. Depending on the insertion site of the epidural catheter motor block of the phrenic nerve, respiratory muscles in the rib cage, abdominal muscles and both upper and lower extremities can occur.

1.5.1 Assessment of motor blockade

Clinical measurement of motor blockade after TEA only seems feasible in the extremities. In our studies we used the epidural scoring scale for arm movements (ESSAM), which tests three active arm movements (hand grip, wrist flexion and elbow flexion)[63] (**Table 1**). This test was designed to monitor and control motoric blockade after TEA. Cephalad neural blockade with motor blockade of arm movement (C5-T1) appears before motor blockade of the C3, 4, 5 nerve roots with possible involvement of the phrenic nerve. Respiratory problems and apnea might be the result. Decreased motoric function of the arm might indicate cephalic spread and possible imminent involvement of the phrenic nerve. In patients scheduled for cardiac surgery 30% of the patients had motor blockade of the arms after induction of TEA[63].

Hangrip (T1/C8), wrist flexion (C8/C7) and elbow flexion (C6/C5) are monitored and scored bilaterally. The Essam score consists of four grades (grade 0 to 3) depending on the absence of the tested arm movements (**Table 1**).

Table 1. Details of the ESSAM scale

ESSAM Scale Grade		
0	No block:	Handgrip, wrist flexion and elbow flexion is present
1	Partial (33%)	Handgrip is missing, wrist flexion and elbow flexion present
2	Almost Complete (66%)	Handgrip and wrist flexion are missing, elbow flexion is present
3	Complete (100%)	Handgrip, wrist flexion and elbow flexion are missing

Reference list

1. Hogan QH. Epidural anatomy: new observations. Can J Anaesth 1998;45:R40-R48.
2. Luyendijk W. The plica mediana dorsalis of the dura mater and its relation to lumbar peridurography (canalography). Neuroradiology 1976;11:147-149.
3. Bridenbaugh PO, Greene NM, Brull SJ. Spinal (Subarachnoid) neural blockade: anatomy. In: Cousins MJ, Bridenbaugh PO, editors. Neural blockade in clinical anesthesia and management of pain. Philadelphia: JB Lipincott Company; 1998. p. 203-241.
4. Igarashi T, Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Thoracic and lumbar extradural structure examined by extraduroscope. Br J Anaesth 1998;81:121-125.
5. Hirabayashi Y, Saitoh K, Fukuda H, Igarashi T, Shimizu R, Seo N. Magnetic resonance imaging of the extradural space of the thoracic spine. Br J Anaesth 1997;79:563-566.
6. Igarashi T, Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H, Mitsuhata H. The lumbar extradural structure changes with increasing age. Br J Anaesth 1997;78:149-152.
7. Bromage PR. Epidural analgesia. Philedelphia, W.B. Saunders Co; 1978. p. 31-35.
8. Shantha TR, Evans JA. The relationship of epidural anesthesia to neural membranes and arachnoid villi. Anesthesiology 1972;37:543-557.
9. Bonica JJ. Anatomic and physiologic basis of nociception and pain. In: Bonica JJ, editor. The management of pain. 2nd ed. Philedelphia, Lea & Febiger; 1990. p. 28-94.
10. Visser WA, Liem TH, van EJ, Gielen MJ. Extension of sensory blockade after thoracic epidural administration of a test dose of lidocaine at three different levels. Anesth Analg 1998;86:332-335.
11. Visser WA, Gielen MJ, Giele JL, Scheffer GJ. A comparison of epidural pressures and incidence of true subatmospheric epidural pressure between the mid-thoracic and low-thoracic epidural space. Anesth Analg 2006;103:1318-1321.
12. Freund PR, Bowdle TA, Slattery JT, Bell LE. Caudal anesthesia with lidocaine or bupivacaine: plasma local anesthetic concentration and extent of sensory spread in old and young patients. Anesth Analg 1984;63:1017-1020.
13. Duggan J, Bowler GM, McClure JH, Wildsmith JA. Extradural block with bupivacaine: influence of dose, volume, concentration and patient characteristics. Br J Anaesth 1988;61:324-331.
14. Veering BT, Burm AG, Vletter AA, van den Heuvel RP, Onkenhout W, Spierdijk J. The effect of age on the systemic absorption, disposition and pharmacodynamics of bupivacaine after epidural administration. Clin Pharmacokinet 1992;22:75-84.
15. Veering BT, Burm AG, van Kleef JW, Hennis PJ, Spierdijk J. Epidural anesthesia with bupivacaine: effects of age on neural blockade and pharmacokinetics. Anesth Analg 1987;66:589-593.
16. Bromage PR. Ageing and epidural dose requirements: segmental spread and predictability of epidural analgesia in youth and extreme age. Br J Anaesth 1969;41:1016-1022.
17. Grundy EM, Ramamurthy S, Patel KP, Mani M, Winnie AP. Extradural analgesia revisited. A statistical study. Br J Anaesth 1978;50:805-809.

18. Sharrock NE. Epidural anesthetic dose responses in patients 20 to 80 years old. Anesthesiology 1978;49:425-428.
19. Park WY, Massengale M, Kim SI, Poon KC, Macnamara TE. Age and the spread of local anesthetic solutions in the epidural space. Anesth Analg 1980;59:768-771.
20. Nydahl PA, Philipson L, Axelsson K, Johansson JE. Epidural anesthesia with 0.5% bupivacaine: influence of age on sensory and motor blockade. Anesth Analg 1991;73:780-786.
21. Curatolo M, Orlando A, Zbinden AM, Scaramozzino P, Venuti FS. A multifactorial analysis of the spread of epidural analgesia. Acta Anaesthesiol Scand 1994;38:646-652.
22. Simon MJ, Veering BT, Stienstra R, van Kleef JW, Burm AG. Effect of age on the clinical profile and systemic absorption and disposition of levobupivacaine after epidural administration. Br J Anaesth 2004;93:512-520.
23. Simon MJ, Veering BT, Stienstra R, van Kleef JW, Burm AG. The effects of age on neural blockade and hemodynamic changes after epidural anesthesia with ropivacaine. Anesth Analg 2002;94:1325-1330.
24. Hirabayashi Y, Shimizu R. Effect of age on extradural dose requirement in thoracic extradural anaesthesia. Br J Anaesth 1993;71:445-446.
25. 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.
26. Yokoyama M, Hanazaki M, Fujii H, Mizobuchi S, Nakatsuka H, Takahashi T, Matsumi M, Takeuchi M, Morita K. Correlation between the distribution of contrast medium and the extent of blockade during epidural anesthesia. Anesthesiology;100:1504-1510.
27. Saitoh K, Hirabayashi Y, Shimizu R, Mitsuhata H, Fukuda H. Extensive extradural spread in the elderly may not relate to decreased leakage through intervertebral foramina. Br J Anaesth 1995;75:688-691.
28. Veering BT, Cousins MJ. Cardiovascular and pulmonary effects of epidural anaesthesia. Anaesth Intensive Care 2000;28:620-635.
29. Arndt JO, Hock A, Stanton-Hicks M, Stuhmeier KD. Peridural anesthesia and the distribution of blood in supine humans. Anesthesiology 1985;63:616-623.
30. Hopf HB, Weissbach B, Peters J. High thoracic segmental epidural anesthesia diminishes sympathetic outflow to the legs, despite restriction of sensory blockade to the upper thorax. Anesthesiology 1990;73:882-889.
31. Brull SJ, Greene NM. Zones of differential sensory block during extradural anaesthesia. Br J Anaesth 1991;66:651-655.
32. Malmqvist LA, Tryggvason B, Bengtsson M. Sympathetic blockade during extradural analgesia with mepivacaine or bupivacaine. Acta Anaesthesiol Scand 1989;33:444-449.
33. Stevens RA, Beardsley D, White JL, Kao TC, Gantt R, Holman S. Does spinal anesthesia result in a more complete sympathetic block than that from epidural anesthesia? Anesthesiology 1995;82:877-883.

34. Benzon HT, Cheng SC, Avram MJ, Molloy RE. Sign of complete sympathetic blockade: sweat test or sympathogalvanic response? Anesth Analg 1985;64:415-419.
35. Wallin BG, Elam M. Insights From Intraneural Recordings of Sympathetic Nerve Traffic in Humans. Physiology 1994;9:203-207.
36. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220-222.
37. Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. Cardiovasc Res 1996;32:208-216.
38. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84:482-492.
39. Hopf HB, Skyschally A, Heusch G, Peters J. Low-frequency spectral power of heart rate variability is not a specific marker of cardiac sympathetic modulation. Anesthesiology 1995;82:609-619.
40. Jokkel G, Bonyhay I, Kollai M. Heart rate variability after complete autonomic blockade in man. J Auton Nerv Syst 1995;51:85-89.
41. Kingwell BA, Thompson JM, Kaye DM, McPherson GA, Jennings GL, Esler MD. Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. Circulation 1994;90:234-240.
42. Magnusdottir H, Kirno K, Ricksten SE, Elam M. High thoracic epidural anesthesia does not inhibit sympathetic nerve activity in the lower extremities. Anesthesiology 1999;91:1299-1304.
43. Stevens RA, Beardsley D, White JL, Kao TC, Teague PJ, Spitzer L. Does the choice of local anesthetic affect the catecholamine response to stress during epidural anesthesia? Anesthesiology 1993;79:1219-1226.
44. Stevens RA, Artuso JD, Kao TC, Bray JG, Spitzer L, Louwsma DL. Changes in human plasma catecholamine concentrations during epidural anesthesia depend on the level of block. Anesthesiology 1991;74:1029-1034.
45. Lakatta EG. Alterations in the cardiovascular system that occur in advanced age. Fed Proc 1979;38:163-167.
46. White M, Roden R, Minobe W et al. Age-related changes in beta-adrenergic neuroeffector systems in the human heart. Circulation 1994;90:1225-1238.
47. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. Physiol Rev 1993;73:413-467.
48. Fleg JL, Schulman S, O'Connor F, Becker LC, Gerstenblith G, Clulow JF, Renlund DG, Lakatta EG. Effects of acute beta-adrenergic receptor blockade on age-associated changes in cardiovascular performance during dynamic exercise. Circulation 1994;90:2333-2341.
49. Schulman SP, Lakatta EG, Fleg JL, Lakatta L, Becker LC, Gerstenblith G. Age-related decline in left ventricular filling at rest and exercise. Am J Physiol 1992;263:H1932-H1938.

50. Rodeheffer RJ, Gerstenblith G, Becker LC, Fleg JL, Weisfeldt ML, Lakatta EG. Exercise cardiac output is maintained with advancing age in healthy human subjects: cardiac dilatation and increased stroke volume compensate for a diminished heart rate. Circulation 1984;69:203-213.
51. Rooke GA. Cardiovascular aging and anesthetic implications. J Cardiothorac Vasc Anesth 2003 August;17(4):512-523.
52. Pearson AC, Gudipati CV, Labovitz AJ. Effects of aging on left ventricular structure and function. Am Heart J 1991;121:871-875.
53. Henein M, Lindqvist P, Francis D, Morner S, Waldenstrom A, Kazzam E. Tissue Doppler analysis of age-dependency in diastolic ventricular behaviour and filling: a cross-sectional study of healthy hearts (the Umea General Population Heart Study). Eur Heart J 2002;23:162-171.
54. Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin 2012;8:143-164.
55. Veith RC, Featherstone JA, Linares OA, Halter JB. Age differences in plasma norepinephrine kinetics in humans. J Gerontol 1986;41:319-324.
56. Esler MD, Turner AG, Kaye DM et al. Aging effects on human sympathetic neuronal function. Am J Physiol 1995;268:R278-R285.
57. Esler MD, Thompson JM, Kaye DM, Turner AG, Jennings GL, Cox HS, Lambert GW, Seals DR. Effects of aging on the responsiveness of the human cardiac sympathetic nerves to stressors. Circulation 1995;91:351-358.
58. Lakatta EG. Deficient neuroendocrine regulation of the cardiovascular system with advancing age in healthy humans. Circulation 1993;87:631-636.
59. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circ Res 1991;68:1560-1568.
60. Rooke GA, Freund PR, Jacobson AF. Hemodynamic response and change in organ blood volume during spinal anesthesia in elderly men with cardiac disease. Anesth Analg 1997;85:99-105.
61. Fleg JL, O'Connor F, Gerstenblith G, Becker LC, Clulow J, Schulman SP, Lakatta EG. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. J Appl Physiol (1985) 1995;78:890-900.
62. Juelsgaard P, Sand NP, Felsby S, Dalsgaard J, Jakobsen KB, Brink O, Carlsson PS, Thygesen K. Perioperative myocardial ischaemia in patients undergoing surgery for fractured hip randomized to incremental spinal, single-dose spinal or general anaesthesia. Eur J Anaesthesiol 1998;15:656-663.
63. Abd Elrazek E, Scott NB, Vohra A. An epidural scoring scale for arm movements (ESSAM) in patients receiving high thoracic epidural analgesia for coronary artery bypass grafting. Anaesthesia 1999;54:1104-1109.