Cardiovascular effects of thoracic epidural anaesthesia

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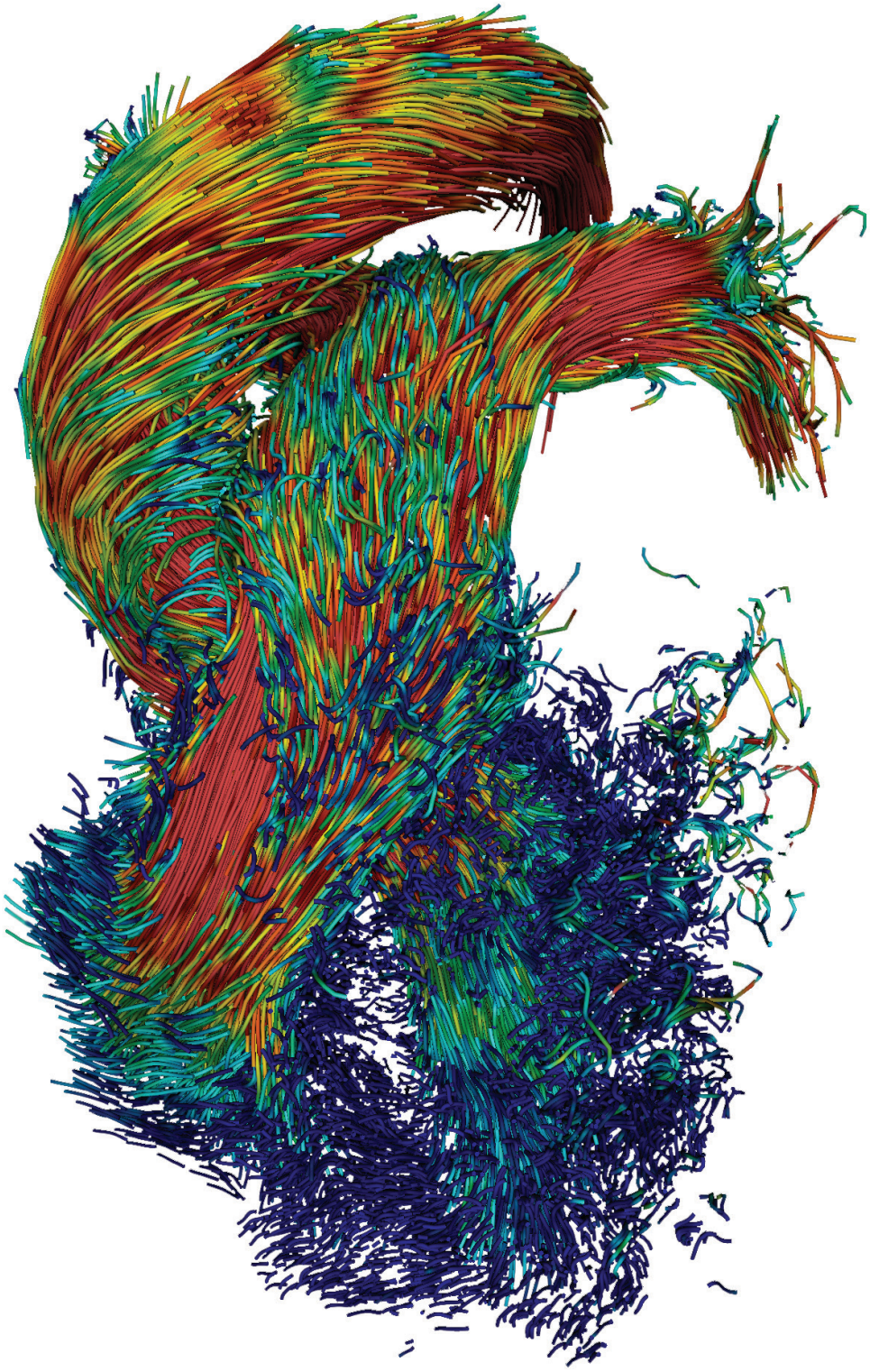

Section V

Conclusions

Chapter 9

Conclusion and perspectives

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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].

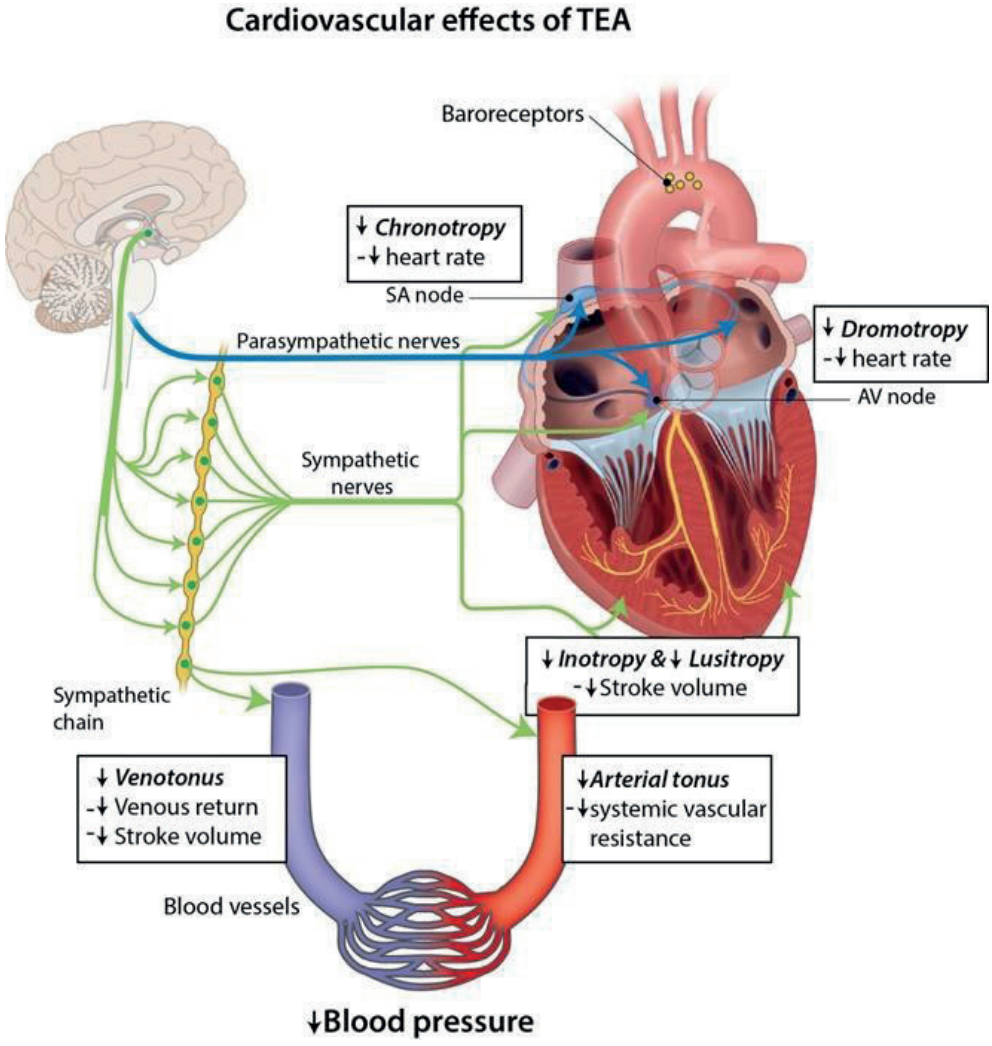

Figure 1. Cardiovascular effects of sympathetic blockade by thoracic epidural anaesthesia (TEA).

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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