Cardiovascular effects of thoracic epidural anaesthesia

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Financial support by the departments of Anesthesiology and Cardiothoracic Surgery , LUMC, Leiden and CD Leycom is gratefully acknowledged.

ISBN: 978-94-923-3634-7

Cover image: 4D flow MRI of the heart of J Wink, constructed by Patrick de Koning and Jos Westenberg
Design and layout by Graphic Square - grafische vormgeving , Wassenaar, The Netherlands
Printed by Puntgaaf drukwerk, Leiden, The Netherlands

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Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 9 mei 2019
klokke 16.15 uur

door

Jeroen Wink
geboren te Almelo
in 1973

Promotores:	Prof. dr. L.P.H.J. Aarts
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Nulla tenaci invia est via

Voor Karin, Ciske, Carmen, Maxime en Karsten
Ter nagedachtenis aan Babette en Pepijn

Contents

Physiologic and cardiovascular symbols

Hemodynamic symbols

HR	Heart rate
MAP	Mean arterial pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
SVR	Systemic vascular resistance
PVR	Pulmonary vascular resistance
CO	Cardiac output
CI	Cardiac index
SV	Stroke volume
SVV	Stroke volume variation

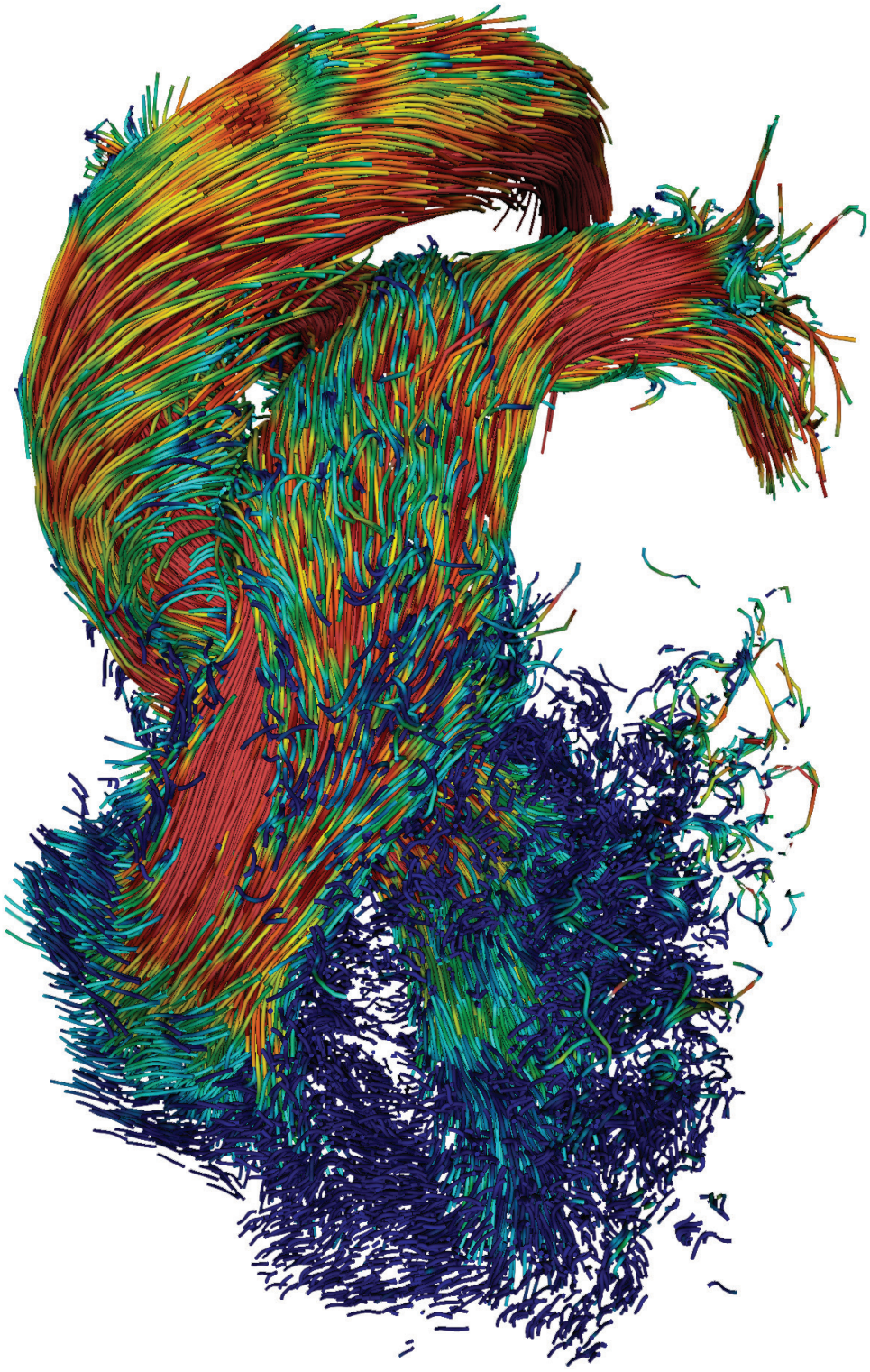
Echocardiographic symbols

PLAX	Parasternal long axis view
A4C	Apical four-chamber view
ALAX	Apical long-axis view
LV	Left ventricle
RV	Right ventricle
LVEDV	Left ventricular end diastolic volume
LVESV	Left ventricular end systolic volume
EF	Ejection fraction
FAC	Fractional area change
MV E	Peak mitral flow velocity during early filling phase
MV A	Peak mitral flow velocity during atrial contraction phase
MV E/A	Ratio of mitral E to A
MV DT	Time interval required for the mitral E velocity to decline from its peak to the baseline
TV E	Peak tricuspid flow velocity during early filling phase
TV A	Peak tricuspid flow velocity during atrial contraction phase
TV E/A	Ratio of tricuspid E to A
TV DT	Time interval required for the tricuspid E velocity to decline from its peak to the baseline

TDI	Tissue Doppler imaging
PW	Pulsed waved
CC	Colour-coded
MV S'	Systolic mitral annular velocities
MV E'	Early diastolic mitral annular velocities
MV A'	Late diastolic mitral annular velocities
TV S'	Systolic tricuspid annular velocities
TV E'	Early diastolic tricuspid annular velocities
TV A'	Late diastolic tricuspid annular velocities
TR max PG	Maximal systolic pressure gradient from tricuspid regurgitation TAPSETricuspid Annular Plane Systolic Excursion
IVA	Myocardial acceleration during isovolumic contraction
ICT	Isovolumetric contraction time
IRT	Isovolumetric relaxation time
ET	Ejection time
MPI	Myocardial performance index or Tei index

Pressure-volume analysis symbols

EDV	End-diastolic volume
ESV	End-systolic volume
EDP	End-diastolic pressure
ESP	End-systolic pressure
SW	Stroke work
dP/dtMAX	Peak rate of ventricular pressure increase
dP/dtMIN	Peak rate of ventricular pressure decrease
ESPVR	End-systolic pressure-volume relationship
EDPVR	End-diastolic pressure-volume relationship
Ees	Slope of the end-systolic pressure-volume relationship
ESV25	Volume intercept of ESPVR at 25 mmHg
Eed	Slope of the EDPVR (stiffness)
EDV7	Volume intercept of EDPVR at 7 mmHg
Tau (T)	Isovolumic relaxation time constant
Ea	Effective arterial elastance
Ees/Ea	Ventricular-pulmonary coupling ratio



Section I

General introduction and intent of the investigations

1. Thoracic epidural neural blockade

2. Intent and preview of the investigations

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].

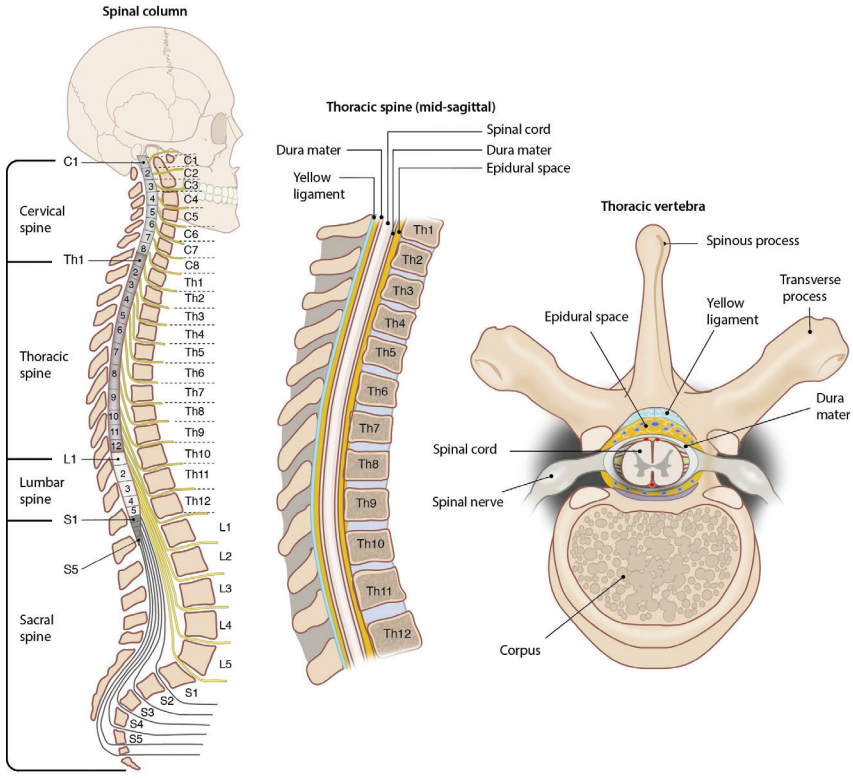


Figure 1. Anatomy of the thoracic spine

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.

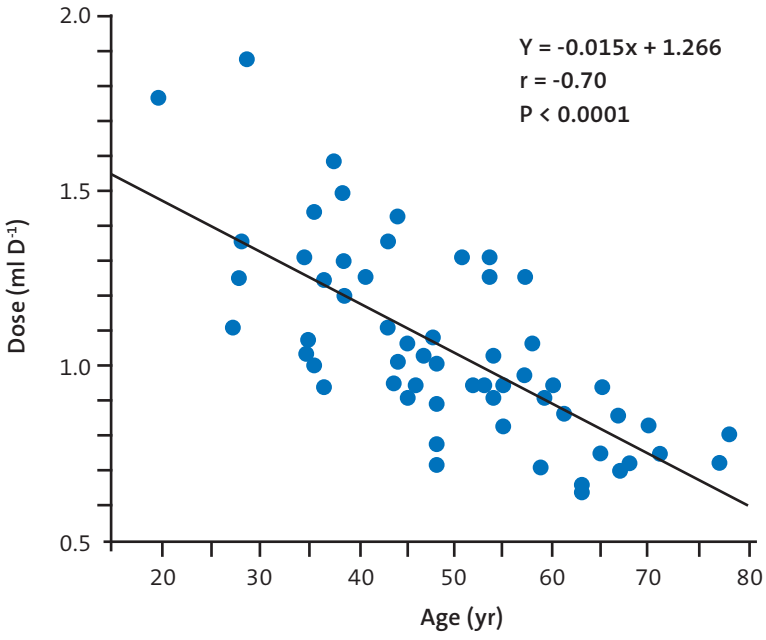


Figure 2. Relationship between age and extradural dose requirement in thoracic extradural anesthesia. From Y. Hirabayashi and R Shimizu, effect of age on extradural dose requirement in thoracic extradural anaesthesia, British Journal of Anaesthesia 1993; 71: 445.

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.

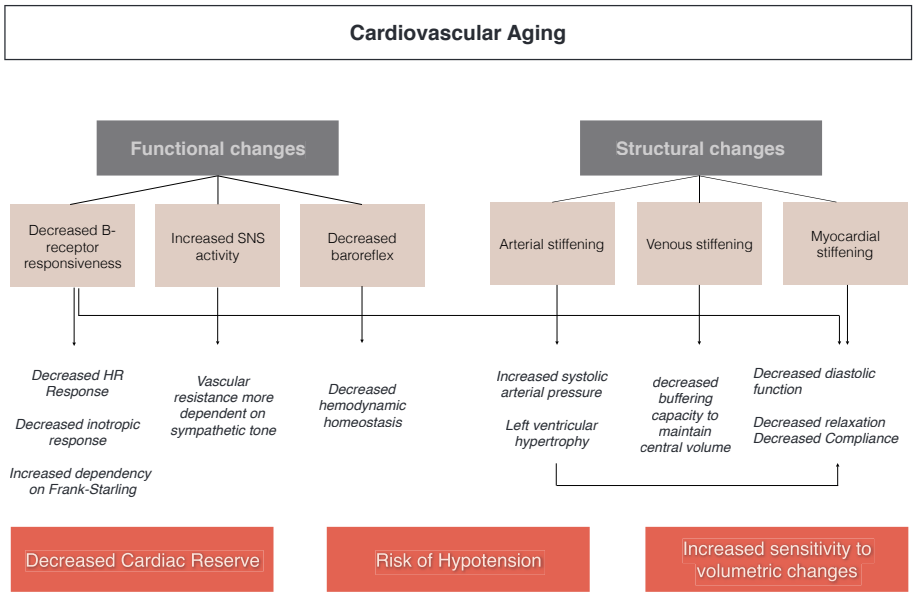


Figure 3. Cardiovascular aging and implications for thoracic epidural anesthesia.

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

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Chapter 2

Intent and preview of the investigations

2.1 Main objectives

The first objective of the investigations described in this thesis is to determine the cardiac effects, in particular right ventricular function, elicited by induction of thoracic epidural anesthesia. The second objective was to assess the TEA-induced cardiac effects during elevated sympathetic tone. The third objective was to assess whether age influences the quality of neural blockade by TEA and whether age influences cardiovascular effects of TEA. Finally, the fourth objective was to describe cardiac sympathetic innervation and to determine which spinal levels carry sympathetic preganglionic neurons that via cardiac nerves innervate the heart.

2.2 General introduction

In **Chapter 1** thoracic epidural anesthesia is introduced addressing the anatomy of the thoracic epidural space and different qualities of neural blockade after TEA. In particular sympathetic blockade is being discussed since it is responsible for the cardiovascular effects associated with TEA.

2.3 Anatomy and Physiology

In **Chapter 3** we aimed to describe cardiac sympathetic innervation from the level of the brain to the heart as an end-organ. The aim of this study was to find out which spinal nerve roots are involved in cardiac sympathetic innervation. This is relevant because TEA blocks sympathetic outflow at the spinal level. We provided a description of the origin of the sympathetic preganglionic neurons based on anatomical studies. In addition embryogenesis of the cardiac autonomic nervous system is described briefly. In **Chapter 4** literature was reviewed to identify studies in which cardiovascular effects of TEA were discussed and cardiac sympathetic nerves (T1-T5) were involved in neural blockade by thoracic epidural anesthesia. In this review we summarized the current knowledge on thoracic epidural anesthesia induced changes in intrinsic left and right ventricular function, distinguished between resting conditions and those associated with elevated sympathetic tone and considered both patients with and without cardiovascular disease.

2.4 Central neural blockade

In **Chapter 5** we examined the effect of age on neural blockade and cardiovascular parameters following administration of ropivacaine for thoracic epidural analgesia. The aim of this study was to determine whether dermatomal spread of analgesia (cold and pinprick), motor block, and cardiovascular parameters following institution of thoracic epidural anesthesia are influenced by age. In **Chapter 6** the effects of TEA on echocardiographic parameters of left and right ventricular systolic and diastolic function were assessed.

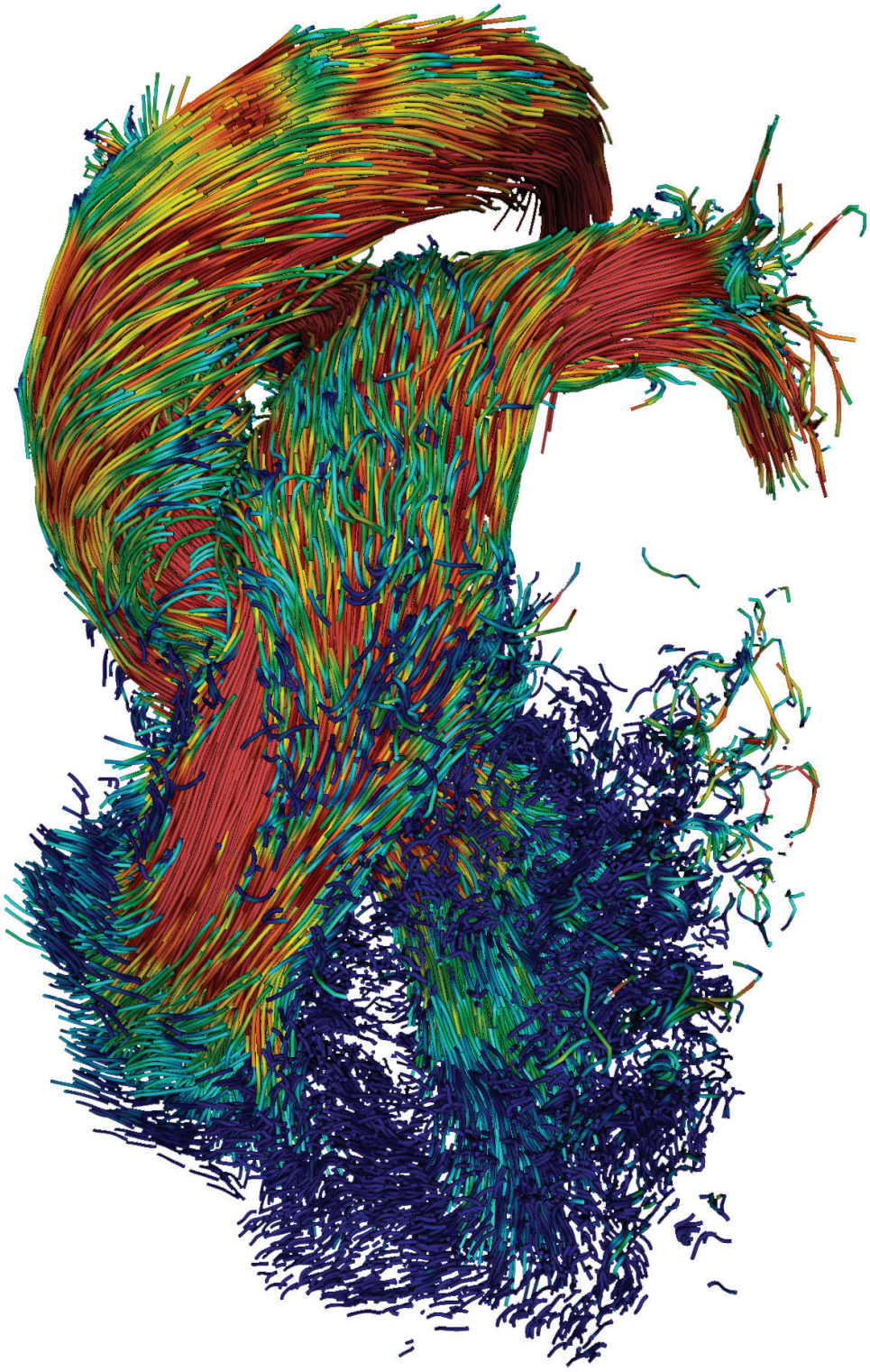
Increasing age is associated with changes in the autonomic nervous system as well as in the cardiovascular system. In order to assess the effect of age on baseline myocardial function and age effects on TEA-induced cardiac effects trans thoracic echocardiography (TTE) was performed.

2.5 Thoracic epidural anesthesia: effects on cardiac performance

The perioperative period is characterized by increases in sympathetic tone. However, most TEA studies have been performed during resting conditions, with consequently low sympathetic tone. In **Chapter 7** we assessed TEA effects on right ventricular (RV) function during baseline and during periods of acutely increased RV afterload. The aim of this study was to test whether thoracic epidural anesthesia (TEA) either affects RV function or right ventricular pulmonary arterial (RV-PA) coupling. During conditions of increased RV afterload the right ventricle raises inotropic state in order to maintain cardiac output without dilating (homeometric autoregulation). Reduction of RV contractility or abolishment of homeometric autoregulation by TEA would be clinically highly relevant since RV function is a major perioperative parameter of outcome. In **Chapter 8** we investigated TEA effects on cardiac function and circulation during increased levels of sympathetic tone generated by physical exercise. In contrast to the afterload challenge described in **Chapter 7** this chapter assesses the influence of TEA during preload challenges of the heart. Echocardiographic parameters of biventricular systolic and diastolic function were obtained by TTE. During sequential progressive workloads TEA effects on cardiovascular parameters were determined with and without TEA. The results of the studies described in **Chapter 7 and 8** shed light on TEA effects during conditions of elevated sympathetic tone which might resemble TEA effects in the perioperative period.

2.6 Conclusion and perspectives

Chapter 9 provides a summary of this thesis and suggestions for future studies.



Section II

Anatomy and physiology

Chapter 3

Human Cardiac Sympathetic Innervation: Controversies in anatomy and relevance for cardiac neuronal modulation

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Submitted

Introduction

A balanced function of the cardiac autonomic nervous system (cANS) is essential to maintain cardiovascular homeostasis. The sympathetic nervous system has been attributed an important role in the perioperative stress response induced by surgery and anesthesia but is also implicated in the genesis and maintenance of atrial and ventricular arrhythmias[1-3] as well as in the pathogenesis of heart failure[4, 5]. Thoracic epidural anesthesia (TEA) and paravertebral blockade are regularly employed as analgesic techniques in cardiothoracic anesthesia. Besides sensory and motor blockade, TEA (T1-T5) and paravertebral blockade also induce blockade of sympathetic outflow to the heart **(Figure 1)**.

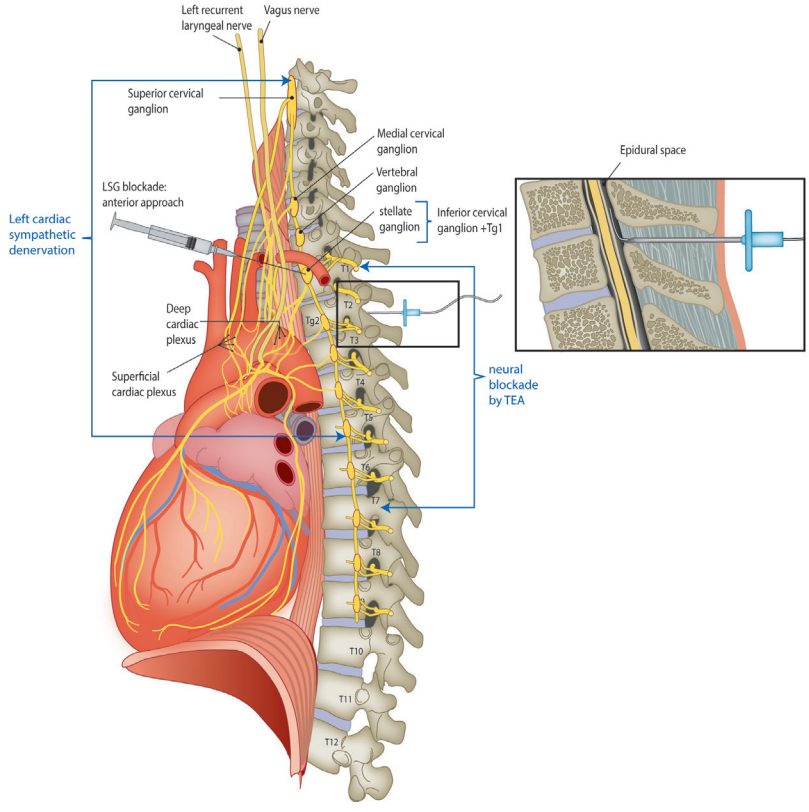


Figure 1. Relationship between level of neuronal modulation and sympathetic input to the heart

Preganglionic cardiac sympathetic axons synapse with postganglionic sympathetic neurons in the cervical or upper thoracic ganglia (Tg); postganglionic fibers from these ganglia form the sympathetic cardiac nerves that innervate the heart via the deep and superficial cardiac plexus. Neuronal modulation of cardiac sympathetic innervation may be achieved by TEA at the spinal level, by left stellate ganglion (LSG) blockade, by blockade of the upper thoracic ganglia, or by paravertebral blockade (i.e. blockade of sympathetic chain ganglia). TEA with upper border of analgesia above spinal segment T7, but certainly above T5, includes blockade of the sympathetic cardiac nerves. The amount of spinal levels blocked depends on the dose of local anesthetic drugs administered epidurally.

This reduces the chronotropic and inotropic state of the heart, the occurrence and magnitude of which seem to vary between individuals and conditions[6]. In heart failure, an increased sympathetic tone is considered to underlie a chain of detrimental effects with detrimental impact on prognosis[5, 7, 8]. Several arrhythmias have been related to an imbalance of autonomic innervation. Blockade of cardiac sympathetic innervation has been shown to improve myocardial blood flow and myocardial oxygen balance during stress[9], but is also a novel therapeutic approach for arrhythmias and heart failure[9-14].

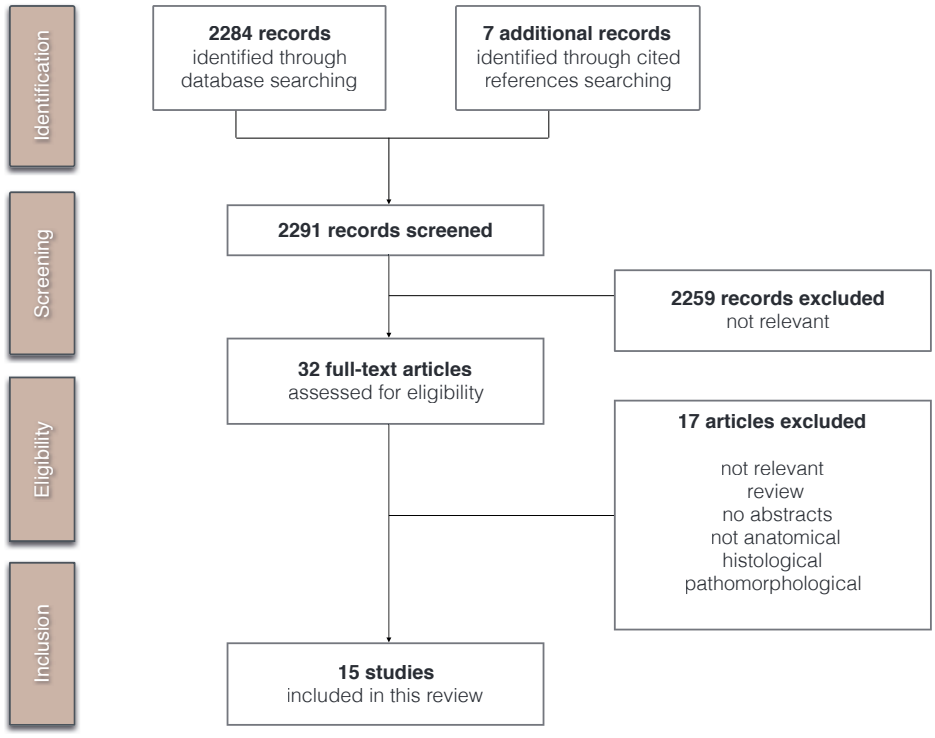
Although these techniques are aimed at targeting cardiac autonomic innervation, controversies regarding the anatomy of the human cardiac autonomic nerve system still exist. State of the art information on unresolved details and controversies regarding the anatomy of cardiac sympathetic innervation is relevant for understanding the cardiovascular effects elicited by cardiac sympathetic denervation. In addition, anatomical variability in cardiac sympathetic innervation between human subjects may contribute to inter-individual diversity in physiological effects and cardiovascular side effects of targeted cardiac sympathetic blockade.

This review aims to provide an update on current knowledge on anatomy and function of the human cardiac sympathetic nervous system and focuses on controversies as well as gaps in knowledge on this subject with reference to the clinical practice of neuraxial modulation of the cardiac sympathetic nervous system. The sympathetic innervation of the heart is known to vary by species[15]. In the current review we will discuss primarily the human anatomical arrangement of sympathetic outflow from the spinal cord and sympathetic ganglia to the heart, its heterogeneity and inter-individual variability. In addition, a brief overview of embryogenesis of cardiac innervation, including the cervicothoracic ganglia, is provided.

Methods

To summarize the current knowledge on human anatomy of cardiac autonomic innervation, below we present a narrative review of the extant literature on this topic. Papers regarding macroscopic human anatomy of the cANS were systemically reviewed. In addition an overview of major morphogenetic processes as well physiological background information is provided, which were not part of the systemic literature search. The database Pubmed was searched to identify anatomical studies of human cardiac sympathetic innervation.

The search strategy consisted of the following thesaurus terms and text words: ("innervation" [Subheading] OR innervat*[ti] OR re-innervat*[ti] OR "nerve"[ti] OR "nerves"[ti] OR "nervous"[ti] OR "neural"[ti]) AND ("sympathetic"[tw] OR "sympathic"[tw] OR "autonomic"[tw]) AND ("Heart"[majr] OR "Heart"[ti] OR "cardiac"[ti] OR "epicardial"[ti] OR "epicardiac"[ti] OR "Pericardium"[majr] OR "epicardium"[ti] OR "intracardiac"[ti] OR "extracardiac"[ti]) AND ("anatomy and histology"[Subheading] OR "anatomy"[tw] OR "anatomy"[MeSH] OR "anatomic"[tw] OR "anatomical"[tw]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) NOT (Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR "trial"[tw] OR "trials"[tw]) AND (Dutch[lang] OR English[lang] OR German[lang]). English papers were included and additional filters on species (human) and language (English or German) were employed. Physiological studies, pathomorphological studies, studies based on microscopy/histological findings only, studies without abstracts reviews, research concerning embryology, animals or organs other than the cardiovascular system were excluded. The search yielded a total of 2284 references an 7 additional references identified through cited references. After screening only 15 studies were included in the review (**Flowchart 1**). The anatomy of the human cardiac autonomic nerve system from the central level towards the end organ (i.e. the heart) was described using these literature sources (**Table 1**) and special attention was given to discrepancies and variations in anatomy as described from these reports.



Flowchart 1. Flow diagram of literature search

Overview of cardiac neural hierarchy: from brain to heart

Several forebrain areas, including the insular cortex, anterior cingulate cortex, central nucleus of the amygdala, and several hypothalamic nuclei project to medullary and spinal nuclei controlling cardiac function **(Figure 2)**; these projections are either direct or via a relay in the periaqueductal gray[16].

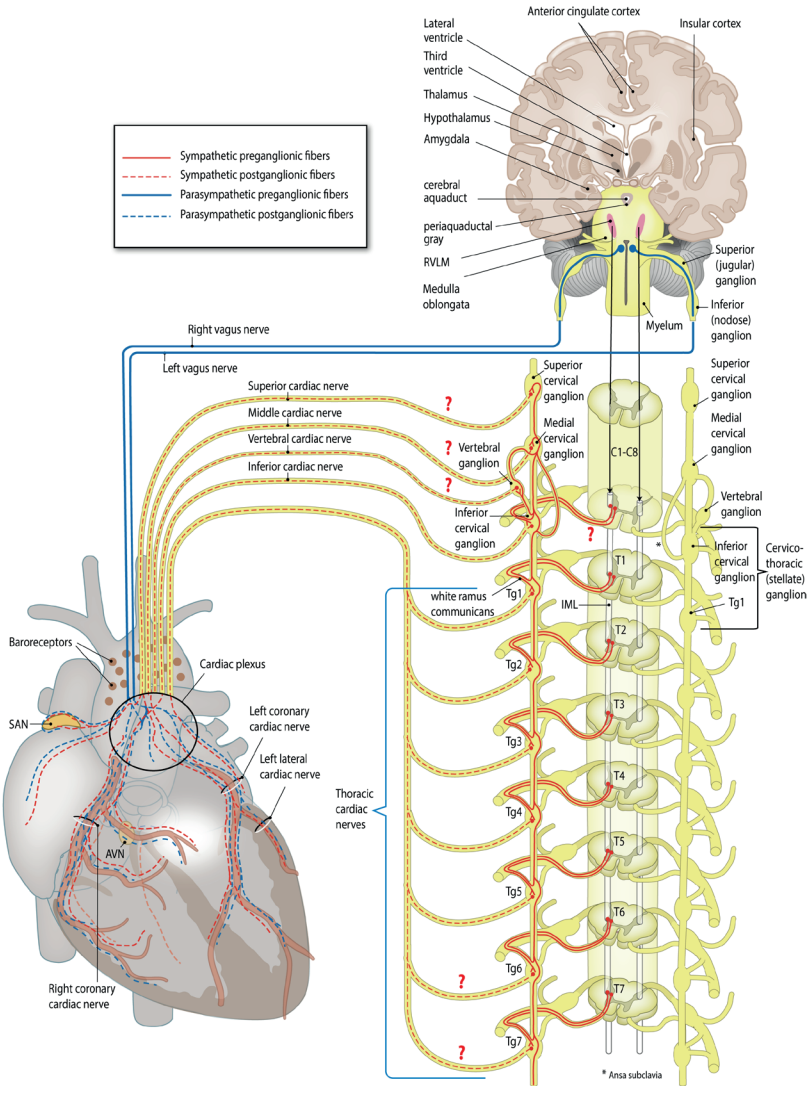


Figure 2. Overview of cardiac innervation

Schematic drawing of the cardiac autonomic nervous system. Preganglionic cardiac parasympathetic axons arise from neurons in either the nucleus ambiguus or dorsal vagal nucleus; they run in vagal cardiac branches vagus nerve (blue, solid lines) to synapse in cardiac plexuses and ganglia from where postganglionic fibers (blue, dotted lines) innervate the sino-atrial node (SAN), atrioventricular node (AVN), coronary arteries and

ventricular myocytes. Preganglionic cardiac sympathetic axons (red, solid lines) arise from neurons in the IMLs of the upper four or five (possibly six or seven) thoracic spinal segments, that receive modulating input from several forebrain centers (e.g. the insular cortex, anterior cingulate cortex, central nuclei of the amygdala, and several hypothalamic nuclei interneurons) via the intermediolateral cell column of the spinal cord (IML); they leave the spinal cord through anterior (ventral) roots, enter the anterior (ventral) rami of spinal nerves and pass to the sympathetic chains through white rami communicantes to synapse in the upper thoracic (Tg) or cervical ganglia; postganglionic fibers (red, dotted lines) from these ganglia form the sympathetic cardiac nerves. At the heart parasympathetic and sympathetic nerves converge to form the cardiac plexus from which atrial and ventricular autonomic innervation is arranged.

The red question marks (?) indicate anatomical structures of which existence and/or involvement in cardiac sympathetic innervation are debated.

The cANS can be divided into extrinsic and intrinsic components. The extrinsic cardiac nervous system (i.e. the part of the cANS outside the heart) comprises sympathetic and parasympathetic nerves that control the intrinsic cardiac nervous system (i.e. the cANS situated at the cardiac surface and within the cardiac chambers) in an opposing fashion. The interaction between sympathetic and parasympathetic activity is complex and is modulated by input from chemoreceptors and baroreceptors via the visceral sensory fibers[17]. The intrinsic cardiac nervous system is formed by a complex network of ganglionated plexuses located in the myocardial wall and pericardial fat[18, 19]. Within this network functional communications between neurons of the ganglionated plexuses exists, supplying the myocardial tissue including the cardiac conduction system[20, 21]. In general, sympathetic activation is triggered by neurons of the rostral ventrolateral medulla (RVLM, situated in the medulla oblongata, **Figure 2**), hich sends excitatory projections to preganglionic sympathetic neurons of the intermediolateral column (IML) of the spinal cord, that extends from spinal levels C8/T1 to T2/T3[22]. After synapsing in paravertebral ganglia, postganglionic sympathetic fibers will eventually innervate heart, via cardiac nerves that sprout directly from the sympathetic chain ganglia. These cardiac nerves (superior, middle, vertebral and inferior nerves) can either innervate the heart directly or may combine with other postganglionic (sympathetic and parasympathetic) nerves to form plexuses consisting of combined nerves innervating the heart (intrinsic cardiac nervous system)[23] (**Figure 2**). From the cardiac plexuses, mixed cardiac nerves arise that largely run along the course of coronary vessels to innervate the coronary vasculature and myocardium (i.e the right coronary, left coronary and left lateral cardiac nerves). Parasympathetic output to the heart is mediated by preganglionic neurons located in either the dorsal motor nucleus of the vagus nerve or near the nucleus ambiguus[24]. In contrast to sympathetic preganglionic neurons that synapse on postganglionic neurons in the sympathetic chain, the parasympathetic preganglionic neurons send long axons that synapse on cholinergic and non-cholinergic postganglionic neurons located in the cardiac ganglia, situated in proximity to the heart (intrinsic cardiac nervous system).

Embryogenesis of cardiac autonomic innervation- overview of major morphogenic processes

Literature on human development of the autonomic nerve system consists of several historical papers describing human embryos based on observations using light and electron microscopy, some dating back as far as 1893[25]. More current molecular studies providing insight into embryological background and genetic pathways involved, are largely conducted in animal models.

Spinal level and intermediolateral column (IML).

The central parts of the nervous system, i.e. the brain and spinal cord (myelum) derive from the embryonic neural tube, which starts to form in humans at approximately 3 week of gestation (reviewed in[26]). In the neural tube, the first sign of preganglionic sympathetic motor neurons has been described in rat in the ventrolateral zone of the spinal cord, where also the somatic motor neurons are situated. During further development, these autonomic motor neurons will separate from the somatic motor neurons and are then found more dorsally where they will form the IML[27] **(Figure 2)**. The autonomic motor neurons in the IML will send their extensions out via the anterior aspect of the neural tube, i.e. the future anterior (ventral) root. These extensions will synapse with clusters of postganglionic motor neurons that develop outside the central nervous system, the sympathetic chain ganglia, that will give rise to the sympathetic innervation of the heart.

Development of sympathetic chain ganglia and output towards the heart.

In chicken embryos, the first clusters of catecholamine positive cells have been observed at the thoracolumbar level and bilateral to the aorta[28]. These cellular clusters will expand from the thoracic to the cervical region. During further development the clusters of cells on both sides of the aorta will form continuous cords, regarded as a primitive sympathetic chain, that will further differentiate and give rise to secondary (permanent) paravertebral chains[28], directed by several ligands and their receptors[29]. The cell type most well established in development of the ganglia of the paravertebral sympathetic chains is the neural crest cell. Neural crest cells are a population of multipotent cells that migrate from the region of the neural tube (Figure 3) and have multiple functions during development[30]. Innervation of heart occurs via the arterial and venous poles, corresponding to different subpopulations of neural crest cells[31] the arterial pole seems to be the major source of input of sympathetic nerves to the heart, whereas parasympathetic nerves arrive at the heart mainly via the venous pole[31].

Not all cardiac autonomic nerves tissues are neural crest cell derived, and other cell types, such as those derived from the neurogenic placode, may also contribute.

The sympathetic chains will give rise to the rami communicanti, connecting them to the anterior (ventral) rami of spinal nerves. In addition, autonomic cardiac nerves will leave the ganglia forming cardiac sympathetic nerves, which is first observed in chick in the lower cervical/upper thoracic region[32]. During further development, sympathetic cardiac nerves will also connect to

vagus nerves and other cardiac sympathetic nerves towards the heart will form[33]. Development of parasympathetic peripheral nerves (derived from the cranially situated cardiac neural crest), precedes the development of sympathetic peripheral nerves[34].

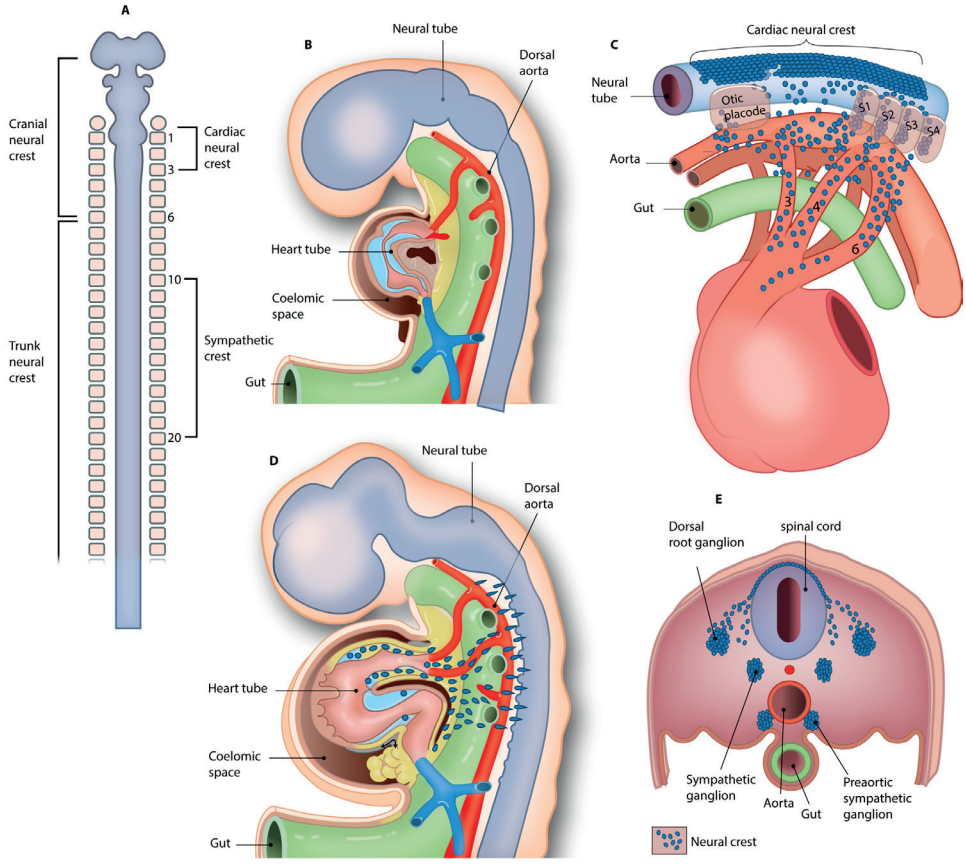


Figure 3. Embryology of cardiac autonomic innervation

a. The central parts of the nervous system, i.e. the brain and spinal cord derive from the embryonic neural tube (light blue), that develops in human at approximately 4 weeks of gestation. **b-d.** During development, neural crest cells (indicated in dark blue) will migrate from the region of the neural tube and will migrate towards multiple locations in the body, including the heart. They can differentiate in multiple cell types Neural crest cells contributing to the sympathetic chain originate from the chain neural crest. The first clusters of cathecholamine positive cells have been observed at the thoracolumbar level and bilateral to the aorta. These cellular clusters will expand from the thoracic to the cervical region. During further development the clusters of cells on both sides of the aorta will form primitive sympathetic chains that will further differentiate and give rise to paravertebral sympathetic chains. Neural crest cells also contribute to other ganglia, including the dorsal root and pre-vertebral (pre-aortic) ganglia. Panel a is modified after Kirby[33]. Panels b and c modified after Vegh et al[38].

Development of cardiac ganglia, plexuses and nerves.

In human embryo's, cardiac ganglia and nerves could be identified at the 20 mm stage, corresponding to approx. 7-8 weeks of gestation[25, 35]. Saburkina et al. describe prenatal development of epicardiac ganglia in 20 hearts of human fetuses of gestational age 15-40 weeks[36] showing the presence of epicardiac neural plexuses in all stages examined. The size of the ganglia, as well as the number of inter-ganglionic nerves, increased with gestational age, although interindividual variations were observed[36].

Navaratnam report development of the deep cardiac plexus to result from fusion of nerves at the venous pole with innervation at the arterial pole at later developmental stages (40 mm stage, > 8 gestational weeks), due to definitive positioning of the heart with the venous and arterial pole becoming more closely situated. The superficial cardiac plexus was recognized at the site of the arterial duct[25]. In human, the first presence of nerve fibers into the heart has been described at approximately 6 weeks intra-uterine life[25]. During development the amount of cardiac innervation is orchestrated by neural chemo-attractants and chemo-repellents, the balance of which determines the extent of cardiac innervation[37, 38].

Innervation of conduction tissues.

In early histological studies in human embryos, the putative sites of the sino-atrial node (SAN) and atrioventricular node (AVN), i.e. the embryonic right sinus horn and the dorsal AV canal, were shown to be heavily innervated at 5-6 weeks post-ovulation, even prior to development of the nodes[25]. Early studies in human report contributions of the so called right sinus nerve to innervation of the sino-atrial node, of the left sinus nerve to the AVN and contributions from both sides of the body to the single pulmonary vein. More recent studies based on lineage tracing in mouse, however, showed innervation of the nodes only at embryonic day (E) 13.5 and E14.5 (corresponding to >7 weeks in human). Of interest, these nerve fibers were not derived from neural crest cells but likely from another source[31]. In postnatal humans, density of innervation was found to be highest in the sino-atrial node, with decreasing density towards AV node and more distal parts of the cardiac conduction system. Moreover, there was an initial sympathetic dominance in nerve supply of the CCS in childhood, with gradual transition into a sympathetic and parasympathetic co-dominance in adulthood[39].

Maturation of the ANS is reflected by an increase in heart rate variability with an overt increment of sympathetic activity[40]. Functional studies based on human fetal cardiotocography indicate that the period from 21 to 31 gestational weeks seem critical to ANS development[41], although many of these functional studies not include embryonic/early fetal stages.

Ventricular innervation.

During development of ventricular innervation, cardiac nerves extend parallel to coronary vessels. Vascular smooth muscle cells of the coronary vessels have been shown to secrete nerve growth factor, a neurotrophic factor, thus guiding the patterning of autonomic (sympathetic)

ventricular innervation[42]. The autonomic nerve system maintains some plasticity after birth and in disease states[43]. This, along with the fact that neural crest cells are multipotent and can currently be derived from human pluripotent stem cells stem cells (hiPSCs), opens avenues for potential future applications in patients with autonomic nerve damage[44].

Controversial issues.

Cervical ganglia have been shown to contribute to cardiac innervation both in animal models as well as in human[45, 46], although reports in literature differ (discussed in paragraph 6.1). The origin of the cervical sympathetic chain ganglia is still debated. Based on the observation that cellular clusters will expand from the thoracic to the cervical region as describe above[26], it has been speculated that cervical ganglia are generated from the thoracic sympathetic chain[45, 47]. As there are only 3-4 cervical ganglia in the cervical region whereas at the thoracic level each spinal level has a corresponding ganglion, alternatively, it has been suggested that the development of sympathetic ganglia is associated initially with the intersegmental vessels[48]. The limited number of cervical ganglia could thus be attributed to regression of most of the cervical intersegmental arteries, and remodeling and fusion of the corresponding ganglia. The upper 4 cervical ganglia would thus form the superior cervical sympathetic ganglion, anatomically related or induced by the developing external carotid artery[48]. The number of ganglionated plexuses reported in fetal hearts differs somewhat between studies: Saburkina et al report the presence of 7 ganglionated plexuses[36], whereas in an earlier study of Smith 4 groups of ganglia were identified[49]. The same study reported "darkly staining cells lying between the aorta and pulmonary artery "to be visible at the 15 mm stage, indicative of a deep cardiac plexus[49], whereas a distinction between deep and superficial plexuses could not be made by Than et al[50].

With regard to innervation of the myocardium, there is controversy on the density of autonomic innervation in atrial versus ventricular tissues. Parasympathetic (vagal) nerves appear to be more densely distributed in the atria at both neonatal and adult stages[51, 52]. Some authors describe equal densities of sympathetic nerve fibers in atria and ventricles, at least in the neonatal stage[51], whereas other authors describe more sympathetic nerves in the ventricles in the adult heart[52]. This might indicate that differentiation of the cANS still occurs after birth, supported by observation of dynamic changes in nerve supply throughout life[39] .

Sympathetic output from the spinal cord towards the sympathetic chain

In general, exit of sympathetic outflow from the spinal cord only occurs in designated levels, primarily from the first thoracic to the second or third lumbar spinal level[22].

Bonica and colleagues documented that the human preganglionic cardiac sympathetic output from the spinal cord originates from the first to the fourth, and sometimes even fifth thoracic spinal cord segment[53]. This study is often cited in thoracic epidural anesthesia studies as an anatomical reference of cardiac sympathetic innervation. To our knowledge the study of Bonica and colleagues is to date the only human anatomical document describing cardiac sympathetic

innervation from the level of the spinal column in humans. The IML fibers contributing to sympathetic autonomic innervation of the heart leave the spinal cord in anterior roots, After leaving the spinal cord in anterior (motor) roots, preganglionic sympathetic fibers enter the spinal nerves, pass through the anterior rami and travel via white (i.e. myelinated) rami communicantes towards the paravertebral ganglia of the sympathetic chain **(Figure 4)**, where they synapse with postganglionic neurons **(Figures 2, 4).** Preganglionic neurons may synapse with as many postganglionic neurons[54]. The synapse may occur at the same level, or the preganglionic fiber may ascend and, possibly, descend before synapsing **(Figure 4)**.

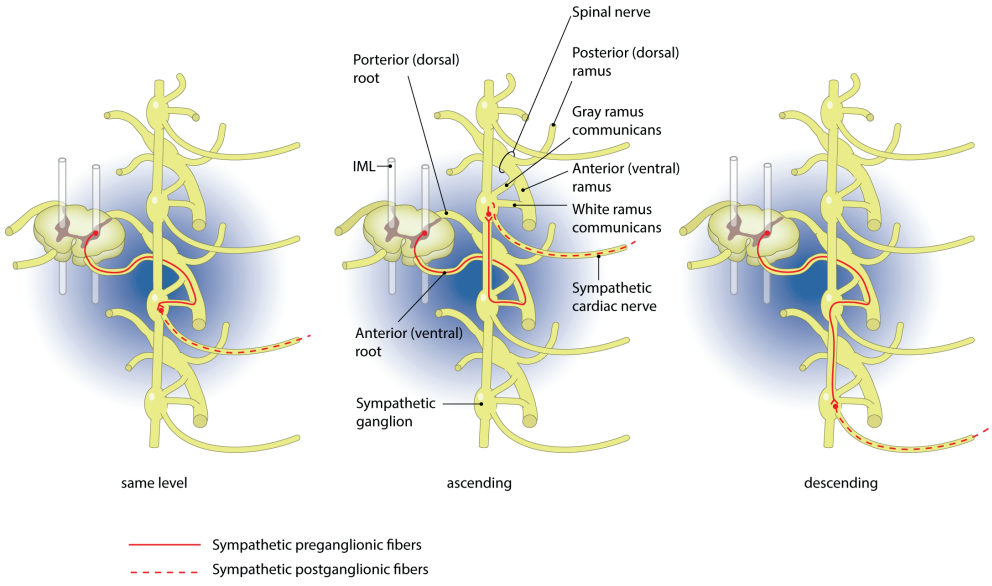


Figure 4. Courses taken by preganglionic sympathetic fibers

After leaving the spinal cord via the anterior (ventral) root, the axons of preganglionic sympathetic neurons enter the anterior (ventral) ramus of the spinal nerve and pass to the sympathetic chain through a white ramus communicans. Within the sympathetic chain preganglionic fibers may 1) synapse immediately with a postganglionic neuron of the paravertebral ganglion at that level, 2) ascend in the sympathetic chain to synapse with a postganglionic neuron of a higher paravertebral ganglion, or 3) descend to synapse with a postganglionic neuron of a lower paravertebral ganglion.

IML, intermediolateral column of the spinal cord.

Controversial issues regarding levels of sympathetic output form the spinal cord towards sympathetic ganglia.

Some authors suggest that sympathetic nerves may also emerge from the cervical myelum[55, 56]. Although there is a clear transition from C8 to T1 in the amount of sympathetic fibers present, Sheehan and colleagues observed sympathetic fibers in the anterior roots of C8 of humans (see question marks in **Figure 2**). It is however important to emphasize that the amount of fibers

observed in the cervical roots was scarce, especially compared to the amount of fibers in the anterior roots of T1-T2[55]. More importantly, presence of sympathetic fibers in the anterior root of C8 does not necessarily imply that these fibers are cardiac destined fibers.Controversy also exists on the level where preganglionic cardiac sympathetic fibers synapse within the sympathetic chain. The sympathetic preganglionic neurons of spinal cord T1-T5 have been described to either synapse in the first sympathetic ganglion they reach or to ascend within the sympathetic chain to synapse in a ganglion at a higher level, particularly to the three or four cervical ganglia[54]. In addition, sympathetic preganglionic neurons of spinal level T6 to as low as T10 have been described to either terminate in the first sympathetic ganglion they reach, ascent or even descent to a higher or lower thoracic ganglion[54] **(Figure 2, Figure 4)**. This raises the question from which thoracic spinal cord levels the preganglionic sympathetic fibers originate that eventually end up as thoracic cardiac nerves innervating the heart. This is relevant since TEA blocks sympathetic outflow at the spinal level. Several animal studies using transneural retrograde labelling support the observation of Bonica that preganglionic sympathetic neurons can ascent or descent to a higher or lower ganglion from where postganglionic fibers are projected towards the heart. Markers injected in the stellate (cervicothoracic) ganglion of rat were found in spinal segments C8 to T8 with a peak at T2[57]. However, whether these spinal segments are involved in sympathetic innervation of the heart or that other regions are targeted remains to be elucidated. In addition, the latter study suggests that the axons of sympathetic preganglionic neurons from one spinal cord segment may branch and have axonal projections to multiple cervical and thoracic ganglia. In another study, rat hearts were injected with retrograde tracers, which were subsequently found in the preganglionic sympathetic neurons of spinal cord levels T1-T7 and in some rats even in spinal levels T8-T11[58].

A problem in interpreting results and extrapolating them to the human situation, is that many studies have been performed on animals and sympathetic innervation of the heart varies by species[15]. Another limitation is that a substantial number of reference studies are dated several decades ago, when limited techniques e.g. for neuronal tracing and specific immunohistochemical labelling were available, or altogether unavailable. Therefore it seems difficult if not impossible to state with certainty that the small fibers described as representing the sympathetic outflow really are of sympathetic origin. Bonica did not describe the method that was used to detail the preganglionic origin of cardiac sympathetic innervation[54]. Moreover, neural tracing techniques cannot be performed in humans. Interpretation of results of immunohistochemical stainings in many cases relies on (alleged) specificity of immunohistochemical stainings to discriminate the different divisions of the autonomic nervous system. If preganglionic sympathetic fibers from spinal level T5-T10 indeed ascent to higher paravertebral ganglia, this would imply that thoracic ganglia Tg1-Tg5 could be innervated from spinal levels below T5. From a theoretical point of view, it is not unlikely that preganglionic sympathetic neurons from spinal levels below T5 might be involved in cardiac sympathetic innervation.

In conclusion, the cranial border of spinal sympathetic outflow to the heart is most likely confined to T1 in most cases. However, sympathetic outflow from the cervical myelum has been described for C8 and to date it remains unclear whether this is a common variation and whether spinal cervical sympathetic outflow is involved in cardiac sympathetic innervation (see question marks in, Figure 2). Therefore the upper border of preganglionic sympathetic neurons originating from the spinal cord to the paravertebral ganglia providing the heart with postganglionic sympathetic fibers, might involve cervical spinal segment C8 as well. Similarly, the lower border of preganglionic cardiac sympathetic neurons may involve spinal levels below T5. This information might be relevant in case where for instance TEA is targeted to block all spinal cardiac sympathetic segments.

Sympathetic ganglia giving rise to postganglionic output to the heart

The sympathetic chain, including the stellate ganglion and other cervical ganglia, is a chain of paravertebral ganglia that exists on both anterolateral sides of the vertebral column. It is within the sympathetic chain that the preganglionic sympathetic neurons synapse to the cell bodies of postganglionic sympathetic neurons that extent via cardiac nerves to the heart (**Figure 2**).
The cervical ganglia, receiving preganglionic sympathetic input from the thoracic spinal cord via ascending fibers within the thoracic ganglia, are a well described extension of the sympathetic chain[45, 54, 59, 60]. Although nomenclature differs in literature over the past 50 years, the most accepted names that are therefore used in this review are: the superior cervical ganglion, the middle cervical ganglion, the vertebral ganglion and the inferior cervical ganglion **(Figure 2)**. Cervical ganglia that are generally accepted to provide postganglionic cardiac nerves are the inferior cervical ganglion, that is fused with the first thoracic ganglion in about 80% of humans to form the cervicothoracic or stellate ganglion[45, 61] **(Figure 2)**.

Controversies regarding involvement of cervicothoracic ganglia in cardiac sympathetic innervation.

As stated earlier, Bonica and colleagues reported preganglionic cardiac sympathetic outflow to emerge from cervical and the upper four to five thoracic spinal cord segments and postganglionic cardiac sympathetic outflow from the upper five thoracic paravertebral ganglia[53, 54]. However, there is controversy on the exact origin of (postganglionic) sympathetic cardiac innervation. Several anatomical studies on human cadavers show a wide variation in the lower limit of origin of cardiac sympathetic innervation. Where most human studies report that the thoracic cardiac nerves emerge from the first to fourth thoracic ganglia, others reported contributions from the fifth thoracic[54, 62], sixth thoracic[63] and even from the seventh thoracic ganglia[64] to the thoracic cardiac nerves (**Figure 2**). By contrast, Janes and colleagues reported no cardiopulmonary nerves arising from the superior cervical ganglia and sympathetic chain inferior of the stellate ganglion[59]. In conclusion the origin of cardiac sympathetic innervation, i.e. the level of the sympathetic ganglia giving rise to postganglionic cardiac nerves, has been shown to differ between anatomical studies and inter-individual variations may occur. Whether cervical ganglia

besides the stellate ganglion play a role in transmission of cardiac sympathetic signals is unclear. Similarly, there is debate on the origin of cardiac nerves from different thoracic ganglia. In some patients, thoracic ganglia Tg6 and Tg7 (see question marks in, **Figure 2**) might be involved in cardiac sympathetic innervation. If so, preganglionic sympathetic neurons from spinal segments T6 and T7 or, if ascending, even from spinal segments below T7 are likely to be involved in cardiac sympathetic innervation. In addition, these anatomical studies demonstrated inter-individual and intra-individual variety (asymmetry in left to right sympathetic innervation) in the anatomy of cardiac autonomic innervation. These variations may be relevant in procedures targeting the cardiac output to the heart, e.g. during left cardiac sympathetic denervation targeting the lower cervical/upper thoracic nerves.

Postganglionic output to the heart: Sympathetic cardiac nerves

The sympathetic chain gives off gray (i.e. unmyelinated) rami communicantes carrying sympathetic fibers to the spinal nerves which serve as motor nerves to the effector organs such as the skin and glands. However, postganglionic nerves to the heart from the cervical and thoracic sympathetic chain do not travel via gray rami with the spinal nerves but originate as separate (unmyelinated) cardiac nerves from the paravertebral ganglia to the heart (**Figure 2**). Thus, after passing the thoracic and cervical ganglia, sympathetic signals reach the heart via different nerves. The cardiac sympathetic nerves enter the heart through the vascular (arterial and venous) pole of the heart. At the arterial pole, the cardiac nerves extend along the common carotid, subclavian and brachiocephalic arteries towards the aorta and branches also extend along the pulmonary chain. At the venous pole, cardiac nerves run along the superior vena cava. Thoracic cardiac nerves are described to descend obliquely along the thoracic vertebrae or the intercostal vessels, sometimes following complex courses through the mediastinum, before heading towards the heart[45].

Cardiac nerves: Variations and controversies

Despite extensive anatomical research, the route and even number of these postganglionic nerves remains unclear. Kawashima described an important connection between the superior cervical ganglion and the heart, by the existence of the so called superior cardiac nerve[45, 60]. He further described the middle cardiac nerve originating from the middle cervical and the vertebral ganglion, and the inferior cardiac nerve originating from the inferior cervical/ cervicothoracic (stellate) ganglion. Besides these cervical ganglia, he reported that each of the upper 4 to 5 thoracic paravertebral ganglia has a sympathetic connection running towards the heart, mostly sharing the combined name of 'thoracic cardiac nerves' (**Figure 2**). This study by Kawashima confirms the previously reported cervical and thoracic sympathetic contributions to the cardiac plexuses by Pather et al[63]. In addition, de Gama and colleagues described in 41% of individuals a separate cardiopulmonary nerve from the vertebral ganglion, the vertebral cardiac nerve[65] (**Figure 2**). As mentioned above, Janes and colleagues, however, state that cardiopulmonary nerves only arise from the stellate (cervicothoracic) ganglia and the caudal halves of the cervical

sympathetic chains[59], leaving no role for transmission of sympathetic input to the heart for the superior cervical ganglion nor the thoracic paravertebral ganglia (see question marks in, **Figure 2**). In conclusion, it is still matter of debate which cervical ganglia play a role in the transmission of cardiac sympathetic signals. Regardless, there is evidence that besides the stellate ganglion other cervical and thoracic ganglia are involved in the transmission of sympathetic signals to the heart with potential relevance for cardiac neuronal modulation.

Combination of cardiac nerves to form mixed cardiac plexuses

Upon entering the heart, both postganglionic sympathetic and preganglionic parasympathetic (branches of vagus and recurrent laryngeal) nerves converge at the cardiac surface to form plexuses[20, 45, 60] (**Figure 1**). The superficial (ventral) cardiac plexus is located near the aortic arch and the left pulmonary artery on the left side and near the ascending aorta and brachiocephalic chain on the right side. The deep (dorsal) cardiac plexus is located between the aortic arch and the tracheal bifurcation[65]. Next to sympathetic nerves, the plexuses also receive parasympathetic contributions from the vagal nerve. Of interest, the vagal nerves have been shown to carry sympathetic nerve fibers[66]. Upon entering the pericardial sac, mixed autonomic nerves project to cardiac ganglia that are interconnected by neurons, thus forming ganglionated plexuses or epicardial neural plexuses at the vascular (arterial and venous) pole of the heart. These plexuses are embedded in the epicardial fat (**Figure 5**). The largest amount of ganglia is located at multiple sides near the atria. Ventricular ganglia are mostly distributed in the epicardial fat near the aortic root and adjacent to major branches of the coronary arteries[18, 67, 68]. With a total amount of cardiac ganglia observed between 706 and 1,506 and an estimated amount of neurons in the epicardial neural plexus between 14,000 and 43,000 the human intrinsic cardiac nervous system is very extensive[67, 69]. The highly interconnected and integrated cardiac ganglia have intrinsic activity that is modulated by sympathetic or parasympathetic (vagal) inputs[16]. These plexuses thus contain mixed cardiac nerves, i.e. nerves originating from different cardiac sympathetic nerves but also from parasympathetic nerves. The use of markers such as tyrosine hydroxylase (TH) and choline acetyltransferase (ChAT) has helped elucidate the composition of cholinergic and adrenergic intrinsic cardiac neurons and nerves in the heart. Petraitiene and colleagues[70] obtained tissue samples of intrinsic nerves from seven ganglionated plexuses from human hearts as described by Pauza et al: the left and right coronary subplexuses, the ventral right atrial and ventral left atrial subplexuses, the left dorsal subplexus, the middle dorsal subplexus, the dorsal right atrial subplexus[67]. They demonstrated that autonomic fibers to the ganglionated plexuses innervating the right atrium predominantly contain cholinergic fibers. In contrast, plexuses innervating the left atrium and left and right ventricle are predominantly innervated by adrenergic fibers[70].

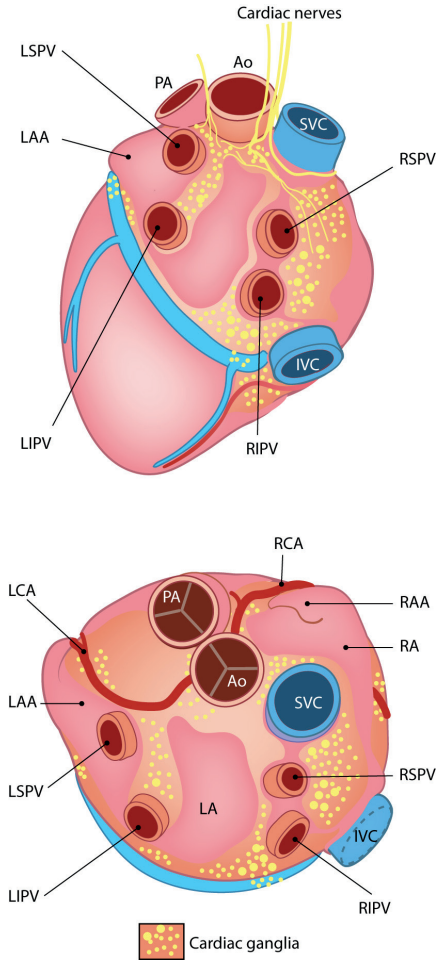


Figure 5. Cardiac plexuses

Drawing of a postero-inferior and a superior view of the human heart illustrating the distribution of ganglionated plexuses on the surface of the atria and ventricles. Modified after Armour et al[18].

Ao, aorta; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LCA, left coronary artery; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; Pa, pulmonary artery; RA, right atrium; RAA, right atrial appendage; RCA, right coronary artery; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava

Three main large (mixed sympathetic and parasympathetic) nerves that follow the coronary arteries or their major branches can be recognized that contribute to innervation of the atria and ventricles: the left coronary cardiac nerve (which runs along the anterior interventricular (descending) branch of the left coronary artery), the left lateral cardiac nerve (which runs along the circumflex artery) and the right coronary cardiac nerve (which runs along the right coronary artery)[59]. Additional cardiopulmonary nerves connect to these (coronary) cardiac nerves distal from the plexuses (**Figure 2**), innervating coronary vessels and myocardial cells. Both cholinergic and adrenergic nerves run from the epicardium into the myocardium[52]. However, there are more cholinergic nerves at the subendocardial than at the subepicardial area of the myocardium. Corresponding to Petraitiene and colleagues[70], Kawano et al.[52] report a general distribution pattern of atria being more densely innervated by cholinergic nerves whereas the ventricles are predominantly innervated by adrenergic fibers. The AVN and SAN are more densely innervated than the His bundle and bundle branches, although the latter components of the cardiac conduction system still receive more innervation than the adjacent ventricular myocardium[71].

Controversies in distribution of cholinergic and adrenergic nerve fibers and location of ganglionated plexuses.

The cardiac topography of the intracardiac ganglionated plexuses, consisting of numerous ganglia on atria and ventricles, seems to be according to a pattern. The epicardial neural plexus has been described as a system of six to 10 subplexuses localized at discrete cardiac regions[18, 67]

(**Figure 5**). Armour and colleagues consistently identified five atrial and five ventricular locations where ganglionated plexuses could be observed. The group of Pauza described a system of seven subplexuses consistently observed at five atrial and two ventricular locations[67]. The ganglionated plexuses are interconnected suggesting that a plexus might have interaction with several topographic regions of the heart[18]. Although ganglionated plexuses were observed to be located at specific cardiac regions, variability seems to exist in the exact location of ganglia. The results of the studies of Kawano[52] and Petraitiene[70] are partly conflicting since Petraitiene reported that the left atrium is predominantly innervated by adrenergic nerve fibers where according to Kawano it is more densely innervated by cholinergic fibers.

Clinical correlation: Physiology of cardiac innervation

Anatomically it seems that the myelum at T1-T3, which incorporates 1/3 of approximately 90,000 preganglionic sympathetic neurons of the thoracic myelum[72] (not specifically cardiac sympathetic neurons), would be an important contributor of sympathetic outflow to the heart. Interestingly, the thoracic cardiac nerves reported to deliver the most substantial contribution to the cardiac plexus are the third and fourth[62] or the fourth and fifth thoracic segments[64]. However, the amount of neurons does not necessarily correlate to the strength of the physiological effects elicited after stimulation of these nerves. Physiological studies examining the effects of electrical stimulation of sympathetic nerves from different spinal cord levels can provide information on the contribution of different spinal segments to the innervation of the heart. Electrophysiological studies in animals reveal that each cervical or thoracic paravertebral ganglion is innervated by a subset of spinal segments. Ganglia are almost always most strongly innervated by one particular spinal segment with contributions from adjacent spinal segments that diminish as a function of distance from the dominant segment[73, 74]. In cats, maximal evoked responses in several cardiac nerves were demonstrated after stimulation of T2 and responses gradually decreased after stimulation of T1, T3, T4 and T5 white rami[73]. Another study in guinea pigs demonstrated that the majority of superior cervical ganglion cells receives input from spinal segments T1-T4, the majority of stellate ganglion cells from spinal segments T2-T6 and the majority of fifth thoracic ganglion cells from T4-T8 with a main supply from spinal level T5. Although the majority of segments involved in innervation of the fifth thoracic ganglion arose from the T4-T8 spinal segments, even the spinal segments of T9 and T10 were occasionally involved[74].

To our knowledge there are no human electrophysiological studies assessing the projections of sympathetic preganglionic neurons to the cervical and thoracic ganglia. However, there is a human study by Randall and colleagues that assessed elevations in blood pressure and cardiac acceleration after stimulation of separate ganglia of the upper thoracic sympathetic chain during surgery. Elevations in heart rate and blood pressure were reported after stimulation of thoracic ganglia Tg1-Tg5, but not after stimulation below Tg5 (cervical levels were not included in this study). Considerable variation was found in thoracic levels of sympathetic innervation of the hearts of different patients. Similarly, there was variability in which thoracic ganglion stimulation elicited the strongest response[75].

Besides variation in which ganglion evokes the strongest cardiac response, differential effects from left and right sided cardiac sympathetic structures have been described. Left stellate ganglion (LSG) and right stellate ganglion (RSG) stimulation have differential effects on heart rate reflected by a more substantial increase in heart rate (73-78 %) after RSG stimulation compared to heart rate effects after LSG stimulation (0-49 %)[76, 76-79]. Stimulation of both ganglia elicits increases of contractile forces in the basal and apical parts of the left ventricle as well as the right ventricle[79]. There remains controversy on which region of the atria and/or ventricles is being innervated by either LSG or RSG. A previous animal study indicates that the LSG primarily innervates the posterior aspect of the right and left ventricle and RSG predominantly innervates the anterior aspect of both ventricles[77]. Other animal studies suggests the same heterogeneous innervation pattern of the left ventricle leading to increased left ventricle asynchrony after unilateral stellate ganglion stimulation[80, 76]. Selective innervation of the anterior and posterior parts of the left ventricle by respectively the RSG and LSG is disputed by other animal studies demonstrating that both the RSG and the LSG innervate the anterior wall of the left ventricle[76, 79, 81] and both innervate the right ventricle[79].

In summary, from electrophysiological studies in animals it can be concluded that each cervical and thoracic paravertebral ganglion is innervated by sympathetic preganglionic neurons from multiple spinal levels. However, there always seems to be one spinal level with the strongest input with input diminishing when adjacent spinal levels are more distant from the main contributing spinal segment. Therefore it seems likely that besides its main supply from spinal level T5, Tg5 in humans is innervated by preganglionic sympathetic neurons from spinal levels below T5, and that inter-individual variations in ganglionic dominancy may occur . Electrophysiological studies also support the aforementioned inter-individual variations in anatomy. Although there remains controversy about exact innervation of the ventricles by the LSG and RSG, both sympathetic chains probably innervate the atria and the ventricles heterogeneously.

Conclusions and clinical implications

The exact origin of preganglionic sympathetic neurons innervating the human heart is controversial and remains a matter of debate. Although human cardiac sympathetic innervation is regularly described to emerge from spinal cord segments T1-T4 or T5, several human anatomical studies report involvement of the sixth and even seventh thoracic ganglia in cardiac sympathetic innervation. Consequently preganglionic sympathetic neurons from spinal levels T6 and T7 (or even more caudal segments) may be involved in cardiac sympathetic innervation. Therefore, complete blockade of cardiac sympathetic innervation may require blockade of spinal segments below T5 or thoracic ganglia below Tg5. Another consequence would be that involvement of sympathetic cardiac segments in neural blockade may, besides high TEA, more likely apply to mid-thoracic epidural analgesia, often used in abdominal surgical procedures, with cranial spread of anesthetic blockade. Human anatomical studies also demonstrate controversial results regarding involvement of the cervical paravertebral ganglia in cardiac sympathetic innervation. Along with the stellate ganglion other cervical paravertebral ganglia

may be involved in the transduction of cardiac sympathetic signals. Besides ambiguous cranial and caudal borders of cardiac sympathetic innervation there is considerable inter-individual and intra-individual anatomical variation. The anatomy of the cardiac sympathetic output to the heart is extremely variable, which likely accounts for part of the anatomical controversies encountered in literature. This variability renders the outcome of procedures targeting neuronal modulation of cardiac sympathetic innervation, such as stellate ganglion and paravertebral blockade, unpredictable.

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Chapter 4

Effects of thoracic epidural anaesthesia on neuronal cardiac regulation and cardiac function

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Anesthesiology 2019;130:472-491

Introduction

Thoracic epidural anaesthesia (TEA) is widely applied in thoracic and abdominal surgical procedures, as it provides excellent analgesia and decreases postoperative pulmonary complications[1,2]. Epidural anaesthesia with local anesthetics produces sensory and motor blockade but also affects the autonomic nervous system. The resultant effects on the cardiovascular system vary with the level and the extend of sympathetic blockade. Involvement of the lower thoracic region (T6-L1) by TEA is associated with increased venous capacitance and redistribution of blood to the dilated splanchnic veins. This results in decreased venous return to the heart and a reduction of cardiac preload[3]. Arterial vasodilation in blocked segments is counteracted by compensatory vasoconstriction in unblocked segments and the effect on cardiac afterload depends on the balance between blocked and unblocked segments[4]. Direct effects of cardiac sympatholysis have not been the subject of detailed investigation. Many studies quantified the cardiac effects of TEA using load dependent indices of contractile performance which does not allow differentiation between direct and indirect effects. Regardless, the effects of TEA have generally been considered beneficial to the cardiovascular system and protective against surgical stress[5]. Interestingly, recent systematic reviews have not been able to confirm improved cardiac outcome in surgical patients treated with TEA[6]. In contrast, some evidence was found for increased cardiovascular problems in high-risk patients receiving neuraxial block[7, 8]. In light of these concerns a reappraisal of the cardiovascular effects associated with the use of TEA seems appropriate. Since the last published review on this subject[9], new data have emerged from experimental and clinical studies addressing previously unexplored domains such as the effects of cardiac sympathectomy on right ventricular function, an important determinant of outcome in surgery [10-12].

We conducted the present review to update the knowledge in this field, with focus on the effects associated with high TEA and cardiac sympathectomy in the normal and diseased cardiovascular system.

Materials and methods

The databases PubMed, Embase and Cochrane were searched by the author and by an independent expert librarian to identify studies in which the cardiac sympathetic nerves (T1-T5) are involved in neural blockade by thoracic epidural anaesthesia. The search strategy consisted of the following thesaurus terms and text words: ("Anesthesia, Epidural"[majr] OR "Epidural Anesthesia"[ti] OR "Epidural Anaesthesia"[ti] OR "Epidural Analgesia"[ti] OR "Analgesia, Epidural"[majr]) AND ("thoracic"[ti] OR "cervicothoracic"[ti]) AND ("sympathectomy"[MeSH] OR "sympathectomy"[tw] OR "sympathicolysis"[tw] OR (("Heart"[tw] OR "Heart"[Mesh] OR "cardiac") AND ("adrenergic activation"[tw] OR "sympathetic innervation"[tw] OR "autonomic innervation"[tw])) OR "Cardiac"[tw] OR "cardiovascular"[tw] OR "blood circulation"[MeSH] OR "circulation"[tw] OR "circulatory"[tw] OR "cardiopulmonary"[tw] OR "heart rate"[MeSH] OR "heart rate"[tw] OR "baroreceptor"[tw] OR "haemodynamic"[tw] OR "hemodynamic"[tw]

OR “hemodynamics”[MeSH] OR “hemodynamics”[tw] OR “haemodynamics”[tw] OR “Echocardiography”[Mesh] OR “Echocardiography”[tw] OR “echocardiographic”[tw] OR “Coronary Vessels”[Mesh] OR “coronary”[tw] OR “ventricular”[tw] OR “Heart Ventricles”[Mesh] OR ventricle*[tw] OR “Ventricular Function”[Mesh] OR “Diastole”[Mesh] OR “Systole”[Mesh] OR “systolic”[tw] OR “diastolic”[tw] OR “myocardial”[tw] OR “Myocardial Contraction”[Mesh] OR “Contraction”[tw] OR “contractility”[tw] OR “contractile”[tw] OR “stress”[tw] OR “exercise”[MeSH] OR “exercise”[tw] OR “ischemic heart disease”[tw] OR “ischaemic heart disease”[tw] OR “Myocardial Ischemia”[Mesh] OR “Coronary Artery Disease”[Mesh] OR “Myocardial Infarction”[Mesh] OR “Hypertension, Pulmonary”[Mesh] OR “pulmonary hypertension”[tw]). This initial search strategy yielded 1189 references.

An additional 20 references were obtained through subsequent hand search for relevant articles and authorative texts in cited references. Only articles published in English were included. Articles were considered relevant if cardiac sympathetic blockade by TEA was demonstrated. If assessment of neural blockade was not reported, articles were excluded unless epidural puncture was mentioned to be at the cervical or high thoracic level or when the combination of puncture level and dose of local anaesthetics were shown earlier to induce cardiac sympathetic blockade. Editorials, letters to the editor, case reports, abstracts only, studies assessing pain or studies targeting children as the study population were excluded.
The first author evaluated titles and abstracts and selected articles according to relevance and to the inclusion and exclusion criteria. The remaining articles were reviewed full-text and screened for eligibility according to the inclusion and exclusion criteria. See **Figure 1**, presenting a flow diagram of literature search. The author’s main objective of this search was to compose an updated narrative review regarding the specific effects of TEA on cardiac function.

Search Results

The search results and study selection flowchart are presented in **Figure 1**. From the initial 1209 records identified through database searching and cited reference searching, 577 were duplicates or not in the English language and 560 records were excluded because the studies did not meet our inclusion criteria.

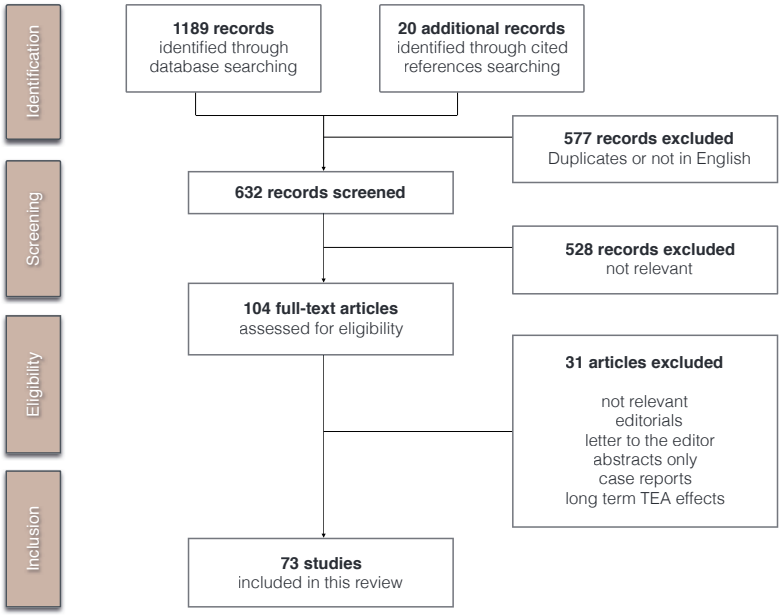

Figure 1. Flow diagram of literature search

Cardiac neurophysiology

The central nervous system exerts a beat-to-beat control on cardiac function. Specific areas in the brain involved in emotional behaviour, stress responses and homeostatic reflexes affect cardiac function[13]. These brain areas give excitatory input to the preganglionic sympathetic fibers originating from the intermediolateral cell column of the spinal cord. Preganglionic sympathetic neurons synapse on postganglionic noradrenergic cardiac nerves in the paravertebral ganglia (**Figure 2**). It is generally assumed that the cardiac sympathetic outflow emerges from spinal levels T1 to T5, with a main supply to the ventricles from T1 to T4[14].

Preganglionic parasympathetic fibers originate predominantly in the nucleus ambiguus and also in the dorsal motor nucleus of the vagal nerve. Upon entering the heart, the postganglionic sympathetic and parasympathetic nerves converge into the cardiac plexus. Electrical or chemical stimulation of neuronal tissue within the cardiac sympathetic nervous system, usually the right and/or left stellate ganglion, has yielded relevant information regarding the interplay between the cardiac autonomic nervous system and cardiac function. In general, cardiac sympathetic stimulation in animals[15-21] and humans[22] increases inotropy, dromotropy and chronotropy of the heart. Increases in peak systolic pressure of the left ventricle LV (20-167 %) and maximum positive rate of pressure change (dP/dt max) (20-213 %) after unilateral or bilateral stellate ganglion stimulation indicate substantial increases in contractility of the LV in animals[15, 16, 19,21] and humans[22]. LV relaxation (lusitropy) was also shown to improve substantially after cardiac sympathetic stimulation[16, 23-25].

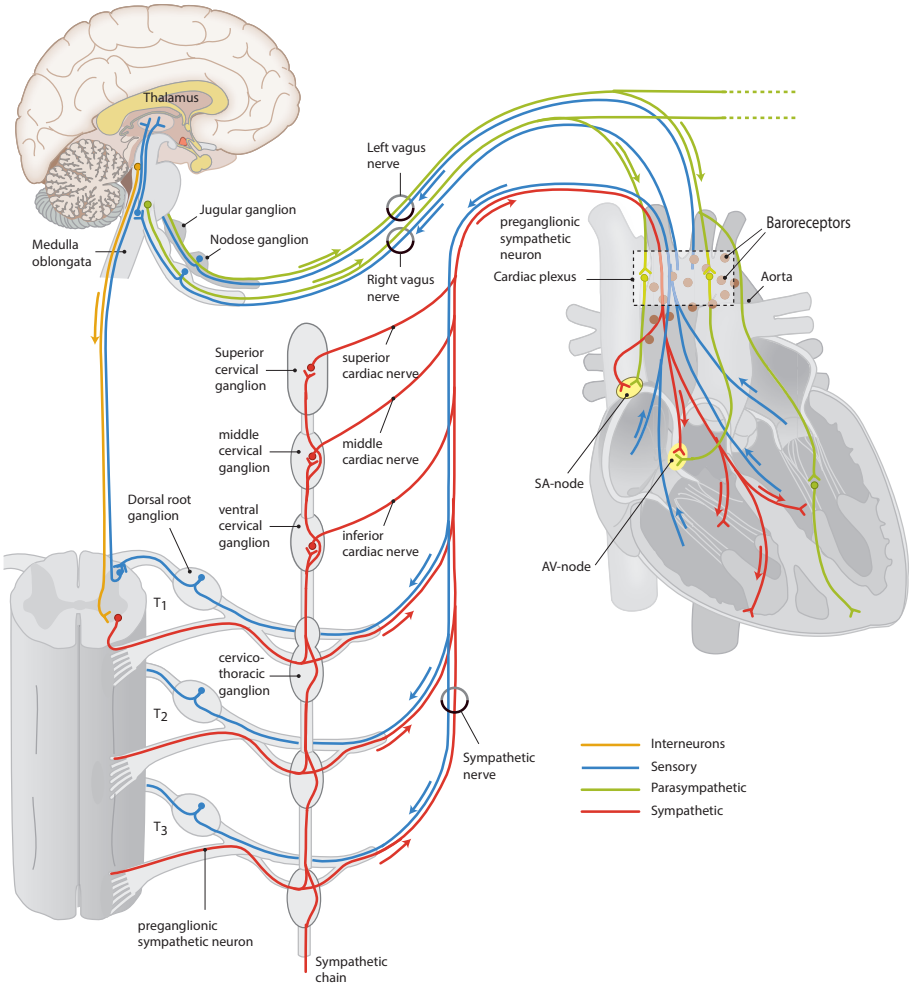

Figure 2. Overview of cardiac innervation

Schematic drawing of the cardiac visceral innervation system. Cardiac innervation starts with a signal from the heart or baroreceptors (e.g., on the aorta), relayed by sensory nerves (blue) giving feedback on, for instance, the levels of oxygen, carbon dioxide and blood pressure. The brain will give a signal to parasympathetic or sympathetic nerves to either relax or stimulate the heart. Parasympathetic innervation is achieved mainly via the vagal nerve (green) that will synapse in cardiac ganglia from where postganglionic nerves innervate the SA node, AV node and ventricular myocytes. Sympathetic neurons (red) start in the grey matter of the spinal cord, where interneurons (orange) from the brain project to the sympathetic neurons. Via the ventral root of the spinal cord, sympathetic nerves synapse in the sympathetic chain, from where postganglionic nerves will enter the heart. Modified with permission from Vegh et al. (Vegh et al: Part and parcel of the cardiac autonomic nerve system: unravelling its cellular building blocks during development. J Cardiovasc Dev Dis 2016, 3:28).

Sympathetic and parasympathetic activity depends on chemo-and/or mechanosensory input from multiple cardiac regions, the coronary vasculature and from major intrathoracic- and cervical vessels. The nucleus of the solitary tract receives input from these chemo-and /or mechanosensory receptors via the glossopharyngeal and vagal nerve and is the first relay for several cardiac and cardiovascular reflexes (**Figure 3**).

The baroreceptor reflex

High-pressure stretch receptors in the aortic arch and the carotid sinus are triggered when mechanical deformation of the vessel wall occurs. Increased blood pressure activates these mechanoreceptors resulting in inhibition of sympathetic outflow, and a subsequent decrease in total peripheral resistance, heart rate and myocardial contractility[26]. Besides this sympatho-inhibitory pathway there is a cardio-inhibitory pathway, which upon excitation of the cardiovagal neurons of the nucleus ambiguous, results in a decrease in heart rate[26].

Cardiac reflexes

Atrial stretch reflex. Distension of low pressure receptors at the (pulmonary) vein-atrial junctions is signalled via vagal afferents to increase sympathetic activity and reduce vagal tone to the sinoatrial node. This results in increased heart rate without increased myocardial contractility (Bainbridge reflex)[27]. Conversely, low atrial pressure causes bradycardia. This positive feedback reflex, creating a direct relationship between filling pressures and heart rate, is rarely observed in clinical practice because it is weaker than and inferior to the baroreflex, a negative feedback system. It is typically observed in neonates and infants however, where the baroreflex is not yet fully developed. In theory, the Bainbridge reflex can become more prominent in clinical conditions associated with impaired baroreflex function[28].

Ventricular reflex. Both ventricles contain mechanosensors and chemosensors most of which can sense mechanical and chemical changes simultaneously[29]. Either chemical stimulation, potentially elicited by a host of chemicals (e.g. after myocardial infarction), and possibly mechanical stimulation by decreased end-systolic volumes[30, 31] activates these receptors to decrease sympathetic outflow and increase parasympathetic tone. This results in bradycardia, vasodilatation and hypotension, a response known as the Bezold-Jarisch reflex. This cardio-inhibitory reflex was suggested to play a cardioprotective role but this has never been confirmed[32].

Coronary baroreflex. Coronary arteries contain arterial baroreceptors that buffer pressure changes. However, these coronary artery receptors operate at much lower pressures than aortic and carotid baroreceptors[33]. Increases in coronary artery pressure cause limited reflex activity but coronary arterial hypotension induces a powerful systemic vasoconstrictor response. The coronary baroreflex is considered a defense mechanism against myocardial hypoperfusion[33].

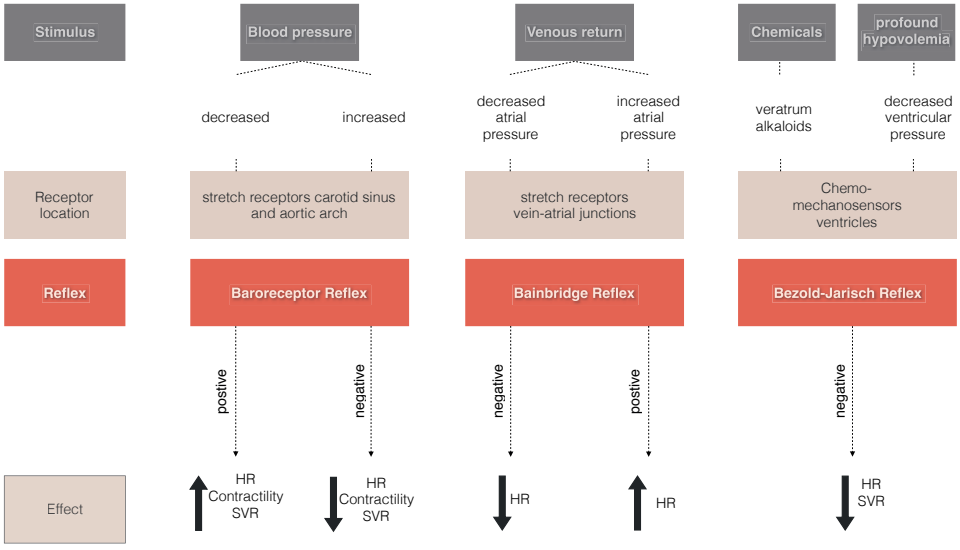

Figure 3. Cardiac and cardiovascular reflexes

Cardiovascular effects of TEA

The focus of this section is primarily on TEA studies where the cardiac sympathetic nerves (T1-T5) are involved in neural blockade. This definitely includes high TEA but may also apply to mid-thoracic epidural analgesia with cranial spread of anaesthetic blockade.

Effect on cardiovascular reflexes

Baroreceptor control of heart rate depends on an integrative role of the parasympathetic and sympathetic nervous system. This balance is affected when cardiac sympathetic innervation is blocked by TEA. Multiple studies have demonstrated that barorelflex sensitivity is altered by cardiac sympathectomy during cervicothoracic epidural anesthesia[34-39]. However, in some studies TEA attenuated the reduction in HR after blood pressure increase (pressure test) without changing the cardiac acceleration in response to blood pressure decrease (depressor test)[34-36] whereas others demonstrated the opposite[37, 38]. Yet another study reports that cervical but not lumbar epidural significantly depresses both "up-and down-sequence" baroreflex sensitivities[39]. However in this study spontaneously occurring fluctuations in arterial pressure and heart period were used as indices of baroreflex function, a method that has been criticized[40]. The contrasting results in above mentioned studies may relate to heterogeneous study design, differences in the management of TEA-induced preload changes and the use of general anesthesia. Finally, age differences between study populations may also have contributed to the differential effects of TEA on baroreflex control.

Sympathetic control of heart rate can operate indirectly by influencing vagal activity as well as directly by acting as a cardiac accelerator. Both mechanisms could be involved in the effects of TEA on baroreceptor control of heart rate. Regardless, it appears that cardiac sympathetic blockade by TEA at least partially suppresses the baroreceptor reflex. There are no studies addressing the effect of cardiac sympathectomy on other cardiovascular reflexes. It has been suggested that life threatening paradoxical bradycardia in hypotensive patients undergoing spinal and epidural anesthesia is due to attenuation of baroreflex control with subsequent unmasking of the reversed Bainbridge and/or Bezold-Jarish reflex[41-44]. Similarly during severe hemorrhage the Bezold-Jarish reflex may predominate resulting in bradycardia and hypotension[43] (**Figure 3**).

Summary:

- Cardiac sympathetic blockade by TEA at least partially suppresses the baroreceptor reflex.
- Extensive neural blockade by TEA with reduction of preload to the heart may evoke hypotension and bradycardia. This has been attributed to impairment of the baroreflex and unmasking of a reversed Bainbridge reflex.

Effect on heart rate

Chronotropic control of the heart is mediated by the balance between sympathetic and parasympathetic tone and is dominated by parasympathetic tone at[45]. The effects of TEA on heart rate depend on the prevailing sympathetic tone, the extent of neural blockade with its proportional impact on pre- and afterload, and the in- or exclusion of cardiac sympathetic nerves. Indeed, TEA effects on heart rate are not solely related to blockade of preganglionic cardiac accelerator nerves but also reflect TEA induced changes in preload and afterload (**Figure 3**) as described in great detail by Veering and Cousins[46]. Clinical studies report no change[47-50] or minor reductions in HR[34, 39, 51-56] after TEA including cardiac sympathetic nerves. Age might affect HR response to TEA since ageing is accompanied by an increased sympathetic nervous system activity at rest[57]. Two studies assessed cardiovascular effects of TEA in different age groups, however results are conflicting. Holman and co-workers[58] showed that HR reductions after TEA were most pronounced in the elderly group whereas we reported HR reductions only in the younger age group with no changes in the middle or older age groups[59]. Interestingly beta blockers, the chronotropic effects of which might be comparable to those of TEA, were found to result in a more pronounced reduction in HR in young as compared to older healthy volunteers[60].

Summary:

- The reported effects of TEA on heart rate are mild and not uniform. Changes result from the complex interaction between direct cardiac sympathetic blockade and cardiovascular reflexes which occur secondary to altered preload and afterload.
- Current studies do not indicate a consistent effect of age on HR response to TEA.

Effect on ventricular contractility (Table 1-3)

The majority of TEA studies use load dependent indicators of global left ventricular (LV) performance indicators, such as ejection fraction, fractional area change, fractional shortening, cardiac output (CO), stroke volume (SV) for the assessment of cardiac function[61]. Load independent assessment of cardiac performance requires advanced and often invasive technology such as pressure-volume catheters . Newer echocardiographic techniques allowing calculation of the slope of the end-systolic pressure-length relationship, or indices of myocardial velocity and deformation may offer a valid noninvasive alternative for this purpose[62-64].

Effects on LV contractile performance

Several studies have shown a reduction in inotropic state (intrinsic function) after blockade of cardiac sympathetic innervation by TEA. In anaesthetised dogs, the maximal rate of ventricular pressure increase (dP/dt max) of the LV decreased after induction of TEA but not after induction of lumbar epidural anaesthesia (LEA)[65, 66]. These results suggest a reduction in LV contractility due to blockade of cardiac sympathetic innervation. This is supported by results obtained in pigs, where load independent indices of contractility based on pressure-volume loop analysis decreased after TEA but not after LEA[49, 50]. In spite of the diminished contractility of the LV after TEA there was no change in global ventricular performance, due to a concomitant reduction of afterload[49, 50, 66]. Echocardiographic studies in awake and healthy volunteers compared the cardiac effects of TEA versus LEA and also found that only TEA, but not LEA, decreased ejection fraction, fractional area change or fractional shortening and increased left ventricular end-diastolic volume and/or left ventricular end-systolic volume. They also suggest that the reduction in LV cardiac function is due to cardiac sympathetic denervation[52, 67, 68]. Our group recently evaluated cardiac performance in awake resting patients scheduled for lung surgery using tissue Doppler based measurement of myocardial velocities. We found no effect of TEA on LV systolic pump performance, however, results may have been confounded by our study design which included pre-interventional volume loading. CO increased after TEA, presumably due to the combination of increased external volume loading and TEA-induced afterload reduction. This study in different age groups showed no effects of age on cardiovascular response to TEA[59]. Using the slope of the end-systolic pressure length relationship as a load independent measure of left ventricular contractility, Goertz and colleagues demonstrated in patients under general anesthesia that TEA but not LEA decreases LV contractility by 50% (**Figure 4**)[47]. The results of above mentioned studies suggest that there is a clinically relevant influence of the cardiac sympathetic nervous system on baseline LV function. Blockade of cardiac sympathetic nerves by TEA is associated with a reduction in LV contractility – the magnitude of which is likely related to the level of sympathetic tone. In cardiovascular healthy patients the cardiodepressant effects of TEA seem to be well tolerated with preservation of CO. Use of TEA in these patients is safe. The impact of cardiac sympathectomy in patients with limited cardiac reserve has not been studied specifically.

Summary:

- Load-independent indices demonstrate a 40-50% reduction in LV contractility following cardiac sympathetic blockade by TEA.
- TEA can be safely applied in patients with normal cardiovascular function.
- There are no studies addressing the clinical impact of TEA-induced cardiac sympathectomy in patients with limited cardiac reserve.

Table 1. Effects of TEA on systolic and/or diastolic cardiac function in animals

Author and Year of Publication	Data Acquisition	Human or Animal	Condition	TEA Level	Level of Analgesia	MAP	HR	SV	CO/CI	LV Systolic Function	RV Systolic Function	LV Diastolic Function	RV Diastolic Function
Hotvedt *et al.*[65] 1984	LV pressure transducer catheter	Animal N = 7	General anesthesia and β-blocker	T3–4 or T4–5	ND	↓	↓	ND	ND	↓ dP/dt_{max} decreased	ND	ND	ND
Hirabayashi *et al.*[66] 1996	LV pressure transducer catheter and flow probe around ascending aorta	Animal N = 16	General anesthesia TEA	T7/T8	C3/C7–T6/T9 (by ink)	↓	↓	↑	▬	↓ dP/dt_{max} decreased LVEDP increased	ND	ND	ND
			General anesthesia LEA	L5/L6	T8/T12–L6/S2 (by ink)	↓	↑	↓	▬	▬ dP/dt_{max} unchanged LVEDP decreased	ND	ND	ND
Rex *et al.*[49] 2007	LV and RV pressure–volume catheters	Animal N = 14	General anesthesia Control compared with TEA	T4/T5 (tip catheter T2)	ND	↓	▬	▬	▬	↓ Ees, Mw and dP/dt_{max} decreased	▬ Ees, Mw, dP/dt_{max} and V25 unchanged	▬ ↓	~ RV:τ increases, $\tau\%RR_{interval}$ and dP/dt_{min} =
			General anesthesia and pulmonary hypertension Control compared with TEA	T4/T5 (tip catheter T2)	ND	↓	↓	↓	↓	↓ Ees, Mw and dP/dt_{max} decreased, V100 increased	↓ Mw decreased and V25 increased		↓ τ increased, $\tau\%RR_{interval}$ = and dP/dt_{min} decreased
Missant *et al.*[50] 2010		Animal N = 18	General anesthesia Control baseline compared with TEA baseline and	T2	C7–T6	↓	▬	ND	▬	↓ Ees, Mw decreased ▬	LV and RV pressure–volume catheters	ND	ND
			LEA baseline	L2	T13–L6	↓	↑	ND	▬	Ees and Mw = ↓		ND	ND
			General anesthesia and pulmonary hypertension Control compared with TEA and	T2	C7–T6	↓	↑	ND	↓	Ees and Mw decreased ▬		ND	ND
			LEA	L2	T13–L6	↓	↑	ND	▬	Ees and Mw =		ND	ND

CI, cardiac input; CO, cardiac output; dP/dt_{max}, peak rate of RV pressure increase; dP/dt_{min}, peak rate of ventricular pressure decrease; Ees, slope of the end-systolic pressure–volume relationship; HR, heat rate; LEA, lumbar epidural anesthesia; LV, left ventricle; LVEDd, left ventricular end-diastolic diameter; LVEDP, left ventricle end-diastolic pressure; LVEDV, left ventricle end-diastolic volume; MAP, mean arterial pressure; Mw, slope of the preload-recruitable stroke work relationship; ND, not determined; RV, right ventricle; SV, stroke volume; τ, time constant of ventricular relaxation; $\tau\%RR_{interval}$, corrected for heart rate by normalizing to the RR interval; TEA, thoracic epidural anesthesia; V_{25} and V_{100}, volume intercept of end-systolic pressure–volume relation, quantified at pressure 25 and 100 mm Hg, respectively.

↑, increased; ↓, decreased; ▬ or =, no effect

Table 2. Effects of TEA on systolic and/or diastolic ventricular function in humans.

Author and Year of Publication	Data Acquisition	Human or Animal	Condition	TEA Level	Level of Analgesia	MAP	HR	SV	CO/CI	LV Systolic Function	RV Systolic Function	LV Diastolic Function	RV Diastolic Function
Wattwil *et al.*[52] 1985	Echo (TTE) and systolic time intervals: PEP/LVET ratio	Human N = 9	Awake Rest Awake Exercise	T4	C8/T1–T5/T7	▬ ↓	↓ ↓	↓ ND	↓ ND	↓ PEP/LVET ratio increased EF decreased LVEDd = and LVESd increased ND	ND ND	ND ND	ND ND
Goertz *et al.*[47] 1993	Echo (TTE): end-systolic pressure–volume relationship (ESPVR)	Human N = 36	General anesthesia TEA compared with control group or LEA group (L2–L5)	T8–T11	C6/T1–T11/L4	▬	▬	ND	ND	↓ E_{max} ESPVR decreased LVEDV, LVESV and fractional area change remained unchanged	ND	ND	ND
Niimi *et al.*[67] 1997	Echo (TTE)	Human N = 24	Awake	T4–T6 T10–T12	T1–T10 T6–L2	ND ND	↓ ▬	▬ ▬	↓ ▬	↓ FAC decreased EF tents to decrease and LVEDV and LVESV increased ▬ FAC, EF, LVEDV and LVESV remained unchanged	ND ND	▬ MV E, MV A and MV E/A unchanged MV DT increased ▬ MV E,MV A, MV E/A and MV DT unchanged	ND ND
Shiga[68] 1998	Echo (TEE)	Human N = 16	General anesthesia Control compared to TEA	T4	At least T1–T5	↓	↓	ND	ND	↓ FS decreased LVEDV = LVESV increased	ND	▬ MV E and MV DT unchanged MV A decreased and MV E/A increased	ND
Wink *et al.*[59] 2014	Echo (TTE): Tissue Doppler imaging	Human N = 31	Awake	T3–T4	C4/6–L1 /4	↓	▬	↑	↑	▬ or ↑ MV S´ and MPI = EF increased	~ TAPSE and TV S´ increased RV MPI = IVA decreased	↑ MV E´ increased	↑ TV E´ increased
Wink *et al.*[71] 2016	RV conductance catheter Atrial pacing	Human N = 11	General anesthesia Control compared with TEA GA and PHT Control compared with TEA	T3–T4	ND	▬ ▬	▬ ▬	▬ ▬	▬ ▬	ND ND	↓ Ees, stroke work, dP/dt_{max} decreased and V25 increased ▬	ND ND	↓ dP/dt_{min} decreased and nonsignificant increase in τ ▬

CI, cardiac input; CO, cardiac output; dP/dt_{max}, peak rate of RV pressure increase; dP/dt_{min}, peak rate of ventricular pressure decrease; DT, deceleration time, time interval required for the E velocity to decline from its peak to the baseline; E/A, ratio of E to A; Ees, the slope of the end-systolic pressure–volume relationship; EF, ejection fraction; E_{max}, maximal elastance; FAC, fractional area change; FS, fractional shortening; GA, general anesthesia; HR, heat rate; LEA, lumbar epidural anesthesia; LV, left ventricle; LVEDd, left ventricular end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVESd, left ventricular end-systolic diameter; LVESV, left ventricle end-systolic volume; LVET, left ventricular ejection time; MAP, mean arterial pressure; MPI, myocardial performance index or TEI index; MV A, peak velocity during atrial contraction phase; MV E, peak velocity during early filling phase; MV E´, early diastolic velocity of the mitral annulus; MV S´, systolic velocity of the mitral annulus; ND, not determined; PEP, pre-ejection period; PHT, pulmonary hypertension; RV, right ventricle; SV, stroke volume; τ, time constant of ventricular relaxation; TAPSE, tricuspid annular plane systolic excursion; TEA, thoracic epidural anesthesia; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; TV E´, early diastolic velocity of the tricuspid annulus; TV S´, systolic velocity of the tricuspid annulus; V_{25} and V_{100}, volume intercept of end-systolic pressure–volume relation, quantified at pressure 25 and 100 mm Hg, respectively.

↑, increased; ↓, decreased; ▬ or =, no effect; ~, unclear effect

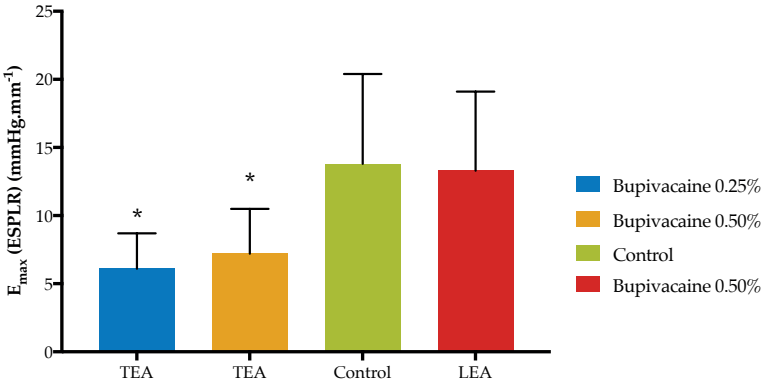

Figure 4. Arithmetic means (± s.d.) of the maximal elastance (Emax) of the left ventricle.
*indicates *Pi*<0.001 versus Group 3 (control) and versus Group 4 (LEA). TEA, thoracic epidural anaesthesia; LEA, lumbar epidural anaesthesia. Modified with permission from Goertz et al. (Goertz et al: influence of high thoracic epidural anaesthesia on left ventricular contractility assessed using the end-systolic pressure-length relationship. Acta Anaesthesiol Scand 1993; 37: 38-44.

Table 3. Effects of TEA on systolic and/or diastolic cardiac function in patients with coronary artery disease

Author and Year of Publication	Data Acquisition	Human or Animal	Condition	TEA Level	Level of Analgesia	MAP	HR	CPP	CO/CI	Global LV Systolic Function	Regional LV Systolic Function	LV Diastolic Function	RV Function
Kock *et al.*[116] 1990	Angiocardiography and ST-segment analysis	Human N = 10	General anesthesia and B-blocker at rest and during stress-induced myocardial ischemia	T3–T5 T3–T5	At least T1–T5 At least T1–T5	▬ ↓	▬ ▬	ND ND	ND ND	▬ Global EF was unchanged after TEA ↑ Improved global EF after TEA	▬ Regional EF was unchanged after TEA ↑ Improved regional EF and wall motion score after TEA	ND ND	ND ND
Saada *et al.*[117] 1992	Echo (TEE) and pulmonary artery catheter	Human N = 26	General anesthesia and TEA	T6–T7 or T7–T8	ND	↓	↓	↓	↓	ND	▬ Wall motion score was unchanged after TEA	ND	ND
Berendes *et al.*[118] 2003	Echo (TEE)	Human N = 73	General anesthesia for CABG Control (n = 37) *vs.* TEA (n = 36)	C7–T1	T1–T7	▬	▬	ND	▬	▬ FAC was unchanged after TEA	↑ Improved wall motion score after TEA	ND	ND
Schmidt *et al.*[119] 2005	Echo (TEE) and pulmonary artery catheter	Human N = 37	Awake	T1–T2 or T2–T3	C7–T7	↓	↓	↓	↓	▬ FAC was unchanged after TEA	ND	↑ Improved flow propagation velocity and myocardial performance index	ND
Jakobsen *et al.*[120] 2009	Echo (TTE): tissue Doppler imaging TTE	Human N = 15	Awake	T2–T3	At least T1–T5	↓	↓	ND	↑	↑ EF and tissue tracking score increased after TEA	ND	↑ Improved E´/A˝ indicative of improved relaxation	ND
Wafaa *et al.*[121] 2011	Echo (TTE)	Human N = 48	General anesthesia Control (n = 24) *vs.* TEA (n = 24)	T2–T5	At least T1–T5	↓	↓	ND	ND	▬ EF and FAC were unchanged after TEA	ND	~ Reported improvement of relaxation pattern after TEA howeverbased on transmitral flow patterns	ND

CAGB, coronary artery bypass grafting; CI, cardiac input; CO, cardiac output; CPP, coronary perfusion pressure; E´/A´, ratio of peak early and late diastolic velocity of the mitral annulus; EF, ejection fraction; FAC, fractional area change; HR, heat rate; LV, left ventricle; MAP, mean arterial pressure; ND, not determined; RV, right ventricle; ST-segment, region between the end of the S-wave and the beginning of the T-wave on the electrocardiogram; TEA, thoracic epidural anesthesia; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

↑, increased; ↓, decreased; ▬, no effect; ~, unclear effect

Effect on RV contractile performance

The sympathetic nervous system plays an important role in the regulation of RV function. This is illustrated by a 100% increase in contractile force of the RV after right and left stellate ganglion stimulation, both containing a significant portion of the sympathetic nerves innervating the heart[17]. Only a few studies assessed the effects of cardiac sympathetic inhibition by TEA on RV performance. Animal studies using load-independent parameters of contractility, did not find decreases in baseline contractility of the RV after induction of TEA during general anaesthesia[49,50] but indicated that TEA inhibited the positive inotropic effect to increased afterload (**Figure 5**). This mechanism referred to as homeometric autoregulation enables the RV to maintain stroke volume without compensatory dilatation of the RV[69, 70.] In awake patients TEA reduced RV isovolumetric acceleration, suggesting decreased RV contractility. However changes in loading conditions prevented clear conclusions regarding effects of TEA on RV contractility[59].

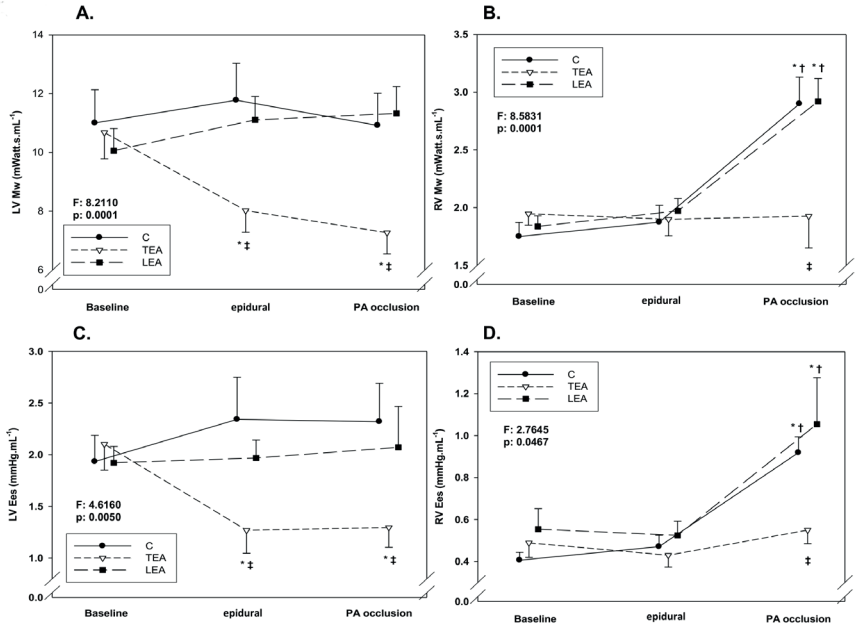

Figure 5. Right and left ventricular contractility during baseline, epidural anaesthesia, and acute PA occlusion in control animals and animals with a thoracic or lumbar epidural anaesthesia.

The effects of epidural anaesthesia on the slope of the preload-recruitable stroke work relationship (Mw) (A and B) and the slope of the end-systolic pressure–volume relationship (Ees) (C and D) during baseline, epidural anaesthesia (EDA), and during acute PA occlusion (PA occlusion) in the left (LV) and right ventricle (RV). Values are presented as mean (SEM). C, control animals; TEA, thoracic epidural anaesthesia; LEA, lumbar epidural anaesthesia; Ees, slope of the ESPVR; Mw, slope of the PRSW relationship; PA, pulmonary artery. *P,0.05 vs baseline; †P,0.05 vs epidural; ‡P,0.05 vs C. Reprinted with permision of Missant et al. (Missant et al: Differential effects of lumbar and thoracic epidural anaesthesia on the haemodynamic response to acute right ventricular pressure overload. BJA 2010; 104: 143–149).

We recently investigated the effects of TEA on RV contractility in patients during lung surgery and one lung ventilation. Using fixed rate pacing and employment of pressure-volume loop analyses load-independent indices of intrinsic RV function were obtained before and after induction of TEA during general anesthesia. Our data demonstrated TEA-induced impairment of baseline RV contractility[71] as reflected by changes in the slope and volume intercept of the end-systolic pressure volume relationship (**Figure 6**). In addition there was a 25% to 30% reduction in stroke work. These observations slightly differed from the animal studies where TEA inhibited the increase in RV function but did not reduce baseline RV performance. However, baseline measurements in our clinical study were obtained during one lung ventilation, a condition known to induce hypoxic pulmonary vasoconstriction. It was postulated therefore that sympathetic tone and RV afterload might have been elevated already prior to the initiation of TEA. This was not the case in the animal studies where baseline values were obtained during normal ventilation[71, 72].

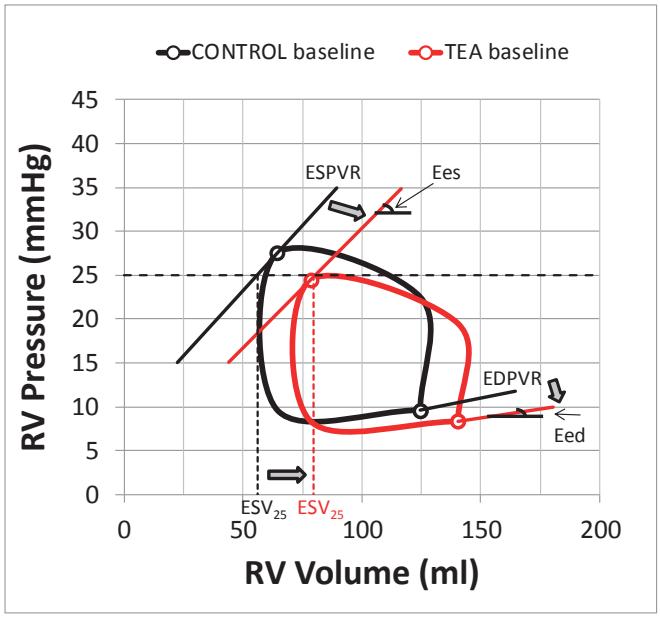

Figure 6. Schematic RV pressure-volume loops based on mean end-diastolic and end-systolic pressures and volumes during one lung ventilation at baseline (black loop) and after induction of TEA (red loop). The increase in ESV^{25} and the rightward shift and more shallow slope of the ESPVR after TEA, indicate a decreased contractile performance. ESPVR, end-systolic pressure-volume relationship; EDPVR, end-diastolic pressure-volume relationship; Eed, slope of the end-diastolic pressure-volume relationship; Ees, slope of the end-systolic pressure-volume relationship; ESV^{25}, volume intercept of ESPVR at 25 mmHg; RV, right ventricle; TEA, thoracic epidural anesthesia. Reprinted with permission from Wink et al. (Wink et al: Thoracic Epidural Anesthesia Reduces Right Ventricular Systolic Function With Maintained Ventricular-Pulmonary Coupling. Circulation 2016; 134: 1163–1175.

Regardless of this discussion, both animal studies and clinical studies were concordant in showing that cardiac sympathectomy with high TEA directly affects RV function. These effects may not have much clinical impact in subjects with normal cardiovascular function, but could be of importance in patients with preexisting or pending RV dysfunction and pulmonary hypertension. It is interesting to note that epidural analgesia was found an important contributing factor to major perioperative complications in patients undergoing pneumonectomy[7], although that evidence appeared not robust enough to support a change in practice. Similarly, in a secondary analysis of the POISE study, Leslie et al found evidence for increased cardiovascular problems in high-risk patients receiving neuraxial block[8]. It is clear that prospective outcome studies in high-risk patients are urgently needed to address this issue. For some patients undergoing major surgery who are at risk for RV failure or for those being treated with TEA who develop sudden RV failure in the postoperative period, potent alternative analgesic techniques such as paravertebral blocks could also provide a solution.

Summary:

- Cardiac sympathetic blockade by TEA directly reduces RV contractility.
- The clinical importance of this effect is not known at present.

Effect on LV and RV diastolic function

Ventricular relaxation and compliance are important determinants of diastolic function, an essential component of cardiac pump performance. Impaired relaxation and/or reduced compliance of the ventricle have been associated with increased perioperative risk for 30-day cardiovascular events and long-term cardiovascular mortality[73]. The effects of TEA on diastolic function have not been well established let alone the relevance of these temporary effects on clinical outcome. In normal conditions, contraction and relaxation are functionally coupled. Sympathetic stimulation of cardiac beta1 receptors causes a rise in c-AMP which enhances calcium release during systole but also facilitates removal of the excess calcium during diastole[16,23-25,74]. It would be reasonable to expect that if TEA-induced cardiac sympathectomy causes a mild decrease in contractile performance, it would also decrease relaxation proportionally. However, most studies reported unchanged LV diastolic function after TEA in patients with normal cardiovascular status but used load dependent parameters[67, 68]. We recently studied the effect of TEA on diastolic RV and LV function in different age groups using tissue Doppler imaging[75,76]. Peak velocity of the mitral and tricuspid annular motion during early diastole were used to assess LV and RV diastolic function[77]. Baseline diastolic function was significantly lower in older patients but TEA did not reduce diastolic function in any of the age groups[59]. Animal studies using invasive load independent measurement techniques also demonstrated that diastolic function of the LV and RV remained unchanged after TEA[49]. Using a similar technique in patients undergoing lung surgery, we found that the decrease in RV inotropic state following TEA was accompanied by a discrete reduction in RV relaxation properties[71, 78]. TEA effects on diastolic function are mild and well tolerated in healthy patients. Whether this also applies to patients with established diastolic

dysfuntion remains to be investigated. This latter group of patients is particularly sensitive to preload changes and for that reason needs specific attention when TEA is applied.

Summary:

- The direct effect of TEA on diastolic function is minimal.
- Patients with diastolic dysfunction are extremely sensitive to changes in preload which almost invariably occur with TEA. Particular attention is required to prevent the hemodynamic consequences of preload reduction following TEA in this subset of patients.

Effects in the healthy coronary system

Coronary arteries are innervated by the parasympathetic and sympathetic nervous system. Parasympathetic stimulation results in coronary vasodilatation[79]. Sympathetic alpha-adrenoceptor-mediated coronary vasoconstriction has been demonstrated[80, 81] but adrenergic activation of the heart will also induce beta- adrenoceptor-mediated coronary vasodilatation[82]. Indirectly, adrenergic activation raises myocardial oxygen demand resulting in increased myocardial blood flow via local vasodilatory mechanisms[83]. These sympathetic-mediated mechanisms compete with local metabolic vasodilatation, making control of myocardial perfusion a complex phenomenon[80].

Hirabayashi and colleagues assessed TEA effects on coronary circulation in healthy dogs[66]. Coronary perfusion pressure, coronary blood flow as well as systemic arterial pressure decreased after TEA and LEA. Interestingly, TEA only increased calculated coronary vascular resistance. The authors suggest that the increased coronary vascular resistance is an autoregulatory response to the decreased myocardial oxygen demand after TEA as a consequence of a lower arterial pressure, heart rate and myocardial contractility. Their data are consistent with an earlier animal study that reported decreases in arterial pressure and increases of coronary diastolic pressures after induction of TEA[84]. Whether these TEA-induced changes in diastolic pressure and resistance in coronary arteries are autoregulatory responses to decreased myocardial oxygen demand or direct effects of blockade of sympathetic efferents to the coronary arteries remains unclear. A recent clinical study in patients with normal cardiovascular physiology failed to demonstrate any effect of TEA on myocardial blood flow in rest. On the other hand, during sympathetic stimulation by the cold pressor test there was a 70% increase in myocardial blood flow in the control group whereas myocardial blood flow in the TEA group remained the same[85]. However, with a mean difference in increase of rate pressure product between the TEA and control group of 2215 (mmHg/min) the increase in cardiac work and myocardial oxygen demand, if any, in the TEA group was substantially lower. Therefore, the lack of an augmented myocardial flow response during the cold pressor test could have been an autoregulatory response as suggested in animal studies. While unique for the fact that it is one of the only studies in men on this subject, the data should be interpreted with caution as myocardial contrast echocardiography is not an accurate technique to quantify myocardial perfusion[86].

Summary:
TEA effects on normal coronary arteries are primarily governed by the reduction in myocardial oxygen demand.

Cardiovascular effects during stress

The concept of cardiac sympathetic innervation being primarily essential in the state of exercise and not in rest is illustrated in heart transplant patients. Reinnervation of the surgically denervated heart occurs only in some cardiac transplant patients. Cardiac pump performance at rest, as measured by global and regional ejection fraction, does not differ between patients with and without reinnervation. However, the group with reinnervation has a significantly better chronotropic and inotropic response to exercise, resulting in better exercise performance[87]. Several animal studies suggest that cardiovascular effects of TEA are more pronounced during stress . TEA had no or minimal effect on HR in baseline conditions yet the substantial increase of HR during raised RV afterload was blunted following TEA[49, 50, 88, 89]. In addition TEA prevented the increase in contractility of the RV and LV to acutely raised RV afterload resulting in a decrease of CO and SV[49, 50] (**Figure 4**). In dogs the cardiovascular response to severe hypoxemia was almost completely abolished by high epidural anesthesia[90]. Although the level of neuroaxial block was not determined in the latter study, HR increase to hypoxia was clearly suppressed, indicating involvement of the cardiac sympathetic efferents in epidural blockade. Several clinical studies demonstrated that TEA significantly reduced increases in blood pressure and/or HR following laryngoscopy and intubation[91-93] whereas baseline values were only minimally changed by TEA. In these studies TEA involved blockade of the sympathetic innervation to the heart as well as to the adrenal glands. In a study by Dohi and colleagues cardiac sympathetic blockade by TEA or adrenal sympathetic blockade by LEA did not attenuate the circulatory response to laryngoscopy or intubation[94].

These contrasting results suggest that sympathetic innervation both to the heart and adrenal glands contribute to the circulatory response following laryngoscopy and intubation. Kirno et al also showed more pronounced effects of TEA in humans during stress. They reported significant TEA-induced reductions in the cardiac norepinephrine spillover compared to a control after, but not prior to the surgical stress of sternotomy[95]. TEA exercise studies in healthy volunteers studies showed that increases in HR during exercise were blunted following TEA and the decrease in HR appeared to be more substantial with increasing workloads[52, 96]. Interestingly TEA did not completely abolish the HR response to stress and/or exercise suggesting either incomplete cardiac sympathetic blockade by TEA or involvement of the adrenal glands. Ottesen and colleagues studied the effects of selective blockade of the sympathetic cardiac segments by TEA in rest and during physical exercise in volunteers using a pulmonary artery catheter. During maximal exercise, SV was maintained and CO decreased only because of a reduction in HR after TEA[96]. The preservation of SV does not indicate preservation of cardiac function however as higher end-diastolic volumes in the presence of reduced ejection fraction would also preserve SV.

Unfortunately, intrinsic ventricular function was not assessed in this study, hence comparisons between TEA effects on ventricular function during rest and during stress could not be made.

In conclusion, both experimental and clinical studies suggest that cardiovascular effects of TEA are more pronounced during stress/exercise than in resting conditions. Data from TEA studies performed in resting conditions do not provide information on its role in the perioperative period, which is typically characterized by surgical and hemodynamic stress. The reduction in cardiac metabolic demands and blunting of the stress response have generally been considered beneficial properties of cardiac sympathectomy with TEA. This is undoubtedly the case for patients with ischemic heart disease but may not apply for other subgroups where the endogenous sympathetic stress response is required to restore cardiovascular homeostasis. Interestingly, systematic reviews failed to show a beneficial effect on cardiovascular outcome in patients treated with TEA.

Summary:

- TEA effects are more pronounced during elevated sympathetic tone.
- Elevation of sympathetic tone is an established short term survival mechanism to preserve cardiovascular homeostasis in the face of hemodynamic disruption. As such sympathicolysis by TEA could interfere with this endogenous defense mechanism when hemodynamic challenges occur in the perioperative setting.

Effects of TEA in cardiovascular disease

Ischemic heart disease

Coronary blood flow is regulated primarily by change in myocardial oxygen demand[83] induced by variations in wall tension, contractile state and heart rate. In addition, large coronary epicardial coronaries and coronary resistance vessels are densely innervated by the sympathetic nervous system[80]. Experimental animal studies have demonstrated that TEA improves endocardial blood flow during acute myocardial infarction[84], reduces myocardial acidosis and ischemia after coronary artery occlusion[97, 98], reduces myocardial ischemic injury and infarct size[99-101] and improves recovery from myocardial stunning[102]. In patients with coronary artery disease TEA has been demonstrated to increase myocardial oxygen availability [103] and to improve myocardial oxygen balance by reducing heart rate, preload and afterload without affecting coronary perfusion pressure[104]. Reiz and colleagues showed that in patients with coronary artery disease TEA reduces coronary vascular resistance and myocardial oxygen consumption[105]. This cardioprotective role of TEA is further supported by observations that TEA compared to controls decreased loading conditions of the heart and myocardial oxygen demand following sternotomy[95].

Coronary atherosclerosis and endothelial dysfunction are associated with an exaggerated response to coronary alpha-adrenergic activation that result in a reduced coronary blood flow response during sympathetic stimulation[106-108]. Cardiac sympathetic inhibition by TEA therefore might improve coronary function in patients with coronary artery disease. Indeed, TEA resulted in an increased luminal diameter in stenotic epicardial coronary arteries but not in the non-stenotic epicardial coronaries[109]. Whether this resulted in increased myocardial blood flow, a phenomenon referred to as reverse coronary steal, is unknown since myocardial blood flow was not measured in this study. In a more recent study by Nygard and colleagues the effects of TEA on myocardial blood flow were assessed in patients with coronary artery disease. While in patients without TEA myocardial blood flow was unchanged during sympathetic stimulation, patients with TEA demonstrated increases in myocardial blood flow at all vascular territories. After sympathetic stimulation by the cold pressor test coronary vascular resistance increased in the group without TEA and decreased in stenotic and non-stenotic vessels with TEA. TEA induced changes in myocardial blood flow were less than 10% at rest whereas 17-100% increases in myocardial blood flow were shown during the cold pressor test[110]. These data suggest that coronary sympathetic innervation is of minor importance at rest, yet plays an important role during sympathetic stimulation[111, 112].

TEA has been used in patients with ischemic heart disease for the treatment of refractory angina pectoris reducing the incidence of myocardial ischemia, decreasing the number and duration of ischemic episodes, producing symptomatic relief of angina and improving quality of life[113-115]. Besides improving myocardial oxygen balance these TEA induced results may at least partially be attributable to the pain relief obtained by blockade of spinal afferents. The improvement in myocardial oxygen balance after TEA may also affect myocardial function in patients with coronary artery disease. In awake patients with coronary artery disease global and regional wall motion during stress-induced myocardial ischemia has been shown to improve after induction of TEA[116]. These results were confirmed in patients with coronary artery disease during general anesthesia and TEA. Despite lower coronary perfusion pressures after the induction of TEA segmental wall motion was unchanged in patients with coronary artery disease whereas segmental wall motion decreased in the patient group without coronary artery disease[117]. TEA significantly improved regional left ventricular wall motion and reduced ischemia and coronary risk in patients with coronary artery disease in another study[118]. Schmidt and co-workers report improved diastolic and maintained systolic LV function after TEA in coronary artery disease patients[119]. Another study using a derivative of tissue Doppler imaging demonstrated TEA-induced improvements of diastolic and systolic LV function in patients with ischemic heart disease[120].

Clinical studies have been performed assessing the effect of TEA on myocardial damage determined by the amount of postoperative Troponin in coronary artery bypass graft patients. The potential myocardial protective effect of TEA is supported by decreases in postoperative

cardiac Troponin I and T after cardiac surgery[55, 118, 121] whereas other studies failed to demonstrate an effect of TEA on postoperative Troponin as a marker of myocardial damage[122-126]. A potential influence of TEA on the incidence of perioperative myocardial infarction is favored by some studies[127-129], but remains to be clarified. A recent meta-analysis by Svircevic and colleagues found no significant effect of TEA on the incidence of perioperative myocardial infarction[130].

Although 2731 patients from 28 studies were included the authors concluded that the meta-analysis was underpowered and estimated the need for a sample size of 10.000 patients to obtain statistical significance for the reported reduction in the incidence of myocardial infarction from 3.8% to 2.8% after TEA. In fact, the majority of meta-analyses available today failed to show a significant clinical impact of TEA on cardiovascular outcome. This is in contrast with the well documented effects of TEA on the cardiovascular system as reported in physiology studies. The apparent discrepancy may be related to the fact that clinical studies have not zoomed-in on specific risk groups but included very heterogeneous populations instead. As a result, any potential beneficial effect in a particular subgroup, as well as any potentially detrimental effect of TEA in a specific risk population, may go unnoticed and even cancel out a statistical effect on outcome. Ideally, randomized controlled trials should focus on specific patient populations, guided by the observations from pathophysiology studies, to better define the benefits and risks of TEA and optimize its application in clinical practice.

Summary:
TEA improves coronary function and myocardial oxygen balance in patients with ischemic heart disease which results in increased myocardial performance and a reduction of the number and duration of ischemic episodes.

Pulmonary Hypertension
Acute pulmonary hypertension is a frequently encountered phenomenon in cardiothoracic surgery and during hypoxic pulmonary vasoconstriction in the critically ill. This is important since pulmonary hypertension may result in RV failure and RV function has been shown to be an important determinant of outcome[10-12]. Jahn and colleagues demonstrated that in a model of ovine pulmonary embolism induction of TEA contrary to lumbar epidural anaesthesia (LEA) improves hemodynamic variables mainly as a result of a decrease in pulmonary vascular resistance. Effects of TEA on right ventricular contractility were not measured and extension of neural blockade was not assessed. Hemodynamic deterioration caused by pulmonary embolism was reduced by TEA and aggravated by LEA[88, 89]. The authors suggest that reduction of sympathetic outflow to the heart and lungs is the underlying mechanism for the beneficial results of TEA during pulmonary hypertension. They also suggest that increased sympathetic tone in the unblocked thoracic spinal levels associated with LEA is responsible for the hemodynamic aggravation during pulmonary hypertension. This is in contrast with the results of earlier experimental studies which demonstrated that in respiratory distress syndrome, during

pulmonary artery constriction and in pulmonary artery embolism, RV contractility increases proportionally to an increase in RV afterload (homeometric autoregulation). In anesthetized pigs, induction of TEA has been shown to abolish this inotropic response to acutely raised RV afterload (**Figure 4**). Combined with an increase in pulmonary vascular resistance induction of TEA resulted in a significant decrease in cardiac output[49, 50]. Moreover lumbar epidural anaesthesia had no effect on the hemodynamic response to pulmonary hypertension (**Figure 4**). Results indicate that the sympathetic nervous system might have an important role in the described inotropic response of the RV to pulmonary hypertension. In humans, however, TEA did not affect the native positive inotropic response of the RV to increased afterload (**Figure 5**)[71]. Cardiac output was maintained. Of importance is that all patients were paced at a constant rate to accurately assess cardiac contractility. This way HR reduction by TEA was prevented and cardiovascular effects might have been more profound without pacing. Overall, cardiac sympathetic blockade by TEA reduces RV contractile performance. The clinical importance of this finding is unknown. The role of the RV has been neglected for a long time and it has never been investigated whether temporary changes in RV function whether drug induced or epidural induced change outcome. In cardiovascular healthy patients during normal circumstances this is not a safety concern. However, during conditions of acutely raised RV afterload TEA might interfere with the capacity of the RV to adapt to increases in afterload resulting in decreases in CO and cardiovascular collapse.

Summary:
High TEA limits cardiac reserve and the capacity of the RV to adapt to increases in RV afterload, which can decrease cardiac output.

Conclusion

There has been renewed interest in the cardiovascular effects of TEA since the latest review on this subject was published ten years ago[9]. The beneficial hemodynamic effects and cardioprotective properties of TEA, demonstrated in a number of experimental studies, did not translate in better cardiac outcome for patients undergoing surgery who were treated with TEA. More recent exploratory studies even suggested that TEA was associated with increased cardiovascular problems in high risk patients. Mechanisms underlying such a potential harmful effect and characteristics of high risk populations remain speculative however.

Recent experimental and clinical studies have added information on the complex interaction between TEA- induced sympatholysis and cardiovascular homeostasis. Using more advanced methodology they clearly demonstrated that cardiac sympathetic blockade by high TEA reduces LV as well as RV contractility. This direct effect of TEA is well tolerated in healthy subjects because concomitant arteriolar vasodilation and the subsequent decrease in LV afterload facilitates cardiac ejection. Hence overall pump performance and cardiac output are preserved provided that alterations in preload are accounted for. Such a compensatory decrease in afterload however

does not occur in the pulmonary circulation and a direct reduction of RV inotropic state can have more impact on pump performance.

The cardiovascular effects of TEA as studied in baseline conditions at low sympathetic tone do not fully reveal the impact of sympatholysis on cardiovascular homeostatic mechanisms when activated by surgical stress or by hemodynamic disruptions such as hypovolemia and bleeding. TEA attenuates baroreflex function and may unmask primary cardiac reflexes to altered volume status. It is not known to what extent the attenuation of endogenous cardiovascular reflexes affects outcome in the overall population treated with TEA.

Finally, the effects of cardiac sympathectomy with high TEA vary with the pathophysiologic substrate. In patients with coronary artery disease the use of TEA improves myocardial oxygen balance and produces relief of angina. TEA was consistently shown to enhance LV diastolic and systolic function in this population.

In conclusion, the conviction that TEA has beneficial hemodynamic effects may not apply to all patients. While protective in particular pathophysiological conditions such as ischemic heart disease, cardiac sympatholysis may also attenuate the hearts capacity to respond to hemodynamic challenges in particular subgroups. This should be considered whenever patients treated with TEA develop hemodynamic instability in the perioperative setting. Since alternative analgesic strategies with equivalent efficacy are now available, it appears prudent to use a more restrictive approach towards recommending high TEA for patients at risk for perioperative RV failure.

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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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Acta Anaesthesiol Scand 2013; 57: 767–775

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).

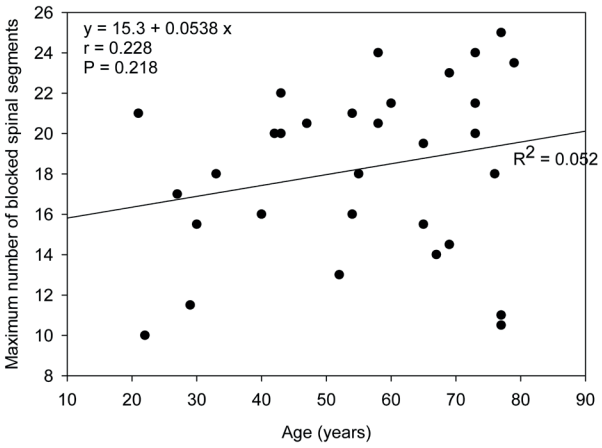

Figure 1. Relationship between maximum number of dermatomes blocked and age after thoracic epidural administration of 8 ml ropivacaine 0.75%.

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.

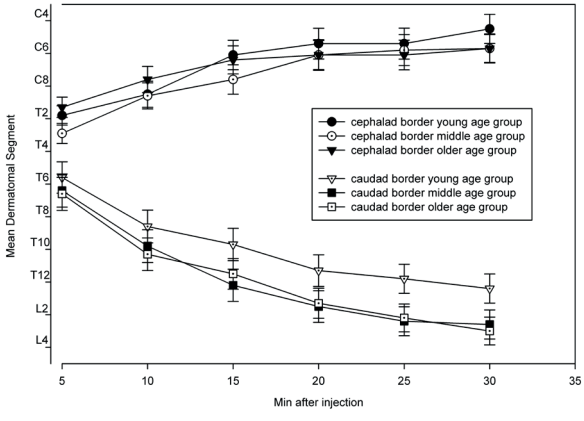

Figure 2. Mean cephalad and caudad borders of the three age groups every 5 minutes after thoracic epidural administration of ropivacaine.

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].

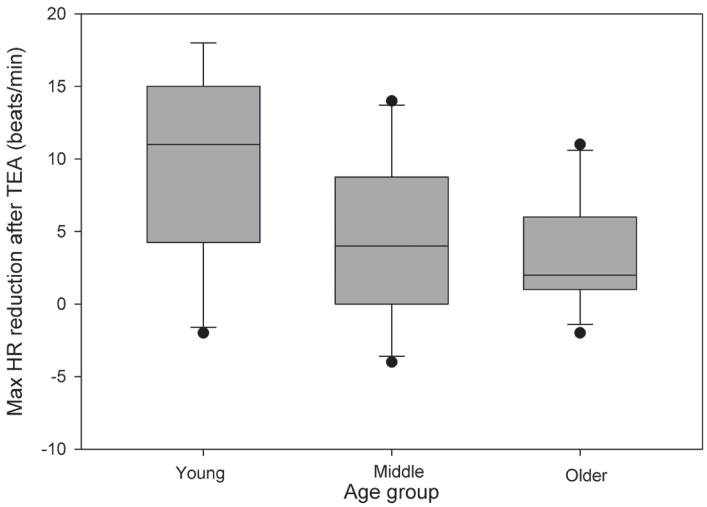

Fig 3. Maximum reduction of Heart Rate (HR) after TEA in the three age groups presented as boxplots. Mean heart rate reduction was different between the young and middle group and between the young and older group (p=0.03 and p=0.01 respectively).

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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Chapter 6

Effect of increasing age on the hemodynamic response to Thoracic Epidural Anaesthesia

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Eur J Anaesthesiol 2014; 31:597–605

Introduction

Thoracic epidural anaesthesia (TEA) combined with general anaesthesia is considered to be the gold standard anaesthetic approach in lung surgery. The cardiac sympathetic outflow emerges from C5 to T5 levels, with the main supply to the ventricles from T1 to T4[1]. TEA results in blockade of these nerves and changes in heart rate, left and right ventricular function and myocardial oxygen demand may occur. TEA might provide cardiac protection[2], has been successfully used in humans to treat refractory angina[3] and may increase the diameter of stenotic epicardial coronary arteries in patients with coronary artery disease[4]. However, TEA decreases arterial and venous vessel tone influencing pre-and afterload of the heart and may directly affect myocardial performance[5]. Ageing is accompanied with a greater sensitivity to volume status of the cardiovascular system[6] due to impaired autonomic nervous system control and impaired diastolic function[7]. These factors suggest that elderly patients may be particularly vulnerable to the hemodynamic side effects of TEA, however, remarkably few data exist on the relationship between age and the hemodynamic response to TEA. In a previous study we did not find that age effected the total amount of spinal segments blocked after TEA with a fixed dose of ropivacaine at the T3-T4 interspace[8].

In the present study we tested the hypothesis that TEA results in more profound cardiovascular effects in the elderly as compared to younger patients. Using contemporary echocardiographic techniques to assess diastolic and systolic function we quantified the effects of TEA on biventricular function in a wide age-spectrum of patients presenting for lung surgery.

Methods

Patients

The protocol of this study was reviewed and approved by the Committee on Medical Ethics of the Leiden University Medical Centre (reg. no: P09060), Leiden, the Netherlands (Chairperson Prof. Dr. A.J. Rabelink) on 6 July 2009 and approved by the Centrale Commissie Mensgebonden Onderzoek (CCMO), as Competent Authority for the review of clinical trials in the Netherlands, NL27041.058.09. The subjects reported in this study have been previously reported in an article presenting data on the effects of age on the segmental spread of local anesthetics[8].

Patients scheduled for pulmonary surgery (full lateral thoracotomies and in case of pleural rubbing video assisted thoracoscopic surgery procedures) under thoracic epidural anaesthesia and general anaesthesia were included in this open, observational, single-center study. All study measurements were done in awake patients. After written informed consent, patients were stratified in one of three age groups (Group 1: 18-45 years; Group 2: 46-65; Group 3: 66 years and older) to ensure an even age distribution across the age spectrum. Patients with a contraindication for epidural anaesthesia and pregnant women were excluded from the study. 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. For the same reason, we did not exclude patients with hypertension, diabetes or patients using anti-arrhythmic drugs. None of the patients included in this study had a history or signs of coronary artery disease.

Procedures

Patients were fasting 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 (IV) catheter was placed in the arm for administration of fluids and medication. A colloid infusion (Voluven®, Hydroxyethyl starch 130/0.4, Fresenius Kabi, Bad Homburg, Germany) was administered at a rate of 10 ml.kg^{-1} over a 40-min period beginning 10 min before the epidural injection of ropivacaine to maintain preload[9]. Epidural puncture was performed with the patient in the sitting position at the T3-T4 interspace, using a paramedian approach. A 20-gauge lateral eye catheter was introduced5 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. During the echocardiographic examination before and after TEA patients were placed in the left lateral decubitus position.

Measurements

Analgesia was assessed bilaterally by temperature discrimination using ice-cubes. An arterial line 20 G was inserted after local infiltration with lidocaine 1% in the radial artery to monitor arterial blood pressure (Edward Lifesciences LLC, Irvine, Ca, USA). Mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured immediately before (baseline) and 30 minutes after epidural injection of ropivacaine. Heart rate (HR) was monitored continuously from the electrocardiogram. If the systolic blood pressure decreased more than 30% below baseline value or to less than 90 mm Hg, ephedrine 5 mg was given IV. Bradycardia (HR< 55 beats per minute (bpm)) was treated with atropine sulphate, 0.25-0.5 mg IV.

Echocardiography

Standard transthoracic two-dimensional, pulsed, color-flow and M-mode Doppler echocardiographic examination was performed with a Vivid 7 ultrasound machine (GE Medical Systems) equipped with a multifrequency phased array transducer. Recordings were made immediately before placement of an epidural catheter and 45 minutes after thoracic epidural injection of ropivacaine. All measurements were acquired from parasternal long axis (PLAX), apical 4 (A4C) – and 2-chamber (A2C) views and apical long- axis view with the patients in lateral decubitus positioning. For Doppler variables, we aimed for correct alignment (< 20°) of the beam of interrogation with the motion of blood and tissue under investigation. All measurements

were carried out unblinded by one examiner certified in TTE by the European Association of Echocardiography (EAE). Echocardiographic images were stored digitally for subsequent off-line analysis with EchoPac software (EchoPAC Dimension version 7.0.0, GE Vingmed Ultrasound AS, Horten, Norway).

Left Ventricular (LV) function:
Interventricular septum thickness at diastole (IVSd) and left ventricle posterior wall thickness at diastole (LVPWd) were measured from M-mode echocardiographic recordings at the mid-ventricular level in the parasternal long-axis view. A minimum of three beats were measured and averaged for all Doppler variables. In the A4C view using pulsed wave Doppler at the tips of the mitral leaflets the following parameters were obtained: peak velocity during early filling phase (MV E), peak velocity during atrial contraction phase (MV A), the ratio of E to A (MV E/A ratio) and the time interval required for the E velocity to decline from its peak to the baseline (MV E deceleration time or MV DT). Left ventricle end- diastolic volume (LVEDV) and left ventricle end-systolic volume (LVESV) were obtained by tracing the end-diastolic and end-systolic endocardial borders in the A2C and A4C views calculating ejection fraction (EF) with biplanar Simpson's rule. Stroke volume (SV) and Cardiac output (CO) were calculated using the LV outflow velocity time integral, heart rate and LV outflow tract diameter. Cardiac index (CI) was calculated by dividing the CO with the body surface area (BSA).

Long-axis function of the heart was evaluated by measuring the longitudinal velocity of the mitral annulus at the medial and lateral site using 2D-colour coded tissue Doppler imaging (TDI). Off line reconstruction of a myocardial velocity-time curve provided the following parameters: systolic velocity of the lateral (MV S' lateral) and medial (MV S' medial) mitral annulus, early and late diastolic velocity of the mitral annulus at the lateral (resp. MV E' lateral and MV A' lateral) and medial site (resp. MV E' medial and MV A' medial), isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET) (**Figure 1**). LV myocardial performance index or Tei index (MPI-LV)is considered a global index for systolic and diastolic ventricular performance, and calculated using the formula: MPI = ([ICT + IRT] / ET)10 (**Figure 1**). E/E' ratio served as a surrogate for left ventricle end-diastolic pressure (LVEDP)[11-13].

Right ventricular (RV) function:
Tricuspid inflow velocities were obtained by placing the sample volume of the pulsed-waved Doppler at the tips of the tricuspid leaflets in the A4C view. Parameters recorded were peak velocity during early filling phase (TV E), peak velocity during atrial contraction phase (TV A) and the ratio of E to A (TV E/A ratio). Continuous wave Doppler was used to calculate the maximal systolic pressure gradient from the tricuspid regurgitation (TR max PG) using the modified Bernouilli equation[14]. RV systolic function was assessed by measuring the Tricuspid Annular Plane Systolic Excursion of the lateral tricuspid annulus (TAPSE) towards the apex in the A4C view. Color-coded TDI of the tricuspid valve annular velocity was recorded in the A4C view for

offline measurement of systolic (TV S'), early diastolic (TV E') and late diastolic (TV A') tricuspid lateral annular velocities, myocardial acceleration during isovolumic contraction (IVA) and myocardial performance index of the RV (MPI-RV)[10, 15, 16].

Statistics

This study was an explorative study with unknown prior effects of age on TEA induced changes in echocardiographic parameters, making sample size calculations unfeasible. 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 paired student's t-test was used to compare the means of continuous variables before and after TEA. Data are presented as mean (SD) or mean (range). We used the Kolmogorov-Smirnov test for normality. To investigate the relationship between age and echocardiographic variables we used linear regression analysis. Data from linear regression are presented as corresponding regression coefficients for age with 95%- confidence interval and a Pearson's correlation coefficient. P-values less than 0.05 were considered significant. 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).

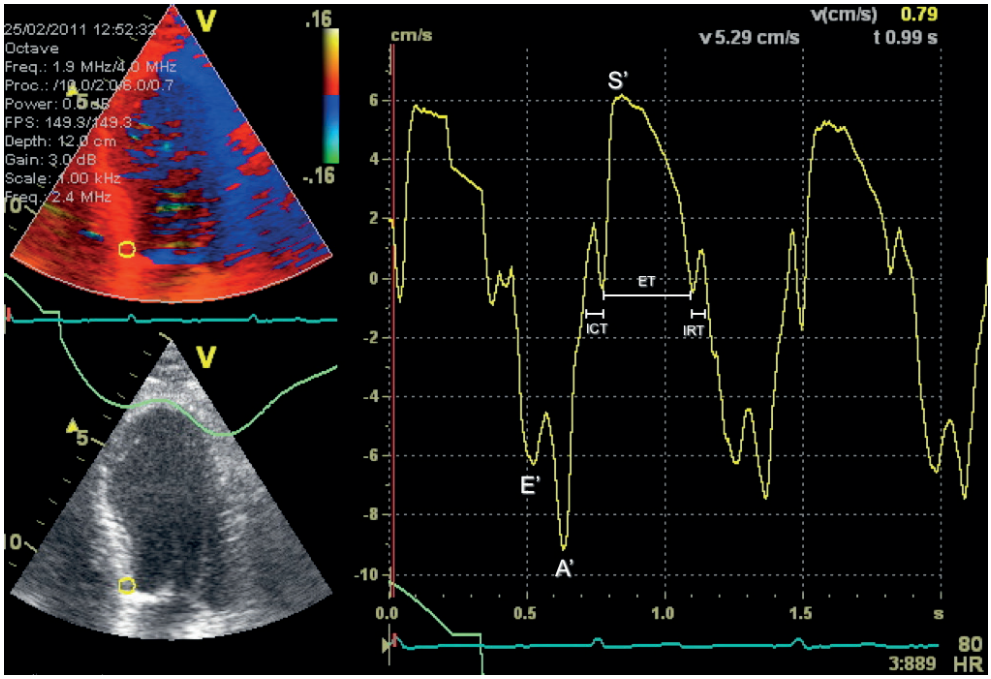

Figure 1. Myocardial velocity-time curve from tissue Doppler recording (TDI) of the medial mitral annulus. MPI is calculated from the time intervals as: MPI = ([ICT + IRT] / ET).

Results

Forty-two patients were asked to participate, of which thirty-five patients gave their written informed consent and were included in this study. Five patients were excluded because either the placement of the epidural catheter technically failed (4 patients) or the rostral border of analgesia only included two (T4-T5) of the thoracic segments innervating the heart (1 patient). All data were normally distributed. Demographic data and characteristics of the groups are presented in **Table 1**. The three groups were comparable according to their height, weight, gender, ASA classification, prevalence of diabetes mellitus (DM), use of antihypertensives and LVPWd. The groups were different with regard to prevalence of hypertension (P=0.02) and use of anti-arrhythmics (P=0.02). Anti-arrhythmics used by patients in this study solely consisted of β-blockers. The group of antihypertensives being used by patients in this study was composed of β-blockers, ACE inhibitors, calcium channel blockers and thiazides.

Table 1. Demographic data and characteristics of patients.

	Group 1 (18-45 years) (*n* = 10)	Group 2 (46-65 years) (*n* = 10)	Group 3 ((≥ 66 years) (*n* = 11)	Total (*n* = 30)
Age (years)	33 (21-43)	57 (47-65)	73 (67-79)	54 (21-79)
Gender (M/F) 6/4 6/4 5/5 17/13	6/4	6/4	5/5	17/13
ASA (I/II/III)	7/3/0	2/7/1	2/6/2	11/16/3
Height (cm)	177 (7)	176(12)	174 (8)	176 (9)
Weight (kg)	71 (13)	85 (17)	74 (11)	77 (15)
Diabetes 0/10 2/8 0/10 2/28	0/10	2/8	0/10	2/28
Hypertension (y/n)*	0/10	2/8	7/3	9/21
Antihypertensives (y/n)	0/10	2/8	4/6	6/24
Anti-arrhythmic (y/n)**	0/10	0/10	5/5	5/25
IVSd (mm)	7.7 (1.9)	9.6 (2.4)	10.6 (2.9)	9.1 (2.6)
LVPWd (mm)	7.9 (2.0)	7.5 (1.6)	8.6 (1.6)	7.9 (1.7)

Data are presented as mean (range), mean (SD) or n. * Overall comparisons,= 12.4; P = 0.002. ** Overall comparisons $\chi 2$ = 12.0; P = 0.002. ASA, American Society of Anesthesiologists' physical status; IVSd, interventricular septum thickness at diastole; LVPWd, left ventricle posterior wall thickness at diastole.

All catheters were placed in the T3-T4 interspace. The mean number of dermatomal segments blocked 30 minutes after epidural injection of 8 ml of ropivacaine 0.75 % was 19.6 (3.5) with a mean cephalad spread to C4 (C2-T1) dermatomal level and a mean caudal spread to L2 (T10-S1) dermatomal level. Thirty minutes after induction of TEA systolic, diastolic and mean arterial blood pressure after 30 minutes decreased in all patients ($P<0.001$) (table 2) and the magnitude of change was similar in all groups. HR only decreased between 0 and 30 minutes and was unchanged 30 minutes after induction of TEA. Bradycardia and/or hypotension occurred in six patients for whom atropine 0.5 mg and ephedrine 5 mg (n=2), 5 mg ephedrine (n=2) and 10 mg ephedrine (n=2) was needed shortly after the injection of ropivacaine. HR and MAP were minimally affected with exclusion of these patients from post-treatment analysis, and therefore these patients were included for analysis. There was a time window of at least 15 minutes between the last administration of vasoactive medication and start of the echocardiographic exam.

Table 2. Haemodynamic and echocardiographic parameters before and 45 min after induction of thoracic epidural anaesthesia

	Group 1 (18-45 years) n=10		Group 2 (46-65 years) n=10		Group3 (≥66 years) n=10		Total n=30	
	Baseline	TEA	Baseline	TEA	Baseline	TEA	Baseline	TEA
Variables of analgesia								
Cephalad border (derma-tome)		C4 (C2-C7)		C4 (C2-T1)		C4 (C2-C8)		C4 (C2-T1)
Caudal border (derma-tome)		L1 (T10-L5)		L4 (T11-S1)		L3 (T12-S1)		L2 (T10-S1)
Maximum number of dermatomes blocked		18.1 (3.3)		20.4 (3.6)		20.3 (3.5)		19.6 (3.5)
Hemodynamic variables								
HR (bpm)	72.7 (9.3)	68.8 (11.7)	73.8 (19.2)	73.6 (14.2)	69.8 (9.4)	68.4 (9.7)	72.1 (13.1)	70.3 (11.8)
SBP (mmHg)	128.9 (14.0)	113.7 (18.4)†	135.3 (21.2)	114.6 (22.8)#	147.8 (24.7)	117.5 (24.6)†	137.3 (21.3)	115.3 (21.4)‡
DBP (mmHg)	66.6 (11.0)	59.2 (8.6)†	66.9 (11.8)	60.2 (9.7)	70.5 (12.1)	57.3 (11.7)#	68.0 (11.4)	58.9 (9.8)‡
MAP (mmHg)	84.4 (15.8)	77.7 (10.6)	91.1 (14.3)	80.5 (14.6)	98.0 (16.3)	79.5 (15.2)†	91.2 (16.0)	79.2 (13.2)‡
LV systolic function								
Ejection Fraction (%)	62.2 (8.8)	62.4 (10.3)	64.0 (6.3)	70.2 (5.5) †	59.9 (7.3)	64.3 (8.2)	62.1 (7.5)	65.6 (8.7) †
MV S' medial (cm sec-1)	6.8 (1.0)	6.9 (1.1)	6.0 (1.1)	6.4 (1.0) †	5.6 (0.8)	6.0 (0.9)	6.1 (1.1)	6.4 (1.0)
MV S' lateral (cm sec-1)	8.9 (1.4)	8.3 (1.4)	6.8 (1.9)	7.0 (2.2)	6.3 (1.7)	6.4 (1.4)	7.3 (2.0)	7.2 (1.8)
Stroke Volume (ml)	79.9 (10.9)	86.0 (19.2)	73.6 (14.6)	84.0 (18.6)#	65.8 (13.5)	77.7 (17.5)#	73.1 (13.9)	82.6 (18.2) †
Cardiac Index (l min-1 m-2)	3.0 (0.6)	3.1 (1.0)	2.6 (0.5)	2.9 (0.6)#	2.4 (0.4)	3.0 (0.7)#	2.7 (0.5)	3.0 (0.8) †
MPI-LV	0.35 (0.07)	0.38 (0.11)	0.42 (0.13)	0.36 (0.08)	0.37 (0.15)	0.37 (0.07)	0.38 (0.12)	0.37 (0.08)
LV diastolic function								
MV E (cm sec-1)	67.5 (16.1)	90.0 (19.8) ‡	58.2 (9.7)	76.8 (14.4) †	54.0 (14.8)	81.3 (13.6) ‡	60.0 (14.7)	82.9 (16.6) ‡
MV DT (ms)	176.9 (40.3)	169.9 (27.1)	200.0 (24.7)	172.9 (22.8)	224.2 (51.4)	199.7 (47.9)	201.2 (44.0)	181.5 (36.5)
MV A (cm sec-1)	53.0 (11.8)	59.4 (8.8)	72.7 (13.2)	75.1 (14.0)	74.0 (17.0)	83.3 (15.0)#	66.3 (16.9)	72.5 (16.1)†
MV E/A ratio	1.4 (0.5)	1.6 (0.5)	0.8 (0.09)	1.0 (0.16) †	0.8 (0.4)	1.0 (0.3)#	1.0 (0.5)	1.2 (0.4) †
MV E' medial (cm sec-1)	9.0 (2.2)	9.6 (1.3)	5.4 (1.0)	6.7 (1.1)#	4.7 (0.8)	5.8 (0.8) ‡	6.4 (2.4)	7.4 (2.0) ‡
MV E' lateral (cm sec-1)	10.5 (2.7)	11.2 (2.4)	6.5 (1.9)	7.8 (1.5)#	5.3 (1.3)	6.5 (1.1) †	7.5 (3.0)	8.5 (2.6) ‡
MV A' medial (cm sec-1)	7.2 (2.0)	6.8 (1.5)	8.7 (2.2)	8.1 (1.9)#	7.6 (1.6)	7.7 (2.0)	7.8 (2.0)	7.5 (1.8)
MV A' lateral (cm sec-1)	6.6 (2.0)	5.7 (1.4)#	8.1 (1.8)	8.6 (2.2)	8.4 (2.3)	8.2 (2.4)	7.7 (2.1)	7.4 (2.4)
MV E/E' medial	7.6 (1.5)	9.7 (1.9)#	11.2 (3.7)	11.9 (4.0)	11.9 (4.3)	13.3 (3.5)	10.2 (3.8)	11.6 (3.5) †
MV E/E' lateral	6.5 (1.1)	8.3 (1.5) †	10.2 (5.5)	10.3 (3.3)	11.7 (4.0)	12.9 (3.6)	9.4 (4.4)	10.5 (3.4)#
LVEDV (ml)	102.8 (17.1)	108.5 (26.7)	103.0 (19.6)	100.0 (17.5)	81.0 (11.0)	93.9 (13.6)	96.4 (18.9)	101.3 (20.7)
RV systolic function								
TAPSE (mm)	21.4 (4.2)	22.2 (3.9)	20.1 (4.5)	22.9 (4.3)#	21.0 (4.8)	25.1 (3.8) ‡	20.7 (4.4)	23.2 (4.1) ‡
TV S' (cm sec-1)	8.8 (1.5)	10.7 (1.2) #	9.5 (2.3)	10.8 (2.1)	9.7 (1.8)	10.7 (1.5)#	9.3 (1.9)	10.7 (1.6) ‡
MPI-RV	0.46 (0.11)	0.37 (0.06) †	0.49 (0.14)	0.43 (0.09)	0.44 (0.12)	0.45 (0.09)	0.46 (0.12)	0.41 (0.08)
IVA (m s-2)	1.7 (0.5)	1.5 (0.7)	2.4 (0.8)	1.9 (0.7)	2.0 (0.27)	1.6 (0.32)#	2.0 (0.6)	1.7 (0.6) †
TR max PG (mmHg)	15.6 (4.3)	19.0 (3.5)	15.6 (5.1)	18.8 (2.8)	23.1 (3.6)	23.1 (6.3)	18.1 (5.4)	20.3 (4.5)#
RV diastolic function								
TV E (cm s-1)	51.2 (8.6)	58.1 (10.7)#	47.8 (4.1)	59.0 (11.2)#	43.2 (16.0)	57.4 (13.3)#	47.2 (11.1)	58.1 (11.4) ‡
TV A (cm s-1)	36.6 (8.4)	41.1 (6.3)	47.9 (17.6)	52.9 (22.3)	40.0 (11.0)	47.4 (13.9)	41.4 (13.3)	47.1 (15.7)#
TV E/A ratio	1.5 (0.5)	1.5 (0.4)	1.1 (0.3)	1.3 (0.5)	1.1 (0.3)	1.2 (0.2)	1.2 (0.4)	1.3 (0.4)
TV E' (cm s-1)	8.9 (1.2)	11.4 (1.4)†	6.9 (1.1)	8.8 (1.1) ‡	6.0 (1.5)	8.4 (2.0) ‡	7.0 (2.1)	9.3 (2.5) ‡
TV A' (cm s-1)	7.9 (2.9)	9.2 (2.1)	11.5 (2.0)	11.2 (3.6)	11.3 (1.9)	12.8 (1.9) ‡	10.2 (2.8)	11.1 (3.0)
TV E/E'	5.9 (1.5)	5.2 (0.8)	7.1 (1.1)	6.9 (1.9)	7.4 (2.3)	7.0 (1.8)	6.8 (1.8)	6.4 (1.8)

Data presented as mean (SD) or mean (range). Difference between baseline values and values 45 min after induction of TEA. HR, heart rate; IVA, isovolumic acceleration; LV, left ventricle; MAP, mean arterial pressure; RV, right ventricle; TAPSE, Tricuspid Annular Plane Systolic Excursion. # P <0.05, † P <0.01, ‡ P <0.001.

Systolic LV function

TEA increased LV EF (P=0.008), SV (P=0.001) and CI (P=0.005). TDI measurements showed no change in MV S' or MPI 45 minutes after induction of TEA (**Table 2**).

Diastolic LV function

MV E (P<0.001), MV A (P=0.005) and E/A ratio (P=0.001) increased significantly 45 minutes after induction of TEA (Table 2). TDI parameters MV E' medial (P<0.001) and MV E' lateral (P<0.001) increased whereas MV A' medial and MV A' lateral (P=0.287) did not change. E/E' RATIO increased. LVEDV remained the same.

RV systolic function

Right ventricular systolic performance measured by TAPSE (P<0.001) and TV S' (P<0.001) showed improvement 45 minutes after induction of TEA while IVA decreased (P=0.002)(**Table 2**). Tricuspid regurgitation pressure gradient (TR max PG), was measurable in only 12 patients and increased from 18.1 ± 5.4 to 20.3 ±4.5 (P=0.042).

RV diastolic function

TEA significantly increased TV E (P<0.001) and TV A (P=0.018), while TV E/A ratio was preserved. Tissue Doppler data showed increases in TV E' (P<0.001) but no changes in TV A' (P=0.094) or TV E/E' (**Table 2**).

Influence of age

There was no effect of age on baseline LV systolic function except for minor decreases in MV S', SV and CI (**Table 3 and 4**). All baseline parameters of LV diastolic function showed a decline with increasing age: MV DT and MV A increased, while MV E decreased. MV E' decreased (0.104 $cm.s^{-1}year^{-1}$; P<0.001; r=-0.79 and 0.13 $cm.s^{-1}year^{-1}$; P<0.001; r=-0.75 for medial and lateral respectively). Finally, MV E/E' increased for the medial (P=0.009) and lateral (P=0.002) wall. LVEDV was not affected by age.

Right ventricular parameters showed an increase in TAPSE with 0.088 mm $year^{-1}$ (P=0.003, R=0.53) but no other changes regarding systolic variables. Diastolic function decreased with advancing age as reflected by a decline in TV E/A ratio (0.1 per 10 years; P=0.021, r=-0.43) and TV E' (0.07 $cm.s^{-1}year^{-1}$, p<0.001) and an increase in TV A' (0.1 $cm.s^{-1}year^{-1}$; P<0.001, r=0.13). There was effect of age on TV E, TV A and TV E/E'.

Except for TAPSE, age did not influence effects of TEA on any echocardiographic parameter (**Table 4**). Linear regression showed that for each additional year, the absolute increase in TAPSE after TEA was 0.09 mm (P=0.003, R=0.53) (**Figure 2**).

Table 3. Correlation between age and baseline echo parameters

	Age coefficient	95%-Confidence Interval	R	P-value
Systolic LV				
Ejection Fraction (%)	0.028	(-0.140 0.196)	0.07	0.736
MV S' medial (cm s^{-1})	-0.022	(-0.044 0.000)	0.37	0.047
MV S' lateral (cm s^{-1})	-0.058	(-0.094 - 0.021)	0.52	0.003
Stroke Volume (ml)	-0.297	(-0.575 - 0.019)	0.38	0.037
Cardiac Index (l $min^{-1}m^{-2}$)	-0.013	(-0.024 - 0.002)	0.44	0.018
MPI-LV	0.000	(-0.003 0.003)	0.04	0.847
Diastolic LV				
IVSd (mm)	0.08	(0.03 0.13)	0.53	0.004
LVPWd (mm)	0.02	(-0.02 0.06)	0.18	0.383
MV E (cm s^{-1})	-0.353	(-0.639 -0.068)	0.44	0.017
MV DT (ms)	1.236	(0.391 2.081)	0.51	0.006
MV A (cm s^{-1})	0.501	(0.194 0.809)	0.54	0.002
MV E/A	-0.014	(-0.022 -0.005)	0.55	0.002
MV E' medial (cm s^{-1})	-0.104	(-0.137 -0.072)	0.79	<0.001
MV E' lateral (cm s^{-1})	-0.13	(-0.17 -0.082)	0.75	<0.001
MV A' medial (cm s^{-1})	0.023	(-0.019 0.066)	0.21	0.271
MV A' lateral (cm s^{-1})	0.054	(0.012 0.095)	0.46	0.013
MV E/E' medial	0.099	(0.027 0.171)	0.48	0.009
MV E/E' lateral	0.116	(0.032 0.200)	0.54	0.009
LVEDV (ml)	-0.345	(-0.746 0.056)	0.33	0.089
Systolic RV				
TAPSE (mm)	0.000	(-0.010 0.090)	0.00	0.98
TV S' (cm/s)	0.021	(-0.021 0.060)	0.20	0.296
IVA (ms-2)	0.007	(-0.008 0.022)	0.21	0.348
MPI-RV	-0.001	(-0.003 0.002)	0.02	0.644
Diastolic RV				
TV E (cm s^{-1})	-0.195	(-0.425 0.034)	0.32	0.092
TV A (cm s^{-1})	0.093	(-0.195 0.381)	0.13	0.513
TV E/A	-0.010	(-0.018 0.002)	0.43	0.021
TV E' (cm s^{-1})	-0.070	(-0.097 0.043)	0.71	<0.001
TV A' (cm s^{-1})	0.098	(0.050 0.146)	0.62	<0.001
TV E/E'	0.000	(0.000 0.001)	0.35	0.070

Data are presented as regression coefficient for age, 95% CI and Pearson's correlation. CI, confidence interval; IVA, isovolumic acceleration; RV, right ventricle; TAPSE, Tricuspid Annular Plane Systolic Excursion.

Discussion

Our data show that TEA increases global hemodynamic performance but has limited effect on Doppler- derived indices of biventricular systolic function. Indicators of diastolic performance showed a modest improvement for both the left and right ventricle after TEA although these changes could have been affected by the mildly elevated preload. Indeed, we used preventive volume loading during TEA, to account for expected reductions in preload, as this is usual clinical practice in order to avoid severe hypotension.

The increase in E/E' ratio, which has been shown in cardiology patients to correspond to increased LV filling pressures[11-13], and the tendency for LVEDV to increase as well, suggest that the amount of colloids administered before TEA was large enough to produce a mild rise in preload. This condition, combined with the documented systemic vasodilatory effects of TEA may largely explain the observed increase in cardiac output present in all age groups studied. Previous reports have shown a decrease in cardiac output with TEA when mild volume loading had no effect on preload[17]. Differences in study design, loading conditions, echo parameters used and patient population all may contribute to these discrepancies.

Tissue Doppler measurements of mitral annular peak velocity are generally considered to be load independent parameters of diastolic function in patients with reduced LV function but are load dependent in hearts with normal function[18]. It therefore appears that the observed increase in mitral and tricuspid annular velocity after TEA combined with volume loading in our study does not necessarily indicate an improvement in diastolic performance but may at least partially be explained by the mild concomitant increase in preload. In any case, these changes are not consistent with, and even directionally opposite to those expected to occur with a deterioration of diastolic function after TEA.

Table 4. Correlation between age and change of echo values 45 minutes after induction of TEA

	Age coefficient	95 % Confidence Interval	R	P-value
Diastolic LV				
MV E (cm s-1)	0.071	(-0.184 0.326)	0.11	0.573
MV DT (ms)	-0.534	(-1.662 0.593)	0.19	0.339
MV A (cm s-1)	0.084	(-0.150 0.318)	0.14	0.467
MV E/A	-0.001	(-0.008 0.005)	0.07	0.733
MV E' medial (cm s-1)	0.014	(-0.0130.041)	0.20	0.289
MV E' lateral (cm s-1)	0.010	(-0.0150.036)	0.16	0.398
MV A' medial (cm s-1)	0.006	(-0.0150.026)	0.11	0.581
MV A' lateral (cm s-1)	0.014	(-0.014 0.041)	0.19	0.324
MV E/E' medial	-0.015	(-0.071 0.042)	0.10	0.600
MV E/E' lateral	-0.014	(-0.073 0.044)	0.10	0.616
LVEDV (ml)	0.182	(-0.217 0.581)	0.19	0.356
Systolic LV				
Ejection Fraction (%)	0.074	(-0.063 0.210)	0.22	0.277
MV S' medial (cm s-1)	0.005	(-0.014 0.025)	0.11	0.566
MV S' lateral (cm s-1)	0.012	(-0.014 0.038)	0.172	0.363
Stroke Volume (ml)	0.088	(-0.2060.382)	0.12	0.544
Cardiac Index (l min -1 m2 -1)	0.006	(-0.0080.020)	0.17	0.388
MPI-LV	-0.001	(-0.004 0.002)	0.15	0.478
Diastolic RV				
TV E (cm s-1)	0.106	(-0.185 0.396)	0.15	0.461
TV A (cm s-1)	0.032	(-0.231 0.295)	0.05	0.802
TV E/A	0.004	(-0.004 0.012)	0.21	0.275
TV E' (cm s-1)	0.001	(-0.030 0.031)	0.01	0.963
TV A' (cm s-1)	-0.013	(-0.071 0.044)	0.09	0.640
TV E/E'	0.004	(-0.036 0.044)	0.04	0.850
Systolic RV				
TAPSE (mm)	0.088	(0.033 0.142)	0.53	0.003
TV S' (cm s-1)	-0.017	(-0.056 0.023)	0.16	0.401
IVA (m/s2)	-0.003	(-0.013 0.008)	0.11	0.610
MPI-RV	0.002	(-0.001 0.005)	0.30	0.159

Data are presented as regression coefficient for age, 95% CI and Pearson's correlation. CI, confidence interval; IVA, isovolumic acceleration; RV, right ventricle; TAPSE, Tricuspid Annular Plane Systolic Excursion.

The effect of age, however, on baseline diastolic performance was unambiguous and consistent with previous publications in cardiology, showing significant decreases in biventricular E', increases in LV E/E' and typical changes in transmitral and transtricuspid flow patterns[19-24]. Most importantly, regardless of baseline function and age, the effects of TEA were similar in all ages. Consequently these data allow us to reject the primary hypothesis and major concern, i.e. that TEA has unfavorable effects in the elderly population because of the age-associated impairment in baseline diastolic performance. In fact we found no influence of age on TEA effects for any of the variables studied with one possible exception for TAPSE. TAPSE is a standard performance indicator for RV ejection and has been widely used to assess RV function in a wide range of pathophysiological conditions. TEA caused increases in TAPSE in all patients but regression analysis showed that the magnitude of change was larger in elderly then in younger patients.

To our knowledge, this is the first study in humans to assess the effects of TEA on RV systolic and diastolic function. Animal studies using invasive measurement techniques to measure contractile performance have found no significant effects of TEA on baseline RV inotropic state[25]. Since TAPSE is a load-dependent ejection index of RV function, the observed increase could be due to either an increase in contractile performance, and/or an increase in RV preload as well as a reduction in RV afterload. Estimated RV systolic pressures, a surrogate for RV afterload slightly increased after TEA in our study while Doppler indices of systolic function were inconclusive. Whereas tricuspid S' increased, IVA which has been proposed as a load-independent index of contractility decreased. Hence, the only possible explanation for the observed increase in TAPSE is the slight increase in preload, induced by the concomitant volume load, and the increased cardiac output secondary to the reduction in LV afterload. It is important to note that some authors have shown IVA to decrease with increased preload[26], a finding that would further support our explanation. However, we have no explanation for the age-related improvement of TAPSE after TEA. Perhaps discrete differences in the effects of volume loading on preload in the elderly could be invoked but further studies are required to address this.

There was a decrease in MAP but not in HR in all patients 30 minutes after induction of TEA. The average decrease in MAP was less than 20% in all age groups. Although the prevalence of pre-existing hypertension was higher and the use of β-blockers was more frequent in the older age group, the decreases in MAP and HR 30 minutes after induction of TEA were not different between the age groups.

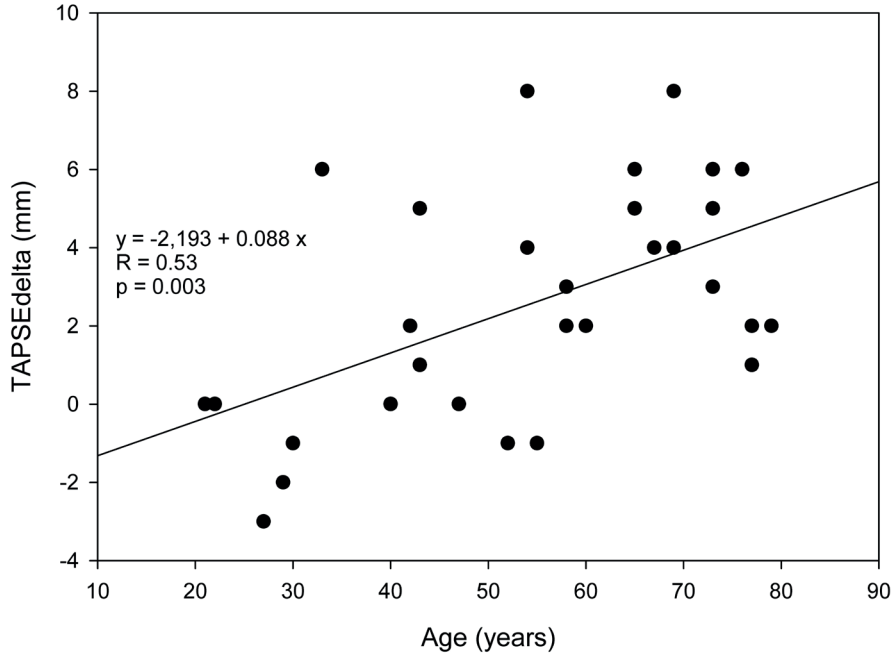

Figure 2. Correlation between delta TAPSE 45 minutes after induction of TEA and age TAPSE, tricuspid annular plane systolic excursion.

Increasing age had no effect on the total amount of spinal segments blocked after TEA with a fixed dose of ropivacaine at the T3-T4 interspace[8].

Discrepancies exist between our study and epidural studies that have evaluated the decrease in MAP and HR in patients following epidural administration of local anesthetic agents. Both with TEA[27] and lumbar epidural anesthesia (LEA)[28] the decrease in MAP and HR was more pronounced in the elderly patients.
Greater extension of the block in the elderly, the type and dose of local anesthetics, preloading, intensity of neural blockade and study design may all have contributed to these age related hemodynamic changes.

Limitations of the study:

Firstly, the analgesic spread after TEA was extensive and certainly not confined to selective blockade of the cardiac sympathetic fibers. To our knowledge there are no data on the spread of analgesic blockade after an epidural loading dose at the T3-T4 level. We aimed for analgesic blockade adequate for lung surgery using a bolus of ropivacaine according to clinical routine. This resulted in an unexpected high amount of blocked spinal segments. Consequently changes in echocardiographic variables might not solely be attributed to sympathicolysis of the cardiac sympathetic fibers, but also to changes in pre- and afterload because of vascular sympathicolysis.

In order to maintain preload and to prevent severe hypotension after TEA we used a high volume load with hydroxyethyl starch (HES) as part of clinical routine and clinical experience[9]. This volume load, despite extensive analgesic blockade, resulted in mildly elevated preload, though LVEDV was not changed.

Six patients needed atropine and/or ephedrine for treatment of hypotension, possibly influencing measurements. In our study population HR before TEA and 30 minutes after TEA was similar. With a time window of at least 15 minutes between the last administration of vasoactive drugs and start of the echocardiographic exam, a substantial influence of this medication on echocardiographic measurements seems unlikely.

Five patients were using anti-arrhythmic drugs (all B-blockers) and six patients were using antihypertensives, possibly influencing hemodynamic parameters. Besides having more difficulties in the inclusion of older patients, excluding older patients using anti-arrhythmic drugs or antihypertensives might introduce selection bias, as stated in the methods section. Moreover, excluding these patients from analysis did not result in significant changes in TEA effects on MAP, HR and echocardiographic indices.

The time point of dermatomal testing (30 min) and that of the echo examination (45 min) varied. The time period of 30 minutes for measurement of neural blockade was based on TEA [27] and LEA[28] studies showing maximal dermatomal spread to occur within 20-30 minutes. According to fig. 2 in our previous article[8], the spread of neural blockade had not yet stopped at 30 min. Consequently the extension of neural blockade might have been larger at the start of the echocardiographic exam at 45 minutes. However we think the progression of neural blockade after 30 minutes most likely was minimal, making the 30 minute values in this study acceptable.

Finally, the echocardiographic variables used in this study all are sensitive to changes in preload and afterload. However, TDI is a sensitive and relatively load-independent[29, 30] method in assessing systolic function and diastolic relaxation[31]. Furthermore, it is non-invasive and equivalent for invasive diastology in cardiology[12, 13] which renders it the current gold standard method for clinical studies.

In conclusion, our data show that TEA is associated with beneficial circulatory effects which are not modified by ageing. Biventricular systolic and diastolic function remain intact and overall cardiovascular performance improves after TEA when volume substitution is used to stabilize preload. The age-related deterioration of diastolic function has not detrimental effects on the hemodynamic response to TEA in elderly patients.

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Chapter
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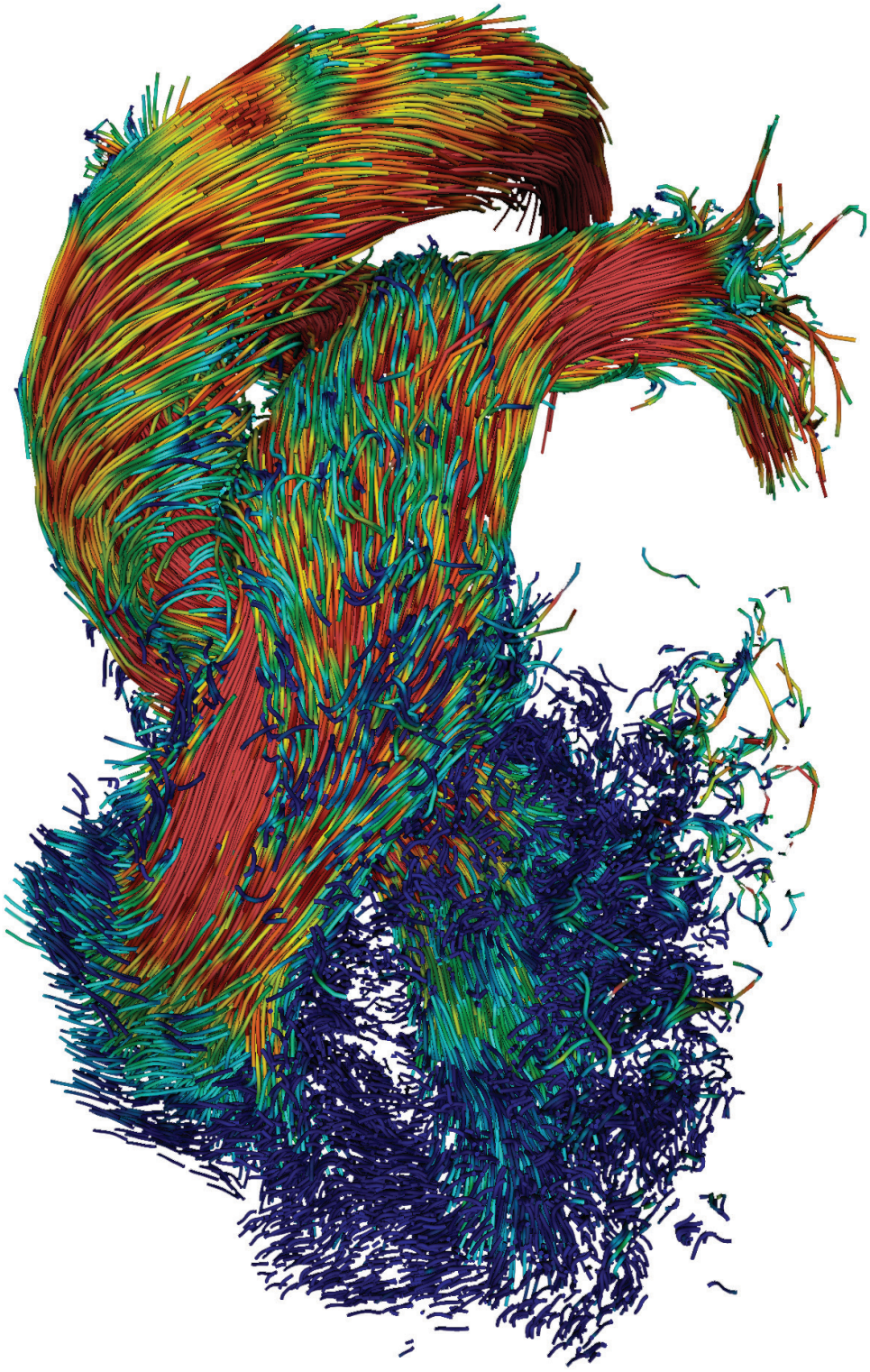

Section IV

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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Circulation. 2016;134:1163–1175

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: $ES = (\mu 1 - \mu 0)/\sigma$) 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).

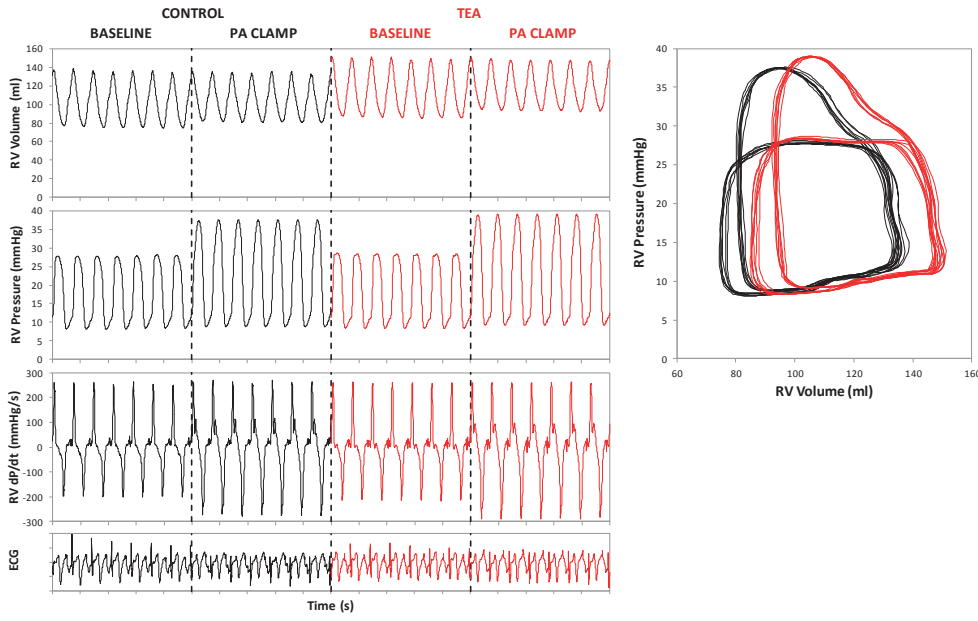

Figure 1. Representative (patient #4) pressure-volume signals obtained during 5 s in all 4 conditions.
The control conditions (baseline and pulmonary artery [PA] clamping) are shown in black, corresponding TEA conditions in red. Right ventricular (RV) volume, pressure, dP/dt, and ECG were recorded from 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**).

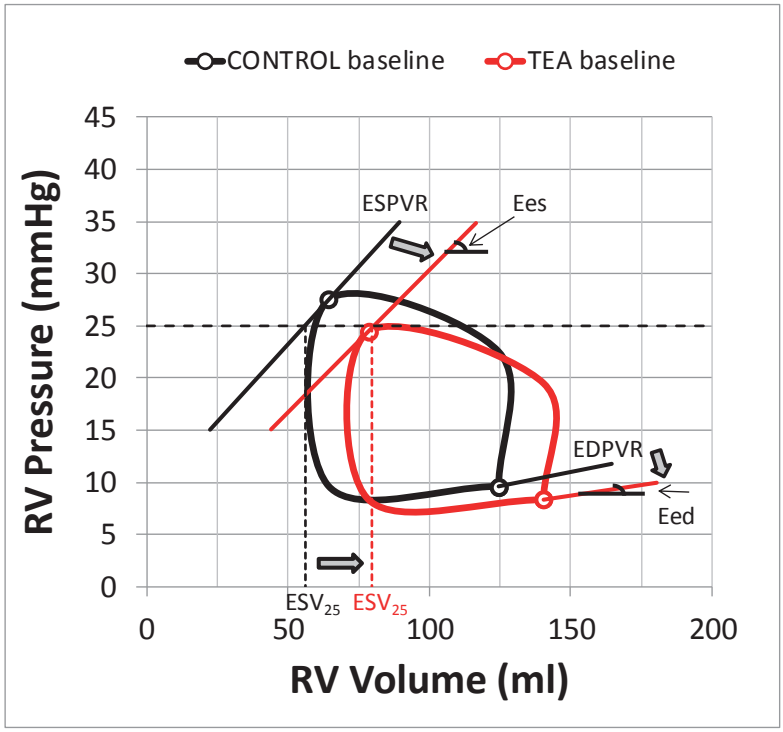

Figure 2. Schematic RV pressure-volume loops based on mean end-diastolic and end-systolic pressures and volumes at baseline (black loop) and after induction of TEA (red loop). The increase in ESV25 and the rightward shift and shallower slope of the ESPVR after TEA indicate a decreased contractile performance. 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.

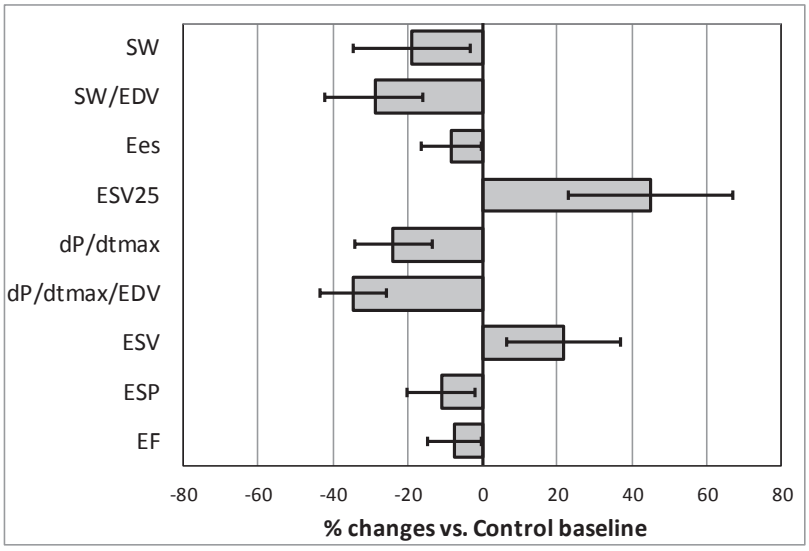

Figure 3. TEA effects on RV systolic function indices presented as % changes versus control baseline. Error bars indicate the 95% confidence interval (CI). All effects were statistically significant (**see Table 2**), indicating decreased systolic RV function after TEA. dP/dtmax indicates peak rate of 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 inter-action 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.

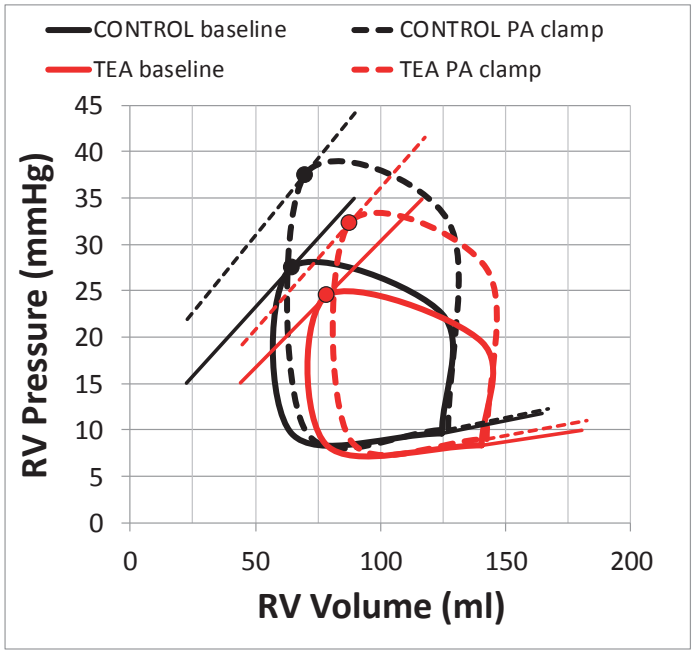

Figure 4. Schematic RV pressure-volume loops based on mean end-diastolic and end-systolic pressures and volumes. Black loops represent the control conditions, solid at baseline and dashed during PA clamp. The red loops represent the same conditions during TEA. The figure illustrates that homeometric 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 anaesthestics, 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

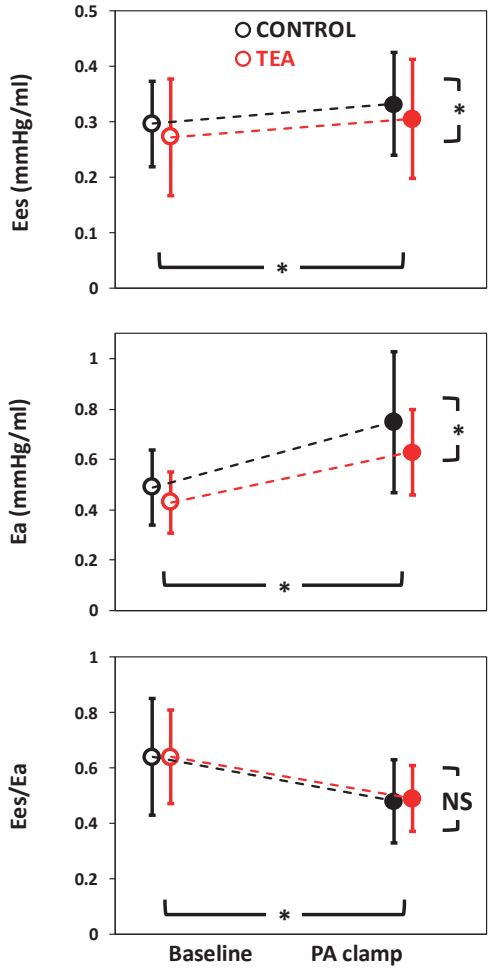

Figure 5. The effects of TEA and PA clamp on Ees, Ea and Ees/Ea . Black symbols indicate the control condition, red symbols TEA. The PA clamp effects (horizontal brackets) were significant for all three parameters, the TEA effects (vertical brackets) were significant for Ees and for Ea, but not for Ees/Ea. 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.

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Chapter 8

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

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Submitted

Introduction

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

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

Methods

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

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

Study design

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

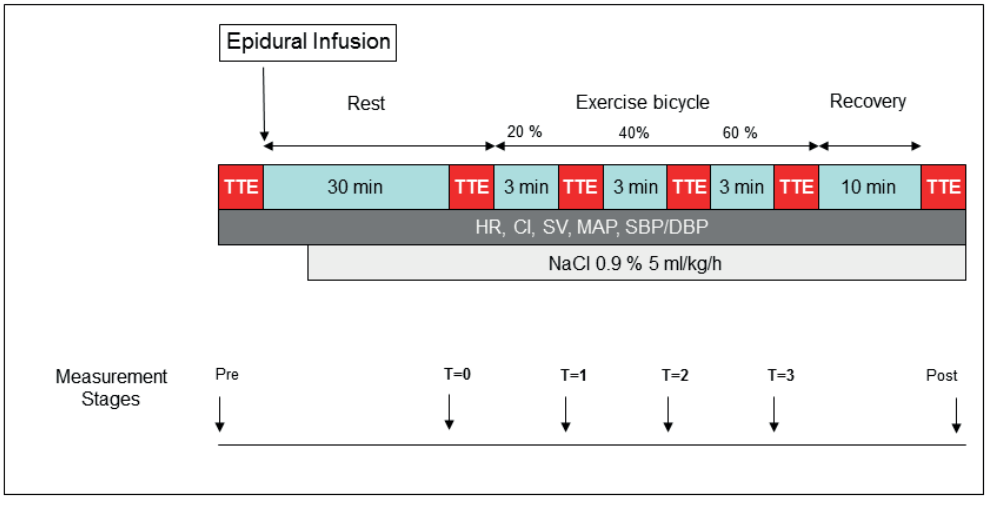


Figure 1. Measurement protocol executed during both test periods (Control and TEA). Hemodynamic and echocardiographic measurements were performed during different measurement stages: Pre (pre-study), immediately before epidural injection of ropivacaine 0.75%/ NaCl 0.9%; T0, 30 minutes after epidural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

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

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

Premedication and preparations

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

Monitoring and general hemodynamics

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

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

Thoracic epidural procedure

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

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

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

Treatment schedule

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

Assessments of analgesia

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

Echocardiography

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

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

Left Ventricular (LV) function:

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

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

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

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

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

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

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

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

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

Results

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

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

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

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

Conditions

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

Measurements

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

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

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

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

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

General hemodynamics (Table 2 and Figure 2)

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

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

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

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

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

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

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

Systolic LV function

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

There were no significant interaction effects between TEA and exercise.

Diastolic LV function

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

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

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

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

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

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

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

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

Systolic RV function

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

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

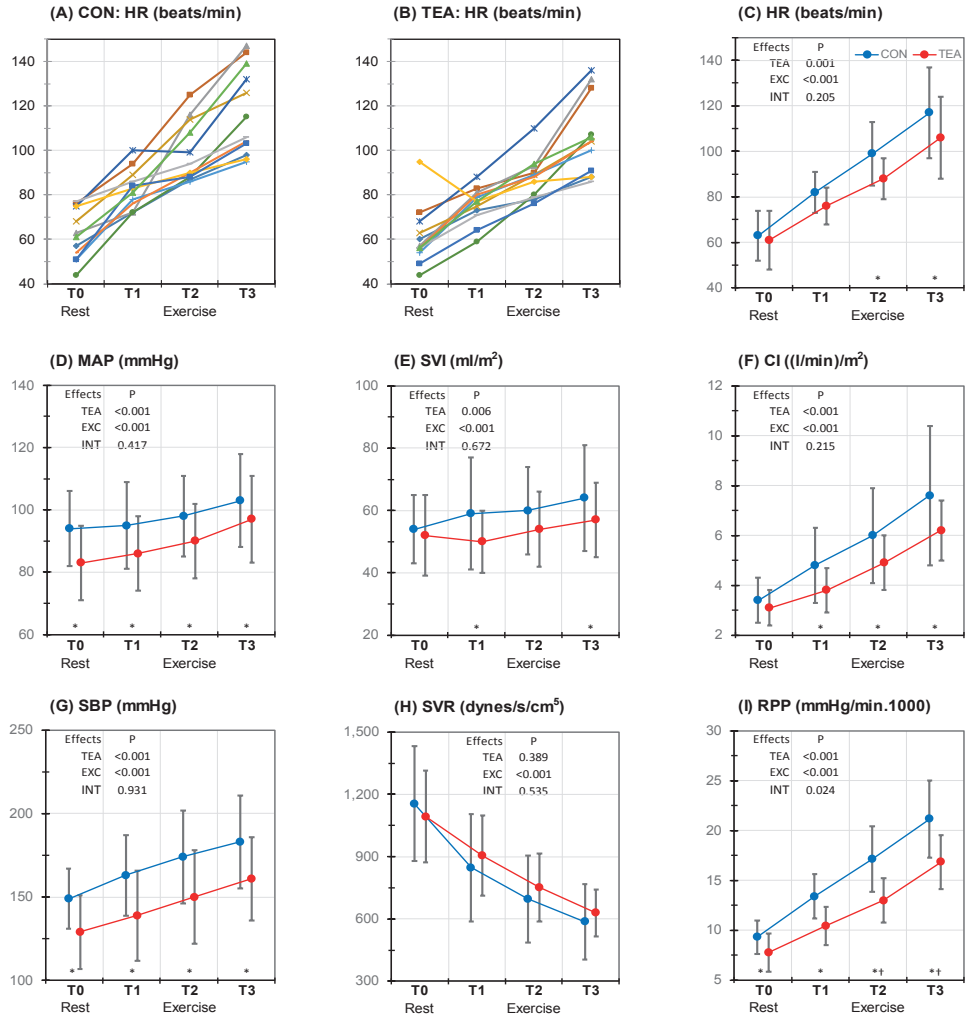
Data suggested an interaction TEA-Exercise effect for TV S', with the effect of TEA being larger at higher levels of exercise. However, after correcting for multiple testing significance was lost (P=0.086).

Diastolic RV function

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

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

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



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

Discussion

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

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

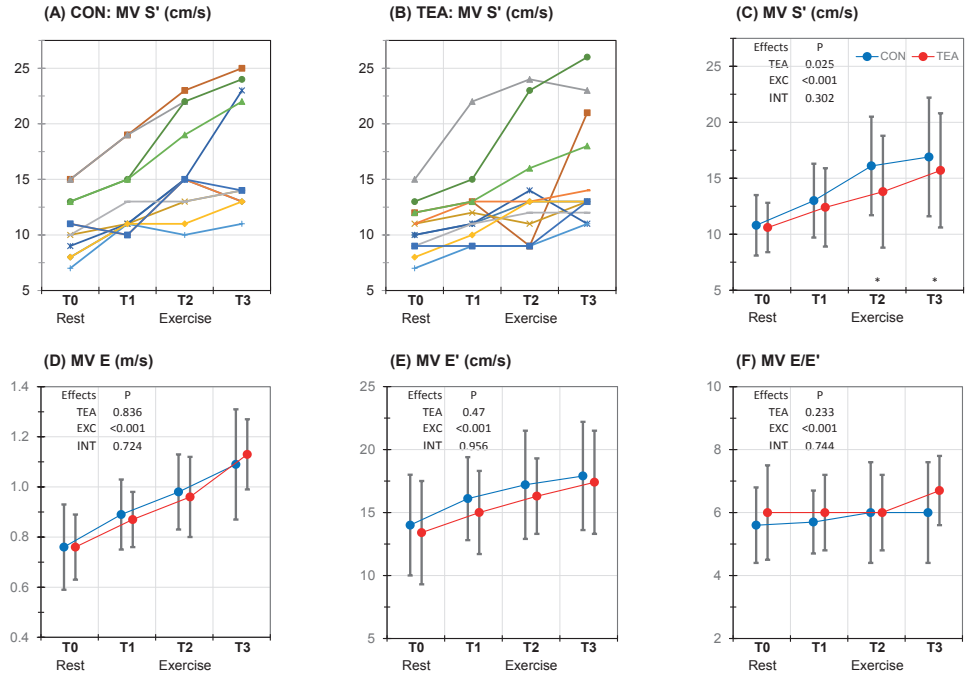


Figure 3. Individual and mean (SD) echocardiographic values for left ventricular function at different measurement stages (Measurement Stages, see Figure 1).

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

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

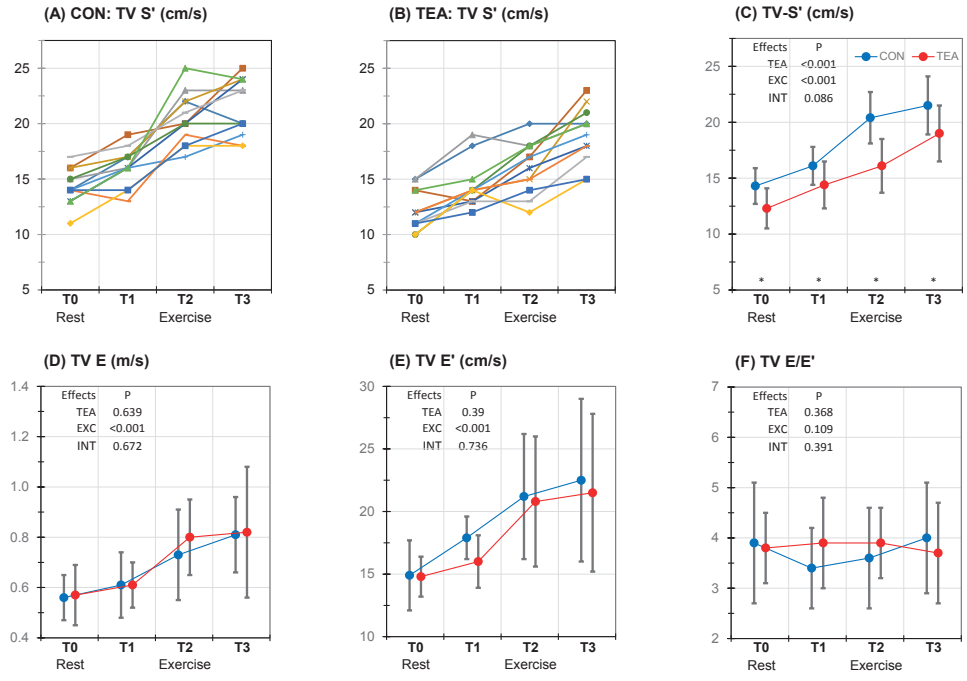


Figure 4. Individual and mean (SD) echocardiographic values for right ventricular function at different measurement stages (Measurement Stages, see Figure 1).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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

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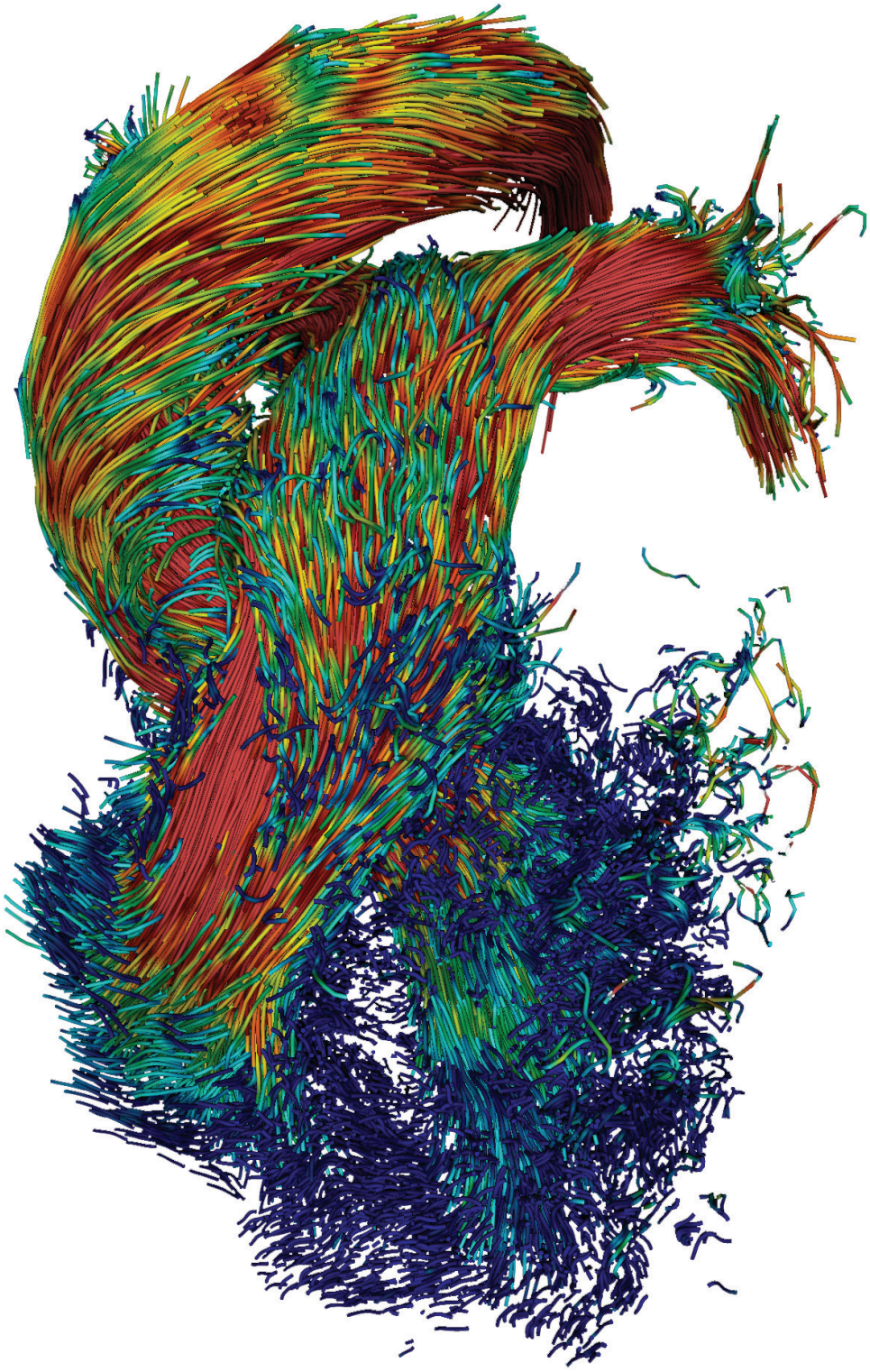

Section V

Conclusions

Chapter 9

Conclusion and perspectives

Conclusions and perspectives

General introduction

The main objective of the investigations described in this thesis was to determine the circulatory and cardiac effects of thoracic epidural anaesthesia (TEA) at rest and during circumstances of increased sympathetic tone. Epidural administration of a local anaesthestic results in blockade of sensory and motor nerve fibers but also in blockade of preganglionic sympathetic fibers (**Chapter 1**). Blockade of the preganglionic sympathetic nerves in the high-thoracic region (T1-T5) may result in a decreased chronotropic, inotropic, lusitropic and dromotropic state of the heart and is associated with minimal vasodilatory effects[1, 2].

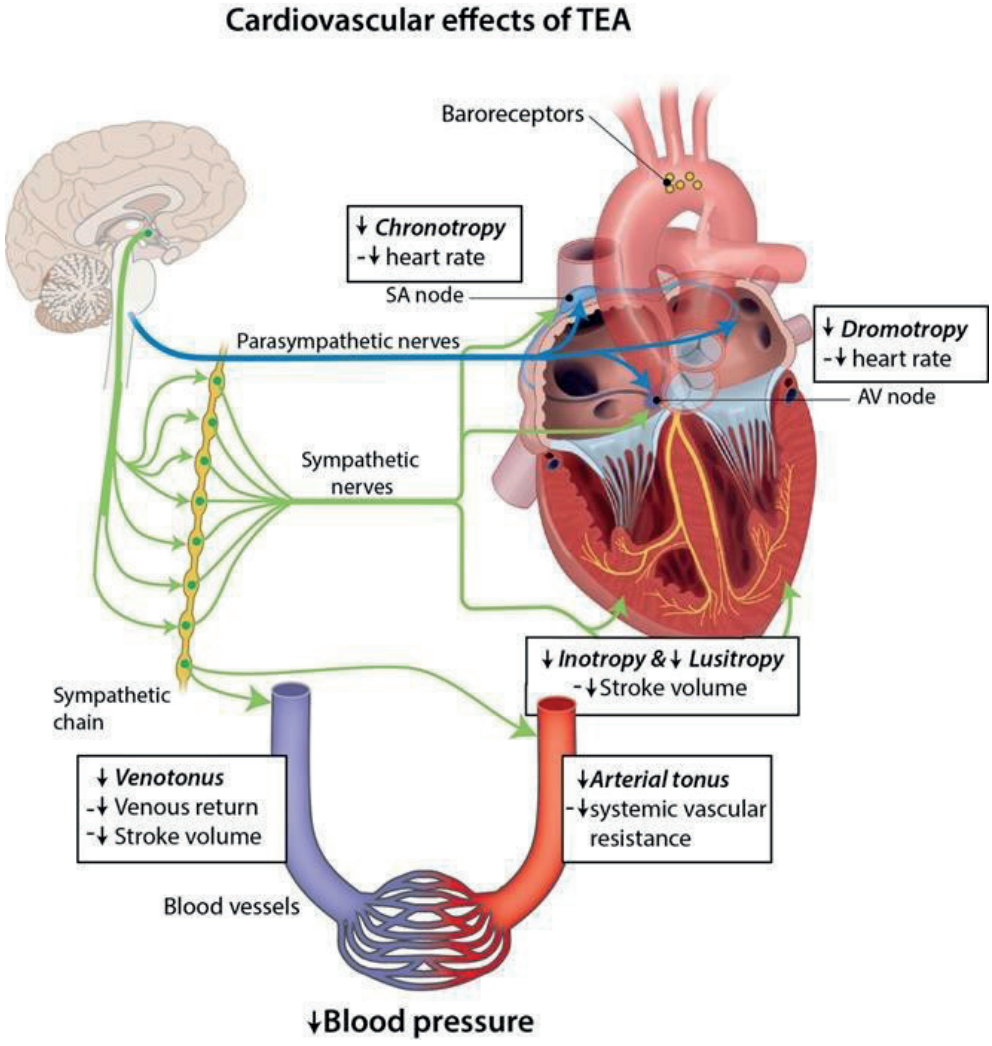

Figure 1. Cardiovascular effects of sympathetic blockade by thoracic epidural anaesthesia (TEA).

TEA with blockade of the low thoracic region (T6-L1) results in a "peripheral" sympathetic blockade with decreased vasomotor tone of the arterial and venous vascular beds, decrease in systemic vascular resistance, increase of the venous capacitance, redistribution of blood to the dilated splanchnic venous bed and a decrease of preload to the heart[3]. The splanchnic veins are predominantly responsible for the total systemic reflex capacitance changes contributing for the almost entirely reflex venoconstriction that buffers the systemic circulatory volume changes[4].

TEA induced changes in vessel tone and depression of cardiac function result in decreases in CO and afterload, finally leading to reductions in blood pressures (**Figure 1**). The size-effects of the hemodynamic changes after induction of TEA depend on the degree of sympathetic tone and functional cardiovascular status of the patient prior to blockade as well on the extension of neural blockade. Structural and functional changes in anatomy and physiology may also influence the cardiovascular effects of TEA in the elderly (**Chapter 1, Figure 3**). Knowledge of these age-related effects is essential in choosing an optimal anesthetic regime in the elderly. From a clinical point of view it is important to assess whether age influences quality of neural blockade and the associated cardiovascular response to high TEA.

Anatomy and Physiology

Anatomy

In **Chapter 3** we reviewed studies on human anatomy of cardiac sympathetic innervation. We described cardiac sympathetic innervation from the level of the brain to the heart as an end-organ as well as embryogenesis of the cardiac autonomic nervous system. Increases in sympathetic tone have been ascribed an important role in the genesis of cardiac arrhythmias and heart failure. Cardiac sympathetic blockade is applied as a novel therapeutic approach for arrhythmias and heart failure. TEA may also induce cardiac sympathetic blockade. Targeted cardiac sympathetic blockade (T1-T5) requires precise knowledge of the spatial location and distribution of cardiac autonomic nerves at the spinal level. However, there is no consensus on this subject.

In contrast to the widespread belief that preganglionic sympathetic cardiac neurons originate solely from thoracic spinal segments T1-T5, there is ample evidence indicating that both cervical spinal segments and thoracic spinal segments below T5 are also involved. This would imply that complete blockade of cardiac sympathetic innervation by high TEA requires cranial and caudal extension of analgesic blockade beyond T1-T5. Preganglionic sympathetic neurons from spinal levels T6 and T7 (or even more caudal segments) may be involved in cardiac sympathetic innervation. Therefore involvement of sympathetic cardiac segments in neural blockade certainly includes high TEA but may also apply to mid-thoracic epidural analgesia, often used in abdominal surgical procedures, with cranial spread of anesthetic blockade.
Similarly, the ganglionic origin of cardiac nerves at the level of the sympathetic trunk and the role

of cervical ganglia other than the stellate ganglion in the transmission of cardiac sympathetic signals are subject to debate. This information might be relevant to procedures targeting for neuronal modulation of cardiac sympathetic innervation, such as stellate ganglion and paravertebral blockade. In addition, inter- individual and intra-individual variety (asymmetry in left to right sympathetic innervation) in the anatomy of cardiac autonomic innervation was demonstrated. Finally, there is no agreement on the precise composition of cardiac nerves at the level of the heart and the contribution of the vagal nerve to autonomic innervation of the ventricles in humans necessitating further investigation.

Physiology

In **Chapter 4** literature was reviewed to identify studies in which cardiovascular effects of TEA were discussed and cardiac sympathetic nerves (T1-T5) were involved in neural blockade by TEA. The beneficial hemodynamic effects and cardioprotective properties of TEA, demonstrated in a number of experimental studies, did not translate in better cardiac outcome for patients treated with TEA undergoing cardiac surgery[5]. More recent exploratory studies even suggested that TEA was associated with increased cardiovascular problems in high risk patients[6, 7]. Mechanisms underlying such a potential harmful effect and characteristics of high risk populations remain speculative however.

Recent animal[8, 9] and clinical[10] studies have added information on the complex interaction between TEA- induced sympatholysis and cardiovascular homeostasis. Using more advanced methodology it was demonstrated that cardiac sympathetic blockade by high TEA reduces LV as well as RV contractility. This direct effect of TEA is well tolerated in healthy subjects because concomitant arteriolar vasodilation and the subsequent decrease in LV afterload facilitate cardiac ejection. Hence overall pump performance and cardiac output are preserved provided that alterations in preload are accounted for. Such a compensatory decrease in afterload however does not occur in the pulmonary circulation and a direct reduction of RV inotropic state can have more impact on pump performance. It would be prudent to consider this potential effect of cardiac sympathectomy with high TEA on RV contractile reserve in patients with preexisting or pending RV dysfunction and pulmonary hypertension. For patients at risk for RV failure or for those being treated with TEA who develop sudden RV failure in the postoperative period, potent alternative analgesic techniques such as paravertebral blocks could also provide a solution.

Central neural blockade

Effect of age on neural blockade and cardiovascular parameters

In **Chapter 5** we examined the effect of age on quality of neural blockade and cardiovascular parameters. Increasing age affecting the hemodynamic response to epidural anaesthesia has been demonstrated in spinal and lumbar epidural anaesthesia[11], but data on TEA are scarce. A previous study documented segmental dose reduction with increasing age after TEA[12]. We

hypothesized that after a fixed loading dose of ropivacaine at the T3-T4 level, increasing age would result in more extended analgesic spread. In addition other aspects of neural blockade and hemodynamic changes were studied.

We included thirty-five lung surgery patients in three age groups (young age group: 18-45 years, middle age group: 46-65, older age group: 66 years and older). Thirty-one patients received an epidural catheter at the T3-T4 interspace followed by injection of 8 mL ropivacaine 0.75%. Analgesia was assessed with pinprick and temperature discrimination. Motor block was tested using the Bromage and ESSAM score. An arterial line was inserted for invasive measurement of blood pressure, cardiac index and stroke volume.

There was no influence of age on quality of TEA except for the caudal border of analgesia being somewhat lower in the middle -and older age group compared to the young age group. 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. We were unable to demonstrate an effect of age on the maximal number of spinal segments blocked after TEA, however the caudad spread of analgesia increased with advancing age. In addition maximal reduction in heart rate after TEA was more extensive in the young age group compared to the other age groups. There was no significant effect of age on other cardiovascular parameters. In conclusion, we were not able to confirm our hypothesis that age influences the total amount of segments blocked after TEA.

Effect of age on the cardiac response to TEA

In **Chapter 6** the effects of TEA on echocardiographic parameters of left and right ventricular systolic and diastolic function were assessed. Sympathetic blockade by high thoracic epidural anaesthesia TEA results in circulatory changes and may directly alter cardiac function. Aging is associated with an impairment of autonomic nervous system control and a deterioration of diastolic performance. We postulated that hemodynamic changes induced by TEA, could vary with age. Thirty five patients scheduled for lung surgery and TEA were stratified into three age groups (G1: 18-45y; G2: 46-65y; G3: ≥ 66 y). Cardiac performance was evaluated in awake patients immediately before and 45 minutes after institution of TEA using Trans Thoracic Echocardiography (TTE). Volume loading was used to stabilize preload. Tissue Doppler Imaging (TDI) and other echo-derived indices were used to quantify biventricular systolic and diastolic function. Baseline systolic and diastolic left ventricular (LV) function and right ventricular (RV) diastolic function decreased with age. 45 minutes after TEA mean arterial pressure decreased (91.2 versus 79.2 mmHg, P<0.001) and cardiac index increased (2.7 versus 3.0 l min^{-1} m^{-2}, P=0.005), while heart rate and Doppler-derived indices of LV contractility remained unchanged. RV ejection indices increased and TDI- derived measures of diastolic performance increased for the LV as well as the RV. Except for Tricuspid Annular Plane Systolic Excursion (TAPSE), that increased with increasing age (R=0.53, P=0.003), TEA effects on biventricular function were

not influenced by age. Our results contrast with previous lumbar and thoracic epidural studies that showed more pronounced hemodynamic changes induced by epidural anaesthesia in the elderly[11, 13]. Use of volume loading may have masked the effects of age on the cardiovascular response to TEA. In addition, the amount of spinal segments blocked following TEA was similar in all age groups in our study, which also may be responsible for the contrasting results. Regardless the effects of age, our data demonstrate that when preload is preserved with volume loading, TEA predominantly causes systemic vasodilatation and increases global hemodynamic performance. Indices of LV systolic function do not change while LV and RV diastolic function appears to improve. TEA effects on RV systolic function are inconclusive. While increasing age causes a consistent decline of baseline diastolic function, the cardiovascular response to TEA is not impaired in the elderly group we studied.

Thoracic epidural anaesthesia: effects on cardiac performance during stress

In **Chapter 7 and 8** the effects of TEA during elevated sympathetic tone are reported. Different experimental models were used to mimic conditions of stress and elevated sympathetic tone encountered in the perioperative period. In **Chapter 7** we assessed TEA effects on right ventricular (RV) function during baseline and during periods of acutely increased RV afterload. The aim of this study was to test whether TEA either affects RV function or right ventricular pulmonary arterial (RV-PA) coupling. RV-PA coupling describes the phenomenon of enhanced RV systolic function as a response to increased afterload. This way RV-PA coupling enables the right ventricle to maintain stroke volume without having to involve the Frank-Starling mechanism[14]. In 10 patients under general anesthesia right ventricular function and its response to increased afterload, induced by temporary, unilateral clamping of the pulmonary artery, was tested before and after induction of TEA. RV function was assessed by invasive pressure-volume loop analysis using combined pressure-conductance catheters. Pressure-volume loop analysis allows for the quantification of ventricular contractility independent of loading conditions. Systolic RV function was quantified by the slope (Ees) and the volume intercept at 25 mmHg (ESV_{25}) of the end-systolic pressure-volume relations. Diastolic RV function was quantified by the slope (stiffness, Eed) and intercept at 7 mmHg (EDV^{7}) of the end-diastolic pressure-volume relations.

Patients were paced at constant heart rate to allow a more accurate assessment of ventricular contractility. TEA resulted in a significant decrease in right ventricular contractility (ΔESV^{25}:+25.5 ml, p=0.0003; ΔEes: -0.025 mmHg/ml, p=0.04). Stroke work, dP/dtMAX and ejection fraction showed a similar decrease in systolic function (all $p<0.05$). A concomitant decrease in effective arterial elastance (ΔEa:-0.094 mmHg/ml, p=0.004), which is an indicator of RV afterload, yielded unchanged ventricular- pulmonary coupling (Ees/Ea). Cardiac output, systemic vascular resistance and mean arterial blood pressure were unchanged. Clamping of the pulmonary artery significantly increased afterload (ΔEa: +0.226 mmHg/ml, $p<0.001$). In response, right ventricular contractility increased (ΔESV_{25}: -26.6 ml, p=0.0002; ΔEes:+0.034 mmHg/ml, p=0.008), but ventricular-pulmonary coupling decreased (Δ(Ees/Ea) = -0.153, $p<0.0001$). None of

the measured indices showed significant interactive effects, indicating that effects of increased afterload were the same before and after thoracic epidural anaesthesia. In conclusion, thoracic epidural anesthesia impairs right ventricular contractility, but does not inhibit the native positive inotropic response of the right ventricle to increased afterload. Right ventricular-pulmonary arterial coupling was decreased with increased afterload, but not affected by the induction of TEA. Whether the findings of our study are clinically important remains to be determined, however, our results may help selecting and managing patients undergoing surgery under TEA.

In **Chapter 8** we investigated TEA effects on biventricular function and circulation during increased levels of sympathetic tone generated by physical exercise. During conditions of increased sympathetic tone the cardiac and circulatory effects of sympathicolysis by TEA may be more pronounced. Therefore we assessed the effects of TEA on biventricular cardiac function and hemodynamics during dynamic ergometric exercise. Cardiac function was measured using pulsed wave tissue Doppler imaging (TDI). Exercise resulted in augmentation of LV and RV contractile state evidenced by significant increases in MV S' (+56%, P<0.001) and TV S' (+54%, P<0.001). LV and RV diastolic function significantly increased during exercise which was reflected by augmented annular velocities MV E' (+30%, P<0.001), MV A' (+78%, P<0.001), TV E' (+51%, P<0.001) and TV A' (+83%, P<0.001), respectively. During exercise HR, SVI and CI increased (86%, 19% and 124%, P<0.001, respectively) which resulted in significantly elevated blood pressures (MAP +17%, P<0.001) despite significant reductions in SVR (49%, P<0.001).

TEA attenuated right ventricular (TV S': max - 21 %, P<0.001) and left ventricular (MV S': -14%, P=0.025) systolic function. Diastolic function was not affected by TEA. HR (max -11%, P<0.001), SVI (max -15%, P=0.006), CI (max -21%, P<0.001) and MAP (-12%, P<0.001) but not SVR were decreased during TEA.

Our data demonstrated that exercise-induced augmentation of right ventricular and left ventricular function was largely preserved with TEA and remained similar to control. No significant interactions between exercise and TEA were found, except for RPP (P=0.024) and MV Dec T (P=0.035). Cardiac sympathetic blockade by TEA reduced LV and RV systolic function without affecting diastolic biventricular function, but augmentation of LV and RV function during exercise was preserved. TEA did not significantly affect homeostatic mechanisms involved in cardiac challenges as occur during stress exercise. These data indicate that besides cardiac sympathetic stimulation other important mechanisms are involved in the regulation of cardiac function during dynamic stress.

Clinical perspectives

Using pressure-volume analysis we demonstrated that TEA decreases RV contractility without affecting ventricular-pulmonary coupling (**Chapter 7**). In this study our patients were paced at a constant heart rate to allow for reliable assessment of ventricular contractility. However, this

may have resulted in underestimation of the full TEA effects on cardiovascular function, as it prevented decreased heart rate by TEA. Moreover, atrial pacing is not part of clinical routine. To assess the effects of TEA on RV function in a more clinical setting, we should repeat our study however without the confounding effects of atrial pacing. This way the full effects of TEA on RV function at baseline and during raised afterload will be revealed.

Controversies exist between physiology studies revealing beneficial effects of TEA and meta-analysis failing to translate these beneficial effects into improved outcome in patients undergoing cardiac surgery treated with TEA[5]. In contrast, use of TEA during non-cardiac surgery has been associated by increased cardiovascular problems in high-risk patients or procedures[6, 7]. There seems to be a gap between the results of experimental studies and those of meta-analysis. This may well be because meta-analyses comprised very heterogeneous study populations. This way, potentially beneficial effects of TEA in certain subgroups might be cancelled out by potentially detrimental effects of TEA in other subgroups. The gap might be bridged with randomized controlled trials targeted to specific risk groups, which are based on data from physiology studies such as described in Chapter 7. Our recent clinical (**Chapter 7**) study and other experimental studies[8, 9] demonstrated that cardiac sympathetic blockade by TEA leads to substantial decreases in RV cardiac function. The clinical importance of this novel finding needs to be addressed.

Outcome studies which focus on use of TEA in patients with pulmonary hypertension or patients at risk for RV dysfunction or pulmonary hypertension are needed. Preoperative assessment and identification of patients at increased risk of worse outcome after use of TEA in cardio-pulmonary surgery enable tailored treatment.

TEA-induced sympathicolysis is often accompanied by systemic hypotension (**Chapter 5, 6 and 8**) due to cardiac depression (T1-T5) and dilatation of arterial and venous vascular beds (T6-T12) (**Figure 1**). It has been shown that TEA results in significant reductions of inotropic state of the heart (**Chapters 6,7, 8**) contributing to hypotension associated with the use of TEA. Also arterial resistance may decrease after TEA, although the effects may be relatively small in case of upper TEA (**Chapters 6, 7, 8**). Hypotension after TEA may also result from decreased venotonus and potential decreases in preload for the heart. Lumbar epidural studies with a sensory block up to T4/5 have been shown to result in pooling of blood in the denervated muscle and skin regions leading to decreases in cardiac filling[3]. High thoracic epidural anaesthesia however results in blockade of different spinal segments and as such the results of lumbar epidural studies cannot be simply translated to TEA. Especially since TEA and not LEA may decrease cardiac function and make the heart more susceptible for changes in preload. Therefore it needs to be clarified to which extent the TEA-induced decreases in venotonus contribute to the formation of hypotension. Furthermore, it remains to be determined what strategy is the best to treat TEA-induced hypotension? Some anaesthetists will start with fluid loading to address hypotension

and others will start using vasopressor medication first. Few studies investigated therapeutic interventions for hypotension after TEA. Two studies examined the effects of administering a bolus of ephedrine[15] or phenylephrine[16] in case of hypotension caused by high TEA (T1-L1) during general anesthesia. However, only short term management of hypotension was addressed. In another study the initial decrease in hepatic blood flow after induction of TEA (T4-T11) was further decreased by continuous administration of noradrenaline to restore TEA-induced decreases in blood pressures[17]. Choosing an optimal treatment regimen for hypotension after TEA is important since infusion of excess fluid perioperative may have undesirable effects on organ function[18]. More importantly, perioperative hypotension in general is a proven risk factor for adverse postoperative outcomes[19], an underlying mechanism by which TEA hypothetically may result in increased perioperative morbidity or mortality. Future studies should focus on effective treatment regimens for TEA-induced hypotension and assess whether these regimens positively affect outcome.

As mentioned in **Chapter 3** knowledge of the human cardiac sympathetic innervation is important as it is the fundamental base upon which targeted cardiac sympathetic blockade for the treatment of arrhythmias and heart failure is performed. Moreover, it explains the cardio-depressant effects of TEA. Still controversies exist on which spinal levels are involved in cardiac sympathetic innervation. Also the composition of cardiac nerves as well as vagal contributions to the ventricles in humans needs further exploration. Cardiac autonomic innervation is often described and studied in animals, using modern tracing techniques. However, the results of these studies are not simply translatable to the human heart since there are important interspecies differences[20]. Human studies on the anatomy of cardiac sympathetic innervation are scarce and future studies in humans are needed to address this issue. Studies exploring the role of preganglionic sympathetic nerves at different spinal levels or thoracic ganglia in the modulation of cardiac function should be encouraged. These studies may not only point out the anatomical structures involved in cardiac autonomic innervation but may also clarify the contribution of these structures to cardiac autonomic innervation. Also separate contributions of the sympathetic nervous system to the LV and RV need further exploration. Rex and colleagues reported that induction of TEA in animals sorted differential effects on LV and RV function. In our studies it also appears that cardiac sympathetic blockade by TEA elicits differential effects on LV and RV function, the RV being depressed to a greater extent than the LV (**Chapter 9**). Whether these differences in LV and RV sympathetic innervation truly exist and are clinically relevant needs to be determined by future studies.

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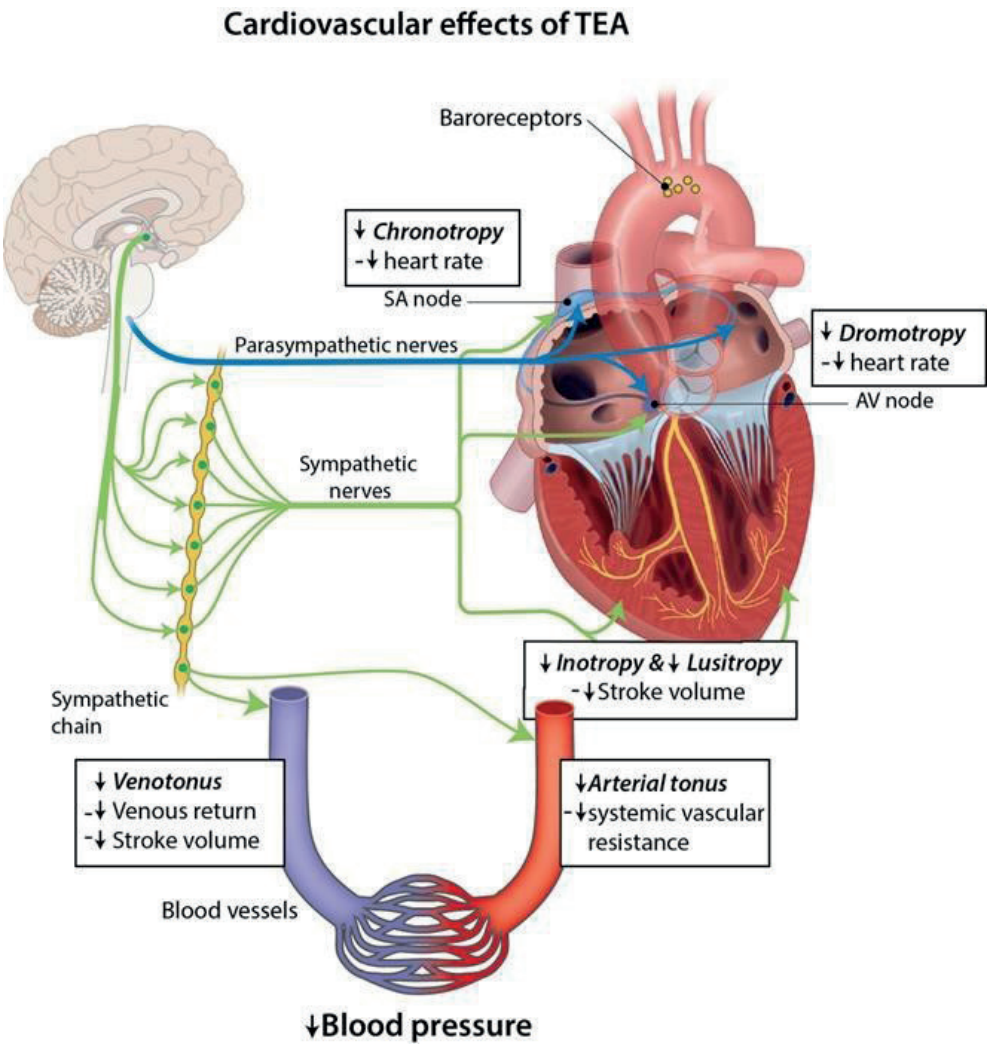
Chapter 10

Nederlandse samenvatting

Samenvatting

Algemene inleiding

Thoracale epidurale anesthesie (TEA) resulteert in uitstekende pijnstilling en wordt als zodanig vaak toegepast bij hart- en longoperaties en bovenbuik chirurgie. Epidurale toediening van een lokaal anestheticum resulteert in zowel blokkade van sensorische en motorische zenuwvezels als ook in blokkade van de sympathische zenuwvezels (**Hoofdstuk 1**). Blokkade van de sensorische zenuwvezels resulteren in verdoving van de lichaamsdelen die door die zenuwen worden verzorgd. De cardiovasculaire bijwerkingen tijdens epidurale anesthesie worden veroorzaakt door blokkade van sympathische zenuwvezels. TEA waarbij de sympathische neuronen van de bovenste thoracale spinale segmenten (hoge-TEA, T1-T5) worden geblokkeerd, kan leiden tot vermindering van de hartfrequentie (chronotropie), kracht waarmee het hart samentrekt (contractiliteit), snelheid van myocard relaxatie (lusitropie) en prikkelgeleiding van het atrioventriculaire systeem (dromotropie). Daarnaast kan hoge-TEA resulteren in verwijding van de bloedvaten (vasodilatatie), maar dit effect lijkt beperkt[1;2]. Blokkade van de sympathische vezels in de lage thoracale regio (lage-TEA, T6-L1) resulteert in een verminderde vaattonus van de arteriële en veneuze vaten, afname van de systemische vaatweerstand, ophoping en redistributie van bloed naar het splanchnisch vaatbed met uiteindelijk afname van de vulling (preload) van het hart[3]. Het splanchnisch vaatbed heeft een grote volume capaciteit voor bloed, die als buffer dient om veranderingen in het circulerend volume op te vangen[4]. Door middel van vasoconstrictie (vernauwing van de bloedvaten), geïnduceerd door sympathische stimulatie, kan deze buffer worden aangesproken en zal bloed worden gedistribueerd naar de systemische circulatie.



Figuur 1. Cardiovasculaire effecten van sympathische blokkade door thoracale epidurale anesthesie (TEA).

De door inductie van TEA veroorzaakte veranderingen in vaattonus en hartfunctie leiden tot vermindering van de hoeveelheid bloed die het hart per minuut uitpompt (cardiac output,CO) en systemische vaatweerstand (SVR), uiteindelijk resulterend in verlaging van de bloeddruk (Figuur 1). De cardiovasculaire status en de sympathicotonus van de patiënt voor inductie van TEA, zijn bepalend voor de intensiteit van de cardiovasculaire bijwerkingen. Daarnaast heeft de uitgebreidheid van de neurale blokkade (aantal verdoofde spinale segmenten) invloed op het ontstaan en de ernst van de cardiovasculaire bijwerkingen. Ook leeftijd kan van invloed zijn op de ernst van de cardiovasculaire effecten na TEA. Veroudering gaat gepaard met structurele en functionele veranderingen in anatomie en fysiologie waardoor de cardiovasculaire effecten van

TEA bij ouderen kunnen veranderen (**Figuur 3, hoofdstuk 1**). Kennis van en inzicht in deze door veroudering veroorzaakte effecten kunnen bijdragen tot een betere anesthesiologische zorg voor ouderen. Vanuit een klinisch oogpunt is het dan ook belangrijk om te onderzoeken of leeftijd invloed heeft op de door TEA veroorzaakte neurale blokkade en cardiovasculaire bijwerkingen.
Het doel van het onderzoek was het bepalen van de bijwerkingen van TEA op het hart en de bloedsomloop (circulatie). De effecten van TEA op het hart en de circulatie werden zowel tijdens rust als gedurende omstandigheden van stress (zoals tijdens operatie of inspanning) onderzocht.

Anatomie en Fysiologie

Anatomie

In hoofdstuk 3 is de literatuur bestudeerd betreffende de humane anatomie van cardiale sympathische innervatie. Zowel de cardiale sympathische innervatie vanaf het brein tot het hart alsmede de embryogenese van het cardiale autonome zenuwstelsel werd in dit hoofdstuk beschreven. Toename van de sympathicotonus speelt waarschijnlijk een belangrijke rol in het ontstaan van hartritmestoornissen en hartfalen. Nieuwe behandelingsmethoden voor hartritmestoornissen en hartfalen zijn op basis van het blokkeren van de cardiale sympathische zenuwvezels. Zoals eerder beschreven kan TEA ook leiden tot blokkade van sympathische zenuwvezels. Van belang is dat voor het gericht blokkeren van de cardiale sympathische innervatie (T1-T5) grondige kennis van de locatie en distributie van de cardiale sympathische zenuwvezels onontbeerlijk is. Echter, hierover bestaat nog geen consensus.
Aangenomen wordt dat de preganglionaire cardiale sympathische neuronen hun oorsprong hebben in de spinale segmenten T1-T5. Echter, cervicale spinale segmenten (C8) en thoracale spinale segmenten lager dan T5 bevatten hoogstwaarschijnlijk ook preganglionaire cardiale sympathische neuronen. Dit zou betekenen dat voor het volledig blokkeren van alle cardiale sympathische zenuwvezels door TEA een uitgebreider neuraal blok nodig is. Naast discussie over welke spinale segmenten betrokken zijn bij de cardiale sympathische innervatie is er eveneens discussie over welke niveaus van de sympathische grensstreng en welke cervicale ganglia naast het ganglion stellatum betrokken zijn bij de transmissie van sympathische signalen. Deze informatie zou mogelijk relevant kunnen zijn voor procedures waarbij gericht de cardiale sympathische innervatie wordt geblokkeerd, zoals bij ganglion stellatum of paravertebrale blokkade. Er is onduidelijkheid over de compositie van cardiale zenuwen rond het hart en over de exacte bijdrage van de nervus vagus aan de innervatie van de kamers in mensen.

Fysiologie

Hoofdstuk 4 beschrijft een overzichtsartikel (review) naar de cardiovasculaire effecten van TEA. Studies werden geïncludeerd als hierin de cardiovasculaire bijwerkingen van TEA werden beschreven en duidelijk was dat de cardiale sympathische zenuwvezels (T1-T5) waren betrokken in de neurale blokkade door TEA. Dit review laat een aantal experimentele studies zien die aangetoond hebben dat TEA een gunstig effect heeft op de postoperatieve outcome en bovendien cardioprotectief kan zijn. Toepassing van TEA bij patiënten voor cardiale chirurgie heeft echter nog niet geleid tot bewezen betere cardiale outcome[5]. Daarentegen zijn er studies die het toepassen van TEA bij hoog-risico patiënten associëren met een toename van cardiovasculaire problemen[6;7]. Onderliggende mechanismen voor nadelige effecten van TEA zijn echter onduidelijk en speculatief, net zoals welke karakteristieken een patiëntgroep maakt dat ze minder baat hebben bij TEA. Recente studies in dieren[8;9] en mensen[10] hebben meer inzicht gegeven in de complexe interactie tussen sympathicolyse door TEA en cardiovasculaire homeostase. Door deze recente onderzoeken welke gebruik maakten van moderne meetmethoden is duidelijk geworden dat sympathicolyse door hoge-TEA resulteert in verminderde contractiliteit van zowel de linker- als de rechterkamer. Deze directe effecten van TEA op de contractiliteit van het hart worden in gezonde mensen goed verdragen vanwege de gelijktijdige arteriële vasodilatatie. De arteriële vasodilatatie (verwijding van bloedvaten) vermindert de afterload (weerstand) voor het hart, wat resulteert in een vergemakkelijkte ejectie van bloed door het hart. Hierdoor zullen, zolang het hart van voldoende preload blijft voorzien, de globale pompfunctie en CO tijdens TEA niet afnemen. De arteriële vasodilatatie en daarmee afterload verlaging zoals die optreedt voor de linkerkamer zal echter niet gebeuren voor de rechterkamer. Directe afname van de kamer contractiliteit door TEA zal dus eerder invloed hebben op de pompfunctie van rechter- dan van de linkerkamer. Voor de anesthesiologische behandeling van patiënten met al bestaande of met risico op verminderde rechterkamer functie en/of verhoogde druk in de longslader, is het raadzaam de directe effecten van TEA in het achterhoofd te houden. Mochten zich cardiovasculaire problemen voordoen rond de operatie dan kan worden overwogen om TEA tijdelijk of definitief te staken en eventueel over te gaan op een alternatieve vorm van pijnstilling.

Centrale neurale blokkade

Effect van leeftijd op neurale blokkade en cardiovasculaire veranderingen

In hoofdstuk 5 werden de effecten van leeftijd op de kwaliteit van neurale blokkade en cardiovasculaire veranderingen door TEA. Bij onderzoek met lumbale epidurale anesthesie is duidelijk naar voren gekomen dat toenemende leeftijd gepaard gaat met extensie van neurale blokkade en toegenomen cardiovasculaire respons 11. Data voor TEA zijn echter beperkt. Een studie van Hirabyashi en collega's heeft laten zien dat in hun onderzoek de hoeveelheid lokaal anestheticum die nodig is om één spinaal segment te verdoven na TEA afneemt met toenemende leeftijd 12 De hypothese voor het onderzoek in hoofdstuk 5 was epidurale toediening van dezelfde hoeveelheidlokaal anesthesticum op thoracaal niveau T3-T4 resulteert bij ouderen in een meer uitgebreide neurale blokkade dan bij jongeren. Vijfendertig patiënten werden geïncludeerd in 3

leeftijdsgroepen: 18-45 jaar (jonge leeftijdsgroep), 46-65 jaar (middelbare leeftijdsgroep) en 66 jaar of ouder (oudere leeftijdsgroep). Uiteindelijk kregen 31 patiënten een epidurale catheter op niveau T3-T4 waardoor 8 ml ropivacaïne 0.75 % werd toegediend. Gevoeligheid van de huid voor pin-prik en discriminatie van temperatuur werd gebruikt om de uitgebreidheid van de sensorische blokkade te testen. Voor het testen van eventuele motorische blokkade werden de Bromage- en de ESSAM-score gebruikt. Voor het bepalen van bloeddruk, slagvolume en hartminuutvolume (cardiac index, CI), kregen patiënten een druklijn in een slagader. De studie toonde geen effect van leeftijd op de kwaliteit van neurale blokkade na TEA, behalve voor de ondergrens van de neurale blokkade. Deze was bij zowel de middelbare als de oudere leeftijdsgroep iets lager dan bij de jongere leeftijdsgroep. Inductie van TEA resulteerde voor de hele groep in een significante maximale daling van hartfrequentie (-6.0 ± 5.9, p< 0.001), gemiddelde bloeddruk (-16.1 ± 15.6, p<0.001), slagvolume (-9.6 ± 14.6, p=0.001) en hartminuutvolume (CI) (-0.55 ± 0.49, p<0.001). De maximale afname in hartfrequentie was groter in de jongere leeftijdsgroep ten opzichte van de middelbare en oudere leeftijdsgroep. Voor andere cardiovasculaire parameters konden geen leeftijdseffecten aangetoond worden.

Effect van leeftijd op de cardiale veranderingen na TEA

De effecten van TEA en leeftijd op echografische indices van linker en rechter kamerfunctie werden beschreven in hoofdstuk 6. Blokkade van sympathische zenuwvezels door TEA kan leiden tot veranderingen in de circulatie en verminderde hartfunctie. Veroudering kan leiden tot stoornissen en aantasting van het sympathisch zenuwstelsel en tot vermindering van de diastolische hartfunctie. Hypothese was dat ouderen meer gevoelig zijn voor de cardiovasculaire bijwerkingen van TEA. Vijfendertig patiënten die gepland stonden om een longoperatie te ondergaan werden onderverdeeld in 3 leeftijdsgroepen: 18-45 jaar (jonge leeftijdsgroep), 46-65 jaar (middelbare leeftijdsgroep) en 66 jaar of ouder (oudere leeftijdsgroep). Alle patiënten kregen vlak voor en 45 minuten na inductie van TEA een echografische beoordeling van hun hartfunctie. Om de preload (vulling) voor het hart te behouden kregen patiënten een bolus vocht via hun infuus toegediend. De systolische en diastolische functie van beide hartkamers werd bepaald met behulp van tissue doppler imaging (TDI) en andere echografische indices voor hartfunctie. Echografisch onderzoek liet zien dat de linker en rechter kamerfunctie met het toenemen van leeftijd waren afgenomen. Inductie van TEA resulteerde in afname van de gemiddelde bloeddruk (91.2 versus 79.2 mmHg, P<0.001) en toename van het hartminuutvolume (CI) (2.7 versus 3.0 l min-1 m-2, P=0.005) zonder verandering in hartfrequentie of linker kamerfunctie. Ejectieparameters voor de rechter kamer en TDI parameters voor diastolische linker -en rechter kamerfunctie verbeterden na inductie van TEA. Leeftijd had geen invloed op de effecten van TEA op de functie van beide hartkamers. Het is mogelijk dat de bolus vocht die werd toegediend voor inductie van TEA de effecten van leeftijd op de hemodynamische veranderingen na TEA heeft gemaskeerd. Daarnaast werd na inductie van TEA in onze patiënten geen invloed van leeftijd op het aantal verdoofde spinale segmenten gevonden. Verschillen tussen leeftijdsgroepen in het aantal verdoofde spinale segmenten zou namelijk een verklaring kunnen zijn geweest voor

eventuele verschillen in hemodynamische respons op TEA. Deze studie toont aan dat indien preload voor het hart wordt gewaarborgd, TEA voornamelijk leidt tot systemische vasodilatatie en verbetering van de globale hemodynamiek. De linker kamerfunctie lijkt onaangetast door TEA terwijl de diastolische linker- en rechter kamerfunctie lijkt te zijn verbeterd. De effecten van TEA op de rechterkamer systolische functie zijn onduidelijk. Ondanks dat de basale diastolische functie van linker- en rechterkamer waren verminderd in de oudste groep, resulteerde dit niet in een andere hemodynamische respons op TEA ten opzichte van de jongere groep.

Thoracale Epidurale Anesthesie: effecten op de hartfunctie gedurende stress

In de hoofdstukken 7 en 8 worden de effecten van TEA tijdens verhoogde sympathicotonus (stress) beschreven. Verschillende experimentele modellen werden gebruikt om condities van verhoogde sympathicotonus na te bootsen.

In hoofdstuk 7 is het effect van TEA op de baseline rechter kamerfunctie en op rechter kamerfunctie tijdens acute toename van afterload voor de rechterkamer beschreven. Verhoging van de afterload voor de rechterkamer resulteert normaliter in een verbeterde rechterkamerfunctie. Hierdoor is de rechterkamer ondanks de verhoogde afterload in staat om het slagvolume te handhaven zonder het eind-diastolisch volume te verhogen en te dilateren (Frank-Starling mechanisme)[13]. Eerder dierexperimenteel onderzoek heeft aangetoond dat TEA dit mechanisme teniet doet[8]. Het doel van de studie was om te onderzoeken of TEA dit mechanisme ook in mensen beïnvloedt. Dee rechter kamerfunctie werd bepaald door druk-volume loops met behulp van conductantie catheters in 10 patiënten die een partiële longresectie ondergingen. Metingen werden verricht onder algehele anesthesie zowel voor als na TEA en voor en na klemmen van de longslagder. Door het afklemmen van de linker of rechter longslagader werd de afterload voor de rechterkamer tijdelijk verhoogd Om eventuele effecten van hartfrequentie op de contractiliteit van het hart te vermijden werden alle patiënten gepaced met een vaste frequentie. De helling (Ees) en het volume-intercept bij 25 mmHg (ESV_{25}) van de eind-systolische druk-volume relatie werden gebruikt als maat voor contractiliteit. Deze studie toonde aan dat TEA de contractiliteit van de RV vermindert met 10-40% (ΔESV_{25}: +25.5 ml, p=0.0003; ΔEes: -0.025 mmHg/ml, p=0.04). De afterload voor de rechterkamer, evenals hartminuutvolume en gemiddelde bloeddruk veranderden niet door TEA. Tijdelijk klemmen van de longslagader teneinde de afterload voor de rechterkamer te verhogen, resulteerde bij onze patiënten in een verbeterde rechter kamerfunctie. Toepassen van TEA had bij onze patiënten geen effect op dit mechanisme. Samenvattend toonde dit onderzoek aan dat TEA de contractiliteit van de rechterkamer verminderde zonder de koppeling tussen rechter kamerfunctie en longslagaderdrukken te veranderen.

In hoofdstuk 8 werden de effecten van TEA op de circulatie en functie van linker- en rechterkamer in rust en gedurende stress bepaald. Stress werd geïnduceerd door patiënten te laten fietsen op een ligfiets en bloot te stellen aan tijdens door fietsergometrie verhoogde sympathicotonus beschreven. Sympathicusblokkade door TEA tijdens verhoogde sympathicotonus leidt waarschijnlijk tot meer uitgesproken effecten op het hart en de bloedsomloop. Twaalf

patiënten kregen een thoracale epidurale katheter op spinaal niveau T3-T4 en werden vervolgens gepositioneerd op een ligfiets. Patiënten moesten twee keer fietsen gedurende twee onderzoeksdagen: één keer na epidurale toediening van NaCl 0.9% en één keer na ropivacaïne 0.75%, in willekeurige volgorde. Tijdens verschillende weerstandsniveaus werden met behulp van TDI echo van het hart de linker- en rechter kamerfunctie bepaald.
Fysieke inspanning resulteerde in een verbetering van de systolische en diastolische kamerfunctie, zowel links als rechts. Hartfrequentie en hartminuutvolume (respectievelijk 86% en 124%, P<0.001) stegen tijdens inspanning waarbij de gemiddelde bloeddruk steeg ondanks significante afname van de vaatweerstand, SVR (-49%, P<0.001).
Inductie van TEA resulteerde in een vermindering van de systolische functie van de rechterkamer (max -21%, P<0.001) en linkerkamer(-14%, P=0.025) systolische functie. De diastolische functie van zowel de linker-als de rechterkamer werd niet beïnvloed door TEA. Hartfrequentie (max -11%, P<0.001), hartminuutvolume (max -21%, P<0.001) en gemiddelde bloeddruk (-12%, P<0.001)namen af tijdens TEA. De vaatweerstand werd niet beïnvloed door TEA.
Dit onderzoek toonde aan dat de toename van de linker- en rechter kamerfunctie tijdens inspanning nauwelijks werd beïnvloed door TEA. Er waren geen significante interacties tussen inspanning en TEA voor de linker- en rechter kamerfunctie. Hieruit kunnen we concluderen dat de homeostatische mechanismen die betrokken zijn bij de toegenomen cardiale functie zoals tijdens fietsergometrie niet significant beperkt werden door inductie van TEA. Naast cardiale sympathische innervatie spelen waarschijnlijk andere belangrijke mechanismen een rol in de regulatie van de hartfunctie tijdens dynamische stress.

Klinische perspectieven

Voor het bepalen van de volledige effecten van TEA op de RV zou de studie in hoofdstuk 7moeten worden herhaald zonder patiënten te pacen.
Hypotensie is een veelvoorkomende bijwerking van TEA. Onderzoek naar de afzonderlijke bijdragen van verminderde venotonus en verminderde contractiliteit aan TEA-geïnduceerde hypotensie is relevant. Daarnaast is het onduidelijk wat de beste strategie is om deze TEA-geïnduceerde hypotensie te behandelen. Studies waarin is gekeken naar de therapeutische interventies voor TEA-geïnduceerde hypotensie zijn beperkt. Het kiezen van een optimale behandelingsstrategie, zoals toediening van vasoconstrictiva, inotropica of vocht of een combinatie, is noodzakelijk. De verschillende behandelingsvormen kunnen mogelijk nadelige effecten op orgaan functies hebben. Studies die de effectiviteit van verschillende behandelingsregimes voor TEA-geïnduceerde hypotensie onderzoeken zijn nodig. Daarnaast zouden deze studies moeten onderzoeken of de toegepaste interventiestrategieën daadwerkelijk invloed hebben op de postoperatieve outcome.
In hoofdstuk 3 wordt beschreven dat kennis van de humane cardiale sympathische innervatie belangrijk is. Toekomstig onderzoek in mensen zou moeten uitwijzen welke spinale ruggenmergsegmenten en welke thoracale ganglia betrokken zijn bij de sympathische innervatie van het hart. Deze studies zouden behalve inzicht in de anatomie van de cardiale

sympathische innervatie ook duidelijk kunnen maken wat de autonome bijdrage is van deze afzonderlijke structuren. Ook eventuele verschillen in sympathische innervatie tussen de linker- en de rechterkamer zouden kunnen worden onderzocht in toekomstige studies.
De studie beschreven in hoofdstuk 7 en dierexperimentele studies[8;9] tonen aan dat cardiale sympathische blokkade door TEA leidt tot substantiële vermindering van RV contractiliteit. Het is echter nog niet duidelijk in hoeverre deze resultaten klinisch relevant zijn. TEA studies bij risicogroepen zijn nodig om zorg op maat te kunnen leveren.

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Addenda

Curriculum Vitae
List of publications
Dankwoord

Curriculum vitae

Jeroen Wink was born on the 17th of July 1973 in Almelo, The Netherlands. Following his graduating from pre-university secondary school (Christelijk Lyceum, Almelo), he started medical school in 1991 at the Vrije University Medical Center (VUMC), Amsterdam. He obtained his Medical Doctor degree in 1999. Subsequently he started as a resident in IC at the Medical Center, Alkmaar. In 2000, he started as a resident in Anaesthesiology at the Leiden University Medical Center (LUMC) under supervision of Prof. dr. J.W. van Kleef. At the start of his residency at the department of Anaesthesiology he did a clinical research project on the epidural administration of ropivacaine.
In 2005, Jeroen finished his specialty training in Anaesthesiology and subsequently started working as an cardiothoracic anesthesiologist at the department Anaesthesiology at the Leiden University Medical Center. In the following years he combined a busy clinical job with his research project. In 2010 he started his PhD project at the same department under supervision of Prof. dr. L.P.H.J. Aarts. Special interests of Jeroen are echocardiography and cardiovascular physiology.

Since his teenage years Jeroen played in several wind orchestra's. He was the concertmaster of the symphonic wind orchestra "The ATH" in Amsterdam, with which he performed in the Concertgebouw in Amsterdam. During those days he doubted whether he aspired a musical or medical career. Eventually it was his father who persuade him not to follow in his footsteps and he started at VUMC. This is where he met his first wife Babette Brugman and their first son, Ciske, was born in 2003. She, while pregnant of their second son, sadly passed away too soon at age 29. Jeroen remarried and together they have 3 more children and live in Amstelveen. Jeroen and his partner Karin Peters have 2 daughters and 1 son: Carmen, Maxime and Karsten.

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- Wink J, van Delft R, Notenboom RGE, Wouters PF, de Ruyter M, Jongbloed MRM. Controversies in anatomical knowledge of fetal and adult human cardiac autonomic innervation – relevance for cardiac neuromodulation. Submitted.
- Wink J, Steendijk P, Tsonaka S, de Wilde RBP, Friedericy HJ, Braun J, Veering BTh, Aarts LPHJ, Wouters PF. Biventricular effects of sympathicolysis by high thoracic epidural anesthesia during dynamic stress. Submitted.

Scientific meetings

21/11/2013 - 24/11/2013 - Poster Presentation age does not affect the cardiovascular response to high thoracic epidural anesthesia"" at the 12th Annual Pain Medicine Meeting ASRA 2013

11/05/2016 - 13/05/2016 - Oral presentatation, abstract: "Thoracic epidural anesthesia reduces right ventricular systolic function with maintained ventricular-pulmonary coupling" at the Annual EACTA Congress in Basel 2016 - Done

17/09/2014 - 19/09/2014 - Oral presentation, abstract "Effect of increasing age on the haemodynamic response to thoracic epidural anesthesia" at the Annual EACTA Congress in Florence 2014 - Done

17/06/2017 - 17/06/2017 - Presentatie "Cardiac effects of thoracic epidural anesthesia during bicycle exercise: an echocardiographic study" op de wetenschapsdag van de afdeling anesthesiologie, 2017 - Done

Dankwoord

Graag wil ik iedereen danken die door hun medewerking en steun hebben bijgedragen aan de totstandkoming van dit proefschrift. Een aantal mensen zou ik hierbij speciaal willen noemen.

Allereerst wil ik alle patiënten bedanken die belangeloos hebben meegedaan aan de experimenten zoals beschreven in de verschillende hoofdstukken van deze thesis. Zonder jullie geloof en vertrouwen in de wetenschap had dit proefschrift nooit gerealiseerd kunnen worden. Heel veel dank hiervoor!

Beste Prof. Dr. L.P.H.J. Aarts, beste Leon, dank voor het vertrouwen in mij en de geboden kans om te promoveren naast mijn klinische werkzaamheden. Beste Prof. Dr. P.F. Wouters, beste Patrick, dank voor alle tijd, energie en kennis die je hebt gedeeld. Dank voor alle prettige gesprekken die we hebben gehad. Voor mij ben je de geestelijk vader van dit proefschrift. Beste Prof. Dr. P. Steendijk, beste Paul, dank voor alle input en interessante discussies over fysiologie. Beste dr. Veering, beste Dettie, mijn eerste wetenschappelijk onderzoek aan de start van mijn opleiding was onder jouw supervisie. Uiteindelijk, na een lange en leerzame weg, is dit proefschrift het resultaat van onze samenwerking en jouw vertrouwen in mij. Dank daarvoor. Dr. R de Wilde, Rob, jij hebt mij tijdens vele experimenten geholpen als mede-onderzoeker. Voor jouw inzet, bijdrage en grenzeloze loyaliteit ben ik je altijd dankbaar.

Prof. Dr. Klautz, Prof. Dr. Prof. dr. D. van Dijk, Prof. dr. T.W.L. Scheeren en dr. M.R.M. Jongbloed ben ik zeer erkentelijk voor hun deelname aan de promotiecommissie.

Het in hoofdstuk 3 beschreven artikel is het resultaat van een zeer prettige samenwerking met de afdeling Anatomie. Dr. M.R.M. Jongbloed, Dr. R.G.E. Notenboom en Prof. Dr. M.C. de Ruiter, dank voor jullie enthousiasme en bijdrage aan dit proefschrift.

Mijn collega thorax-anesthesiologen, dank voor jullie geduld, hulp en steun. Mede door jullie inzet is er ruimte voor mij gecreëerd om aan dit proefschrift te werken. Collega's van de thoraxchirurgie, in het bijzonder Drs. M.I.M. Versteegh en Dr. J. Braun, dank voor jullie medewerking aan mijn onderzoeken. Anesthesie- en ok medewerkers, verkoever personeel, dank voor jullie ondersteuning.

Ron Slagter dank voor het maken van de prachtige illustraties van hoofdstuk 3. Drs. Wolterbeek en Dr. S. Tsonaka ben ik zeer erkentelijk voor hun hulp met de statistische analyses.

Shirin Bemelmans en Bert Jan Egberink, ik ben blij met jullie aan mijn zijde tijdens de verdediging van mijn proefschrift.

Lieve papa en mama, dankbaar ben ik jullie voor een onbezorgde jeugd en het warme nest waarin ik mocht opgroeien. Jullie hebben mij normen en waarden, discipline en doorzettingsvermogen meegegeven, eigenschappen die uitstekend van pas kwamen bij het realiseren van dit proefschrift.

Lieve Karin, het promotietraject is niet altijd makkelijk geweest. Enorm dankbaar ben ik je voor de ruimte die je me hebt gegeven, voor het geduld met me en voor je nooit aflatende steun en liefde.

Lieve Ciske, Carmen, Maxime en Karsten, ik prijs me enorm gelukkig dat ik jullie vader mag zijn. Iedere dag met jullie is een feestje.