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Chapter 4

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

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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.

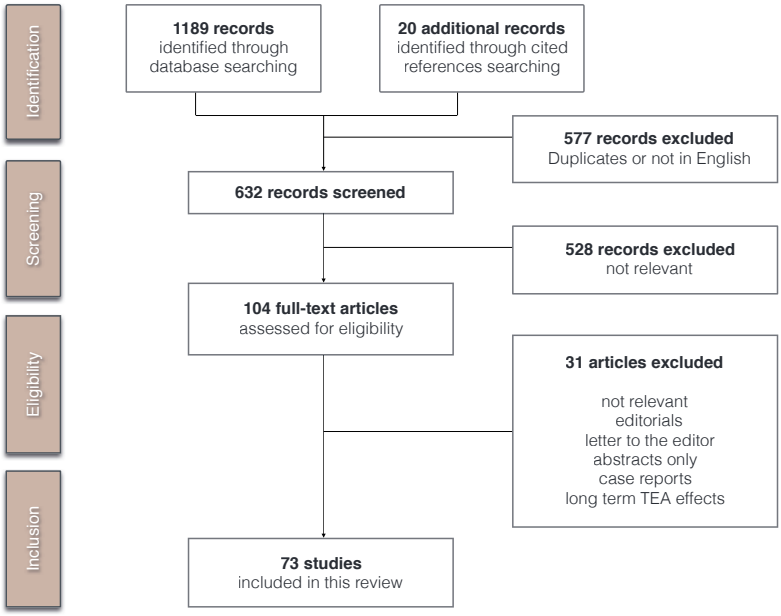

Figure 1. Flow diagram of literature search

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].

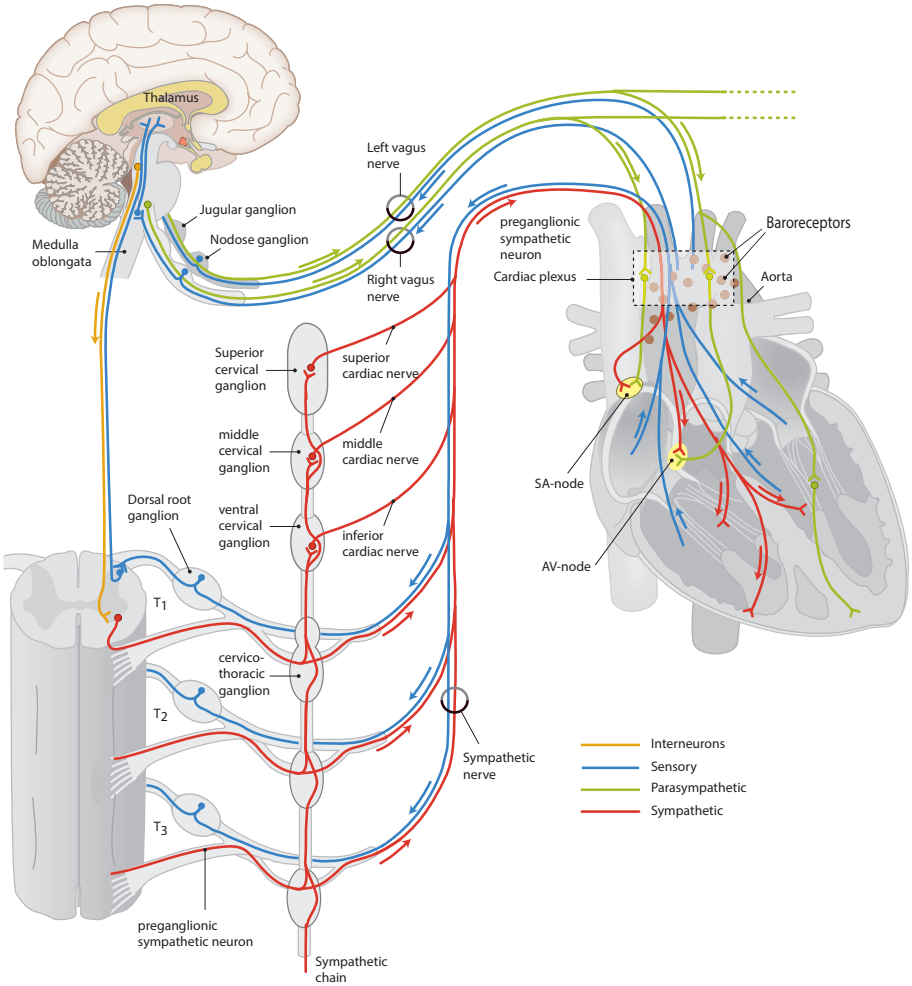

Figure 2. Overview of cardiac innervation

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].

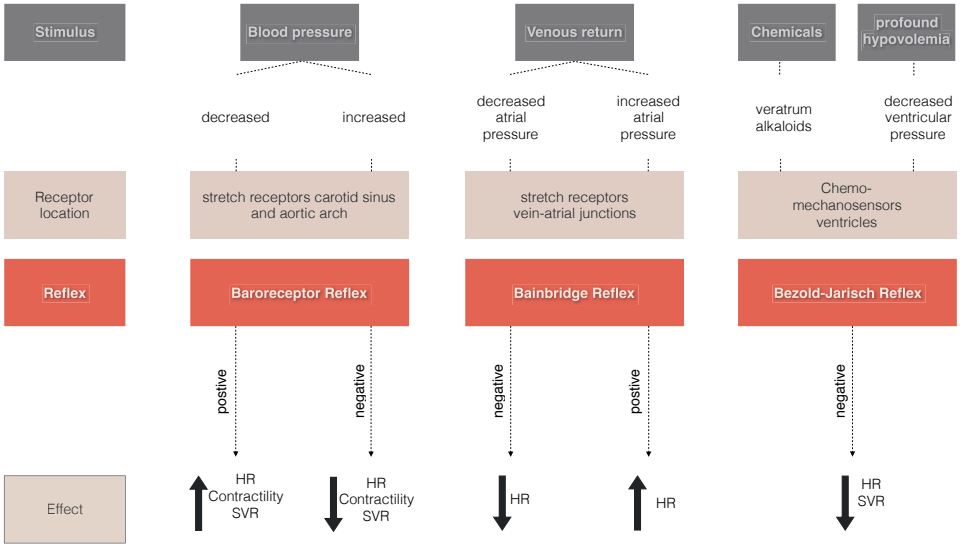

Figure 3. Cardiac and cardiovascular reflexes

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

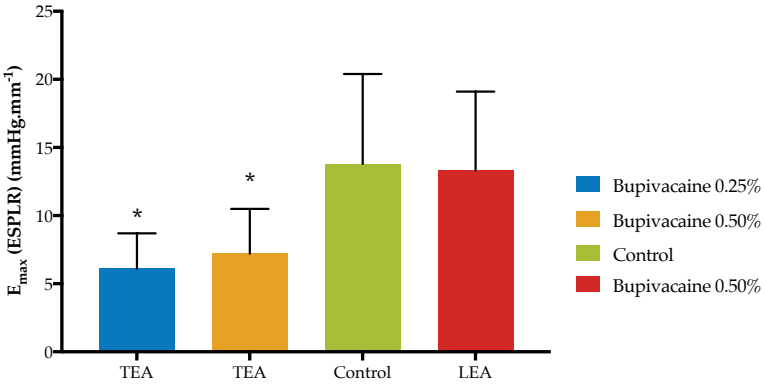

Figure 4. Arithmetic means (± s.d.) of the maximal elastance (Emax) of the left ventricle.
*indicates *Pi*<0.001 versus Group 3 (control) and versus Group 4 (LEA). TEA, thoracic epidural anaesthesia; LEA, lumbar epidural anaesthesia. Modified with permission from Goertz et al. (Goertz et al: influence 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].

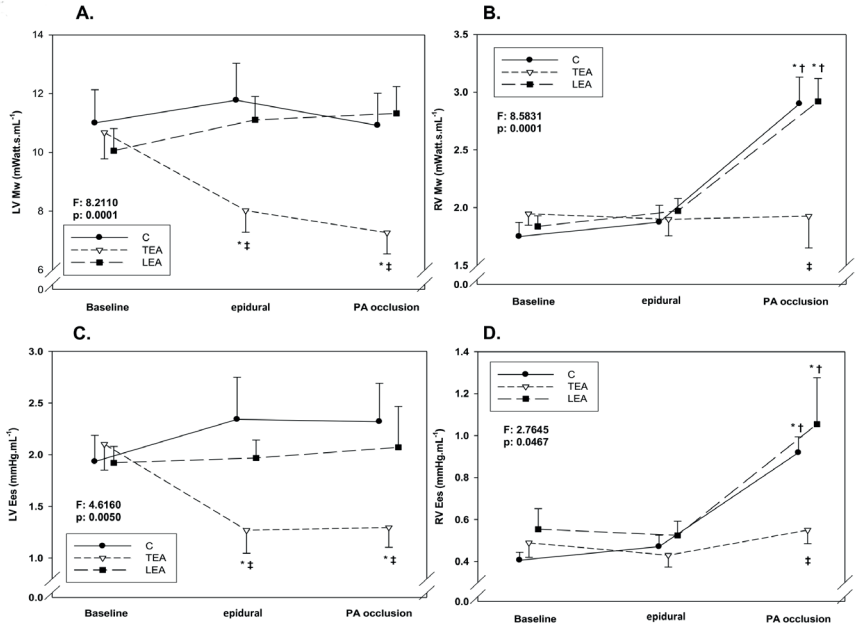

Figure 5. Right and left ventricular contractility during baseline, epidural anaesthesia, and acute PA occlusion in control animals and animals with a thoracic or lumbar epidural anaesthesia.

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].

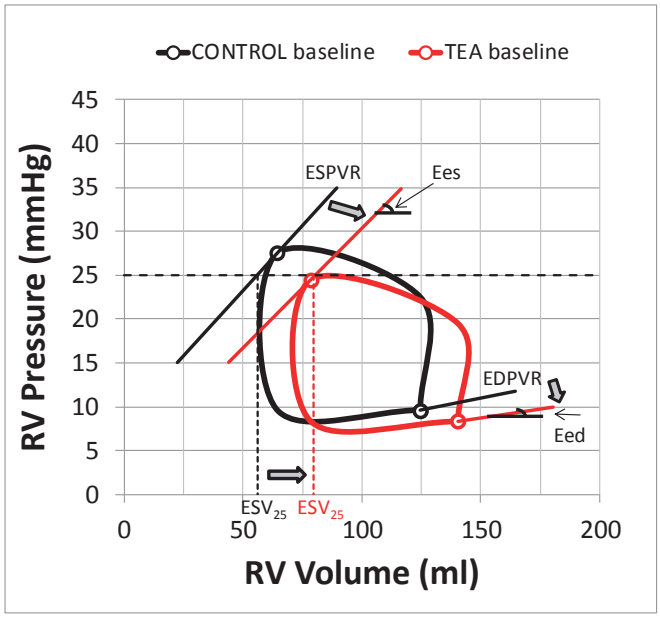

Figure 6. Schematic RV pressure-volume loops based on mean end-diastolic and end-systolic pressures and volumes during one lung ventilation at baseline (black loop) and after induction of TEA (red loop). The increase in ESV^{25} and the rightward shift and more shallow slope of the ESPVR after TEA, indicate 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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