ANESTHESIOLOGY

# Effects of Thoracic Epidural Anesthesia on Neuronal Cardiac Regulation and Cardiac Function

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## ABSTRACT

Cardiac sympathetic blockade with high-thoracic epidural anesthesia is considered beneficial in patients undergoing major surgery because it offers protection in ischemic heart disease. Major outcome studies have failed to confirm such a benefit, however. In fact, there is growing concern about potential harm associated with the use of thoracic epidural anesthesia in high-risk patients, although underlying mechanisms have not been identified. Since the latest review on this subject, a number of clinical and experimental studies have provided new information on the complex interaction between thoracic epidural anesthesia–induced sympatholysis and cardiovascular control mechanisms. Perhaps these new insights may help identify conditions in which benefits of thoracic epidural anesthesia may not outweigh potential risks. For example, cardiac sympathectomy with high-thoracic epidural anesthesia decreases right ventricular function and attenuates its capacity to cope with increased right ventricular afterload. Although the clinical significance of this pathophysiologic interaction is unknown at present, it identifies a subgroup of patients with established or pending pulmonary hypertension for whom outcome studies are needed. Other new areas of interest include the impact of thoracic epidural anesthesia–induced sympatholysis on cardiovascular control in conditions associated with increased sympathetic tone, surgical stress, and hemodynamic disruption. It was considered appropriate to collect and analyze all recent scientific information on this subject to provide a comprehensive update on the cardiovascular effects of high-thoracic epidural anesthesia and cardiac sympathectomy in healthy and diseased patients.

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Thoracic epidural anesthesia is widely applied in thoracic and abdominal surgical procedures, because it provides excellent analgesia and decreases postoperative pulmonary complications.[1,2] Epidural anesthesia 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 extent of sympathetic blockade. Involvement of the lower thoracic region (T6 to L1) by thoracic epidural anesthesia 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 thoracic epidural anesthesia using load-dependent indices of contractile performance, which does not allow differentiation between direct and indirect effects. Regardless, the effects of thoracic epidural anesthesia 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 thoracic epidural anesthesia.[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 thoracic epidural anesthesia 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-thoracic epidural anesthesia 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 to T5) are involved in neural blockade by thoracic epidural anesthesia. An extensive list of used

This article is featured in "This Month in Anesthesiology," page 5A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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medical subject headings (MeSH) terms is presented in Supplemental Digital Content 1 (http://links.lww.com/ALN/B822). This initial search strategy yielded 1,189 references. An additional 20 references were obtained through subsequent hand search for relevant articles and authoritative texts in cited references. Only articles published in English were included. Articles were considered relevant if cardiac sympathetic blockade by thoracic epidural anesthesia 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 anesthetics 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 (J.W.) 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. The figure in Supplemental Digital Content 2 (http://links.lww.com/ALN/B823) presents a flow diagram of the literature search. The authors' main objective of this search was to compose an updated narrative review regarding the specific effects of thoracic epidural anesthesia on cardiac function.

## Search Results

The search results and study selection flowchart are presented in Supplemental Digital Content 2 (http://links.lww.com/ALN/B823). From the initial 1,209 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.

## Cardiac Neurophysiology

The central nervous system exerts a beat-to-beat control on cardiac function. Specific areas in the brain involved in emotional behavior, 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 (fig. 1). 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 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 (20 to 167%) and maximum positive rate of pressure change ($dP/dt_{max}$; 20 to 213%) after unilateral or bilateral stellate ganglion stimulation indicate substantial increases in contractility of the left ventricle in animals[15,16,19,21] and humans.[22] Left ventricle relaxation (lusitropy) was also shown to improve substantially after cardiac sympathetic stimulation.[16,23–25]

Sympathetic and parasympathetic activity depends on chemo- 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- or mechanosensory receptors *via* the glossopharyngeal and vagal nerve and is the first relay for several cardiac and cardiovascular reflexes (fig. 2).

### 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 (HR), and myocardial contractility.[26] In addition to this sympathoinhibitory pathway there is a cardioinhibitory pathway that upon excitation of the cardiovagal neurons of the nucleus ambiguous results in a decrease in HR.[26]

### Cardiac Reflexes

*Atrial Stretch Reflex.* Distension of low pressure receptors at the (pulmonary) vein–atrial junctions is signaled *via* vagal afferents to increase sympathetic activity and reduce vagal tone to the sinoatrial node. This results in increased HR 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 HR, 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

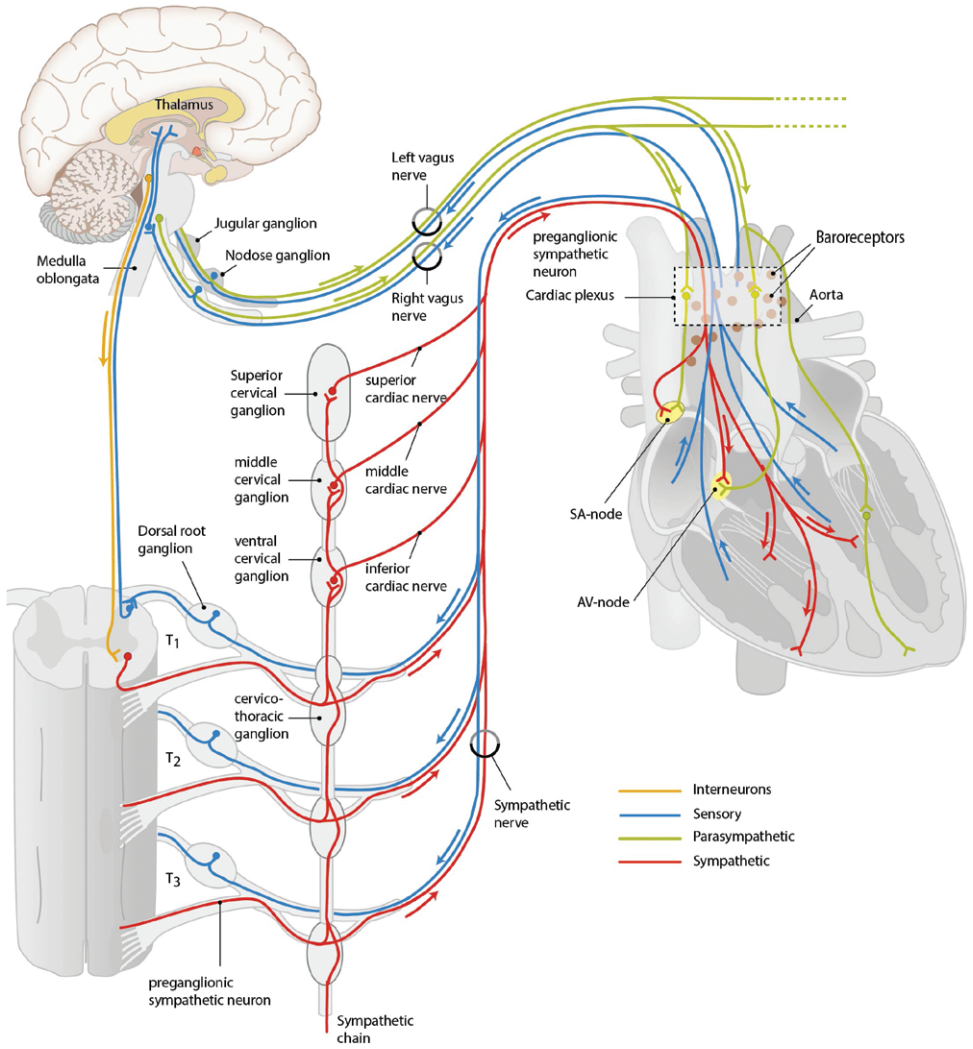


**Fig. 1.** Overview of cardiac innervation. Shown is a schematic drawing of the cardiac visceral innervation system. Cardiac innervation starts with a signal from the heart or baroreceptors (*e.g.*, on the aorta), relayed by sensory nerves (*blue*) giving feedback on, for instance, the levels of oxygen, 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*), which will synapse in cardiac ganglia from where postganglionic nerves innervate the sinoatrial (SA) node, atrioventricular (AV) node, and ventricular myocytes. Sympathetic neurons (*red*) start in the gray 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 Végh *et al.* (Végh AMD, Duim SN, Smits AM, Poelmann RE, ten Harkel ADJ, DeRuiter MC, Goumans MJ, Jongbloed MRM: Part and Parcel of the Cardiac Autonomic Nerve System: Unraveling Its Cellular Building Blocks during Development. *J Cardiovasc Dev Dis* 2016, 3:28).

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 cardioinhibitory 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]

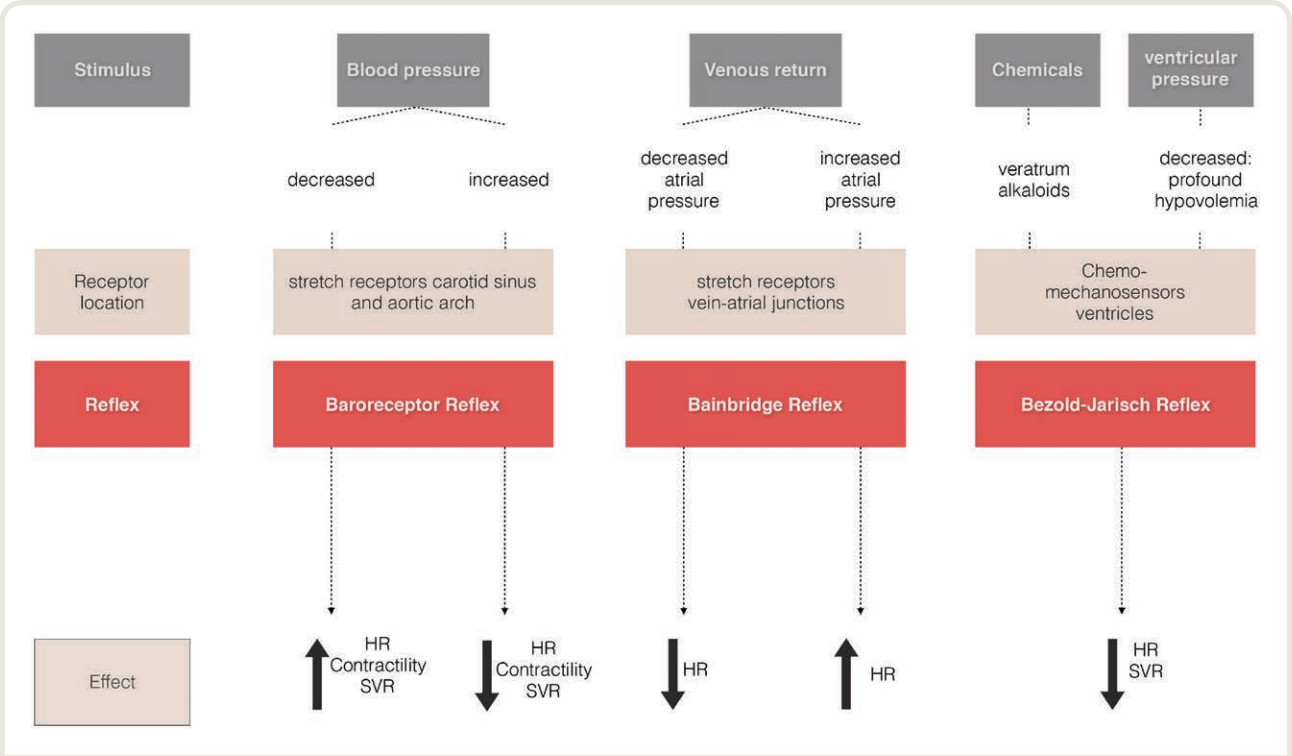


**Fig. 2.** Cardiac and cardiovascular reflexes. HR, heart rate; SVR, systemic vascular resistance.

## Cardiovascular Effects of Thoracic Epidural Anesthesia

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

### Effect on Cardiovascular Reflexes

Baroreceptor control of HR depends on an integrative role of the parasympathetic and sympathetic nervous system. This balance is affected when cardiac sympathetic innervation is blocked by thoracic epidural anesthesia. Multiple studies have demonstrated that baroreflex sensitivity is altered by cardiac sympathectomy during cervicothoracic epidural anesthesia.[34–39] However, in some studies thoracic epidural anesthesia 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 the studies mentioned in the Effect on Cardiovascular Reflexes section above may relate to heterogeneous study design, differences in the management of thoracic epidural anesthesia–induced preload changes, and the use of general anesthesia. Finally, age differences between study populations may also have contributed to the differential effects of thoracic epidural anesthesia on baroreflex control.

Sympathetic control of HR 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 thoracic epidural anesthesia on baroreceptor control of HR. Regardless, it appears that cardiac sympathetic blockade by thoracic epidural anesthesia 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 attributable to attenuation of baroreflex control with subsequent unmasking of the reversed Bainbridge or Bezold–Jarisch reflex.[41–44] Similarly, during severe hemorrhage the Bezold–Jarisch reflex may predominate, resulting in bradycardia and hypotension (fig. 2).[43]

### Summary

- Cardiac sympathetic blockade by thoracic epidural anesthesia at least partially suppresses the baroreceptor reflex.
- Extensive neural blockade by thoracic epidural anesthesia 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.[45] The effects of thoracic epidural anesthesia on HR 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, thoracic epidural anesthesia effects on HR are not solely related to blockade of preganglionic cardiac accelerator nerves but also reflect thoracic epidural anesthesia induced changes in preload and afterload (fig. 2) 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 thoracic epidural anesthesia, including cardiac sympathetic nerves. Age might affect HR response to thoracic epidural anesthesia because ageing is accompanied by an increase in sympathetic nervous system activity at rest.[57] Two studies assessed cardiovascular effects of thoracic epidural anesthesia in different age groups; however, the results are conflicting. Holman *et al.*[58] showed that HR reductions after thoracic epidural anesthesia 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, β-blockers, the chronotropic effects of which might be comparable with those of thoracic epidural anesthesia, were found to result in a more pronounced reduction in HR in young as compared with older healthy volunteers.[60]

### Summary

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

## Effect on Ventricular Contractility

The majority of thoracic epidural anesthesia studies use load-dependent indicators of global left ventricular performance indicators, such as ejection fraction, fractional area change, fractional shortening, cardiac output (CO), and stroke volume for the assessment of cardiac function (tables 1–3).[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 Left Ventricular Contractile Performance.* Several studies have shown a reduction in inotropic state (intrinsic function) after blockade of cardiac sympathetic innervation by thoracic epidural anesthesia. In anesthetized dogs, the maximal rate of ventricular pressure increase ($dP/dt_{max}$) of the left ventricle decreased after induction of thoracic epidural anesthesia but not after induction of lumbar epidural anesthesia.[65,66] These results suggest a reduction in left ventricular contractility attributable 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 thoracic epidural anesthesia but not after lumbar epidural anesthesia.[49,50] In spite of the diminished contractility of the left ventricle after thoracic epidural anesthesia, there was no change in global ventricular performance, because of a concomitant reduction of afterload.[49,50,66] Echocardiographic studies in awake and healthy volunteers compared the cardiac effects of thoracic epidural anesthesia *versus* lumbar epidural anesthesia and also found that only thoracic epidural anesthesia, but not lumbar epidural anesthesia, decreased ejection fraction, fractional area change, or fractional shortening and increased left ventricular end-diastolic volume or left ventricular end-systolic volume. They also suggest that the reduction in left ventricular cardiac function is attributable 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 thoracic epidural anesthesia on left ventricular systolic pump performance; however, the results may have been confounded by our study design, which included preinterventional volume loading. CO increased after thoracic epidural anesthesia, presumably because of the combination of increased external volume loading and thoracic epidural anesthesia–induced afterload reduction. This study in different age groups showed no effects of age on cardiovascular response to thoracic epidural anesthesia.[59] Using the slope of the end-systolic pressure–length relationship as a load-independent measure of left ventricular contractility, Goertz *et al.*[47] demonstrated in patients under general anesthesia that thoracic epidural anesthesia but not lumbar epidural anesthesia decreases left ventricular contractility by 50% (fig. 3). The results of the studies mentioned in the Effects on Left Ventricular Contractile Performance section above suggest that there is a clinically relevant

**Table 1.** Effects of TEA on Systolic 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 LEA baseline | T2 | C7–T6 | ↓ | ▬ | ND | ▬ | ↓ Ees, Mw decreased ▬ | LV and RV pressure–volume catheters | ND | ND |
| | | | | L2 | T13–L6 | ↓ | ↑ | ND | ▬ | Ees and Mw = ↓ | | ND | ND |
| | | | General anesthesia and pulmonary hypertension Control compared with TEA and LEA | T2 | C7–T6 | ↓ | ↑ | ND | ↓ | Ees and Mw decreased ▬ | | ND | ND |
| | | | | 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 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<br>Rest<br>Awake<br>Exercise | T4 | C8/T1–T5/T7 | ▬<br>↓ | ↓<br>↓ | ↓<br>ND | ↓<br>ND | ↓<br>PEP/LVET ratio increased<br>EF decreased<br>LVEDd = and LVESd increased<br>ND | ND<br>ND | ND<br>ND | ND<br>ND |
| Goertz *et al.*[47] 1993 | Echo (TTE): end-systolic pressure–volume relationship (ESPVR) | Human N = 36 | General anesthesia<br>TEA compared with control group or LEA group (L2–L5) | T8–T11 | C6/T1–T11/L4 | ▬ | ▬ | ND | ND | ↓<br>$E_{max}$ ESPVR decreased<br>LVEDV, LVESV and fractional area change remained unchanged | ND | ND | ND |
| Niimi *et al.*[67] 1997 | Echo (TTE) | Human N = 24 | Awake | T4–T6<br>T10–T12 | T1–T10<br>T6–L2 | ND<br>ND | ↓<br>▬ | ▬<br>▬ | ↓<br>▬ | ↓<br>FAC decreased<br>EF tents to decrease and LVEDV and LVESV increased<br>▬<br>FAC, EF, LVEDV and LVESV remained unchanged | ND<br>ND | ▬<br>MV E, MV A and MV E/A unchanged<br>MV DT increased<br>▬<br>MV E,MV A, MV E/A and MV DT unchanged | ND<br>ND |
| Shiga[68] 1998 | Echo (TEE) | Human N = 16 | General anesthesia<br>Control compared to TEA | T4 | At least T1–T5 | ↓ | ↓ | ND | ND | ↓<br>FS decreased<br>LVEDV = LVESV increased | ND | ▬<br>MV E and MV DT unchanged<br>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 ↑<br>MV S´ and MPI = EF increased | ~<br>TAPSE and TV S´ increased<br>RV MPI = IVA decreased | ↑<br>MV E´ increased | ↑<br>TV E´ increased |
| Wink *et al.*[71] 2016 | RV conductance catheter<br>Atrial pacing | Human N = 11 | General anesthesia<br>Control compared with TEA<br>GA and PHT Control compared with TEA | T3–T4 | ND | ▬<br>▬ | ▬<br>▬ | ▬<br>▬ | ▬<br>▬ | ND<br>ND | ↓<br>Ees, stroke work, dP/$dt_{max}$ decreased and V25 increased<br>▬ | ND<br>ND | ↓<br>$dP/dt_{min}$ decreased and nonsignificant increase in τ<br>▬ |

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

**Table 3.** Effects of TEA on Systolic 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<br>T3–T5 | At least T1–T5<br>At least T1–T5 | ▬<br>↓ | ▬<br>▬ | ND<br>ND | ND<br>ND | ▬<br>Global EF was unchanged after TEA<br>↑<br>Improved global EF after TEA | ▬<br>Regional EF was unchanged after TEA<br>↑<br>Improved regional EF and wall motion score after TEA | ND<br>ND | ND<br>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 | ▬<br>Wall motion score was unchanged after TEA | ND | ND |
| Berendes *et al.*[118] 2003 | Echo (TEE) | Human N = 73 | General anesthesia for CABG<br>Control (n = 37) *vs.* TEA (n = 36) | C7–T1 | T1–T7 | ▬ | ▬ | ND | ▬ | ▬<br>FAC was unchanged after TEA | ↑<br>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 | ↓ | ↓ | ↓ | ↓ | ▬<br>FAC was unchanged after TEA | ND | ↑<br>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 | ↑ | ↑<br>EF and tissue tracking score increased after TEA | ND | ↑<br>Improved E′/A″ indicative of improved relaxation | ND |
| Wafaa *et al.*[121] 2011 | Echo (TTE) | Human N = 48 | General anesthesia<br>Control (n = 24) *vs.* TEA (n = 24) | T2–T5 | At least T1–T5 | ↓ | ↓ | ND | ND | ▬<br>EF and FAC were unchanged after TEA | ND | ~<br>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

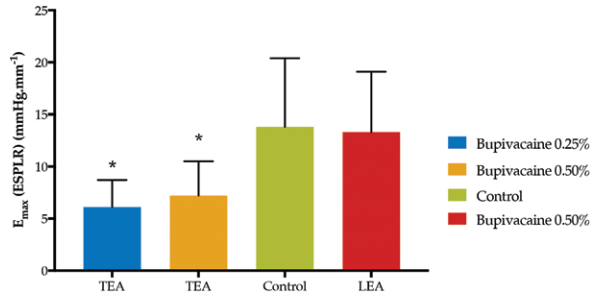


**Fig. 3.** Arithmetic means (± SD) of the maximal elastance ($E_{max}$) of the left ventricle. ***$P < 0.001$ *versus* group 3 (control) and *versus* group 4 (lumbar epidural anesthesia [LEA]). ESPLR, end-systolic pressure length relationship, TEA, thoracic epidural anesthesia. Modified with permission from Goertz *et al.* (Goertz AW, Seeling W, Heinrich H, Lindner KH, Schirmer U: Influence of high-thoracic epidural anesthesia on left ventricular contractility assessed using the end-systolic pressure-length relationship. *Acta Anaesthesiol Scand* 1993; 37:38–44.)

influence of the cardiac sympathetic nervous system on baseline left ventricular function. Blockade of cardiac sympathetic nerves by thoracic epidural anesthesia is associated with a reduction in left ventricular contractility—the magnitude of which is likely related to the level of sympathetic tone. In cardiovascular healthy patients, the cardiodepressant effects of thoracic epidural anesthesia seem to be well tolerated with preservation of CO. Use of thoracic epidural anesthesia 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 to 50% reduction in left ventricular contractility after cardiac sympathetic blockade by thoracic epidural anesthesia.
- Thoracic epidural anesthesia can be safely applied in patients with normal cardiovascular function.
- There are no studies addressing the clinical impact of thoracic epidural anesthesia–induced cardiac sympathectomy in patients with limited cardiac reserve.

### *Effect on Right Ventricular Contractile Performance*

The sympathetic nervous system plays an important role in the regulation of right ventricular function. This is illustrated by a 100% increase in contractile force of the right ventricle after right and left stellate ganglion stimulation, both containing a significant portion of the sympathetic nerves innervating the heart.[17] Only a few studies have assessed the effects of cardiac sympathetic inhibition by thoracic epidural anesthesia on right ventricular performance. Animal studies using load-independent parameters of contractility did not find decreases in baseline contractility of the right ventricle after induction of thoracic epidural anesthesia during general anesthesia[49,50] but indicated that thoracic epidural anesthesia inhibited the positive inotropic effect to increased afterload (fig. 4). This mechanism, referred to as homeometric autoregulation, enables the right ventricle to maintain stroke volume without compensatory dilatation of the right ventricle.[69,70] In awake patients thoracic epidural anesthesia reduced right ventricular isovolumetric acceleration, suggesting decreased right ventricular contractility. However, changes in loading conditions prevented clear conclusions regarding effects of thoracic epidural anesthesia on right ventricular contractility.[59] We recently investigated the effects of thoracic epidural anesthesia on right ventricular 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 right ventricular function were obtained before and after induction of thoracic epidural anesthesia during general anesthesia. Our data demonstrated thoracic epidural anesthesia–induced impairment of baseline right ventricular contractility,[71] as reflected by changes in the slope and volume intercept of the end-systolic pressure volume relationship (fig. 5). In addition there was a 25 to 30% reduction in stroke work. These observations slightly differed from the animal studies in which thoracic epidural anesthesia inhibited the increase in right ventricular function but did not reduce baseline right ventricular 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 right ventricular afterload might have been elevated already before the initiation of thoracic epidural anesthesia. This was not the case in the animal studies in which baseline values were obtained during normal ventilation.[71,72] Regardless of this discussion, both animal studies and clinical studies were concordant in showing that cardiac sympathectomy with high-thoracic epidural anesthesia directly affects right ventricular 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 right ventricular dysfunction and pulmonary hypertension. It is interesting to note that epidural analgesia was found to be 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 PeriOperative ISchemic Evaluation (POISE) study, Leslie *et al.*[8] found evidence for increased cardiovascular problems in high-risk patients receiving neuraxial block. 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 right ventricular failure or for those being treated with thoracic epidural anesthesia who develop sudden right ventricular failure in the postoperative period,

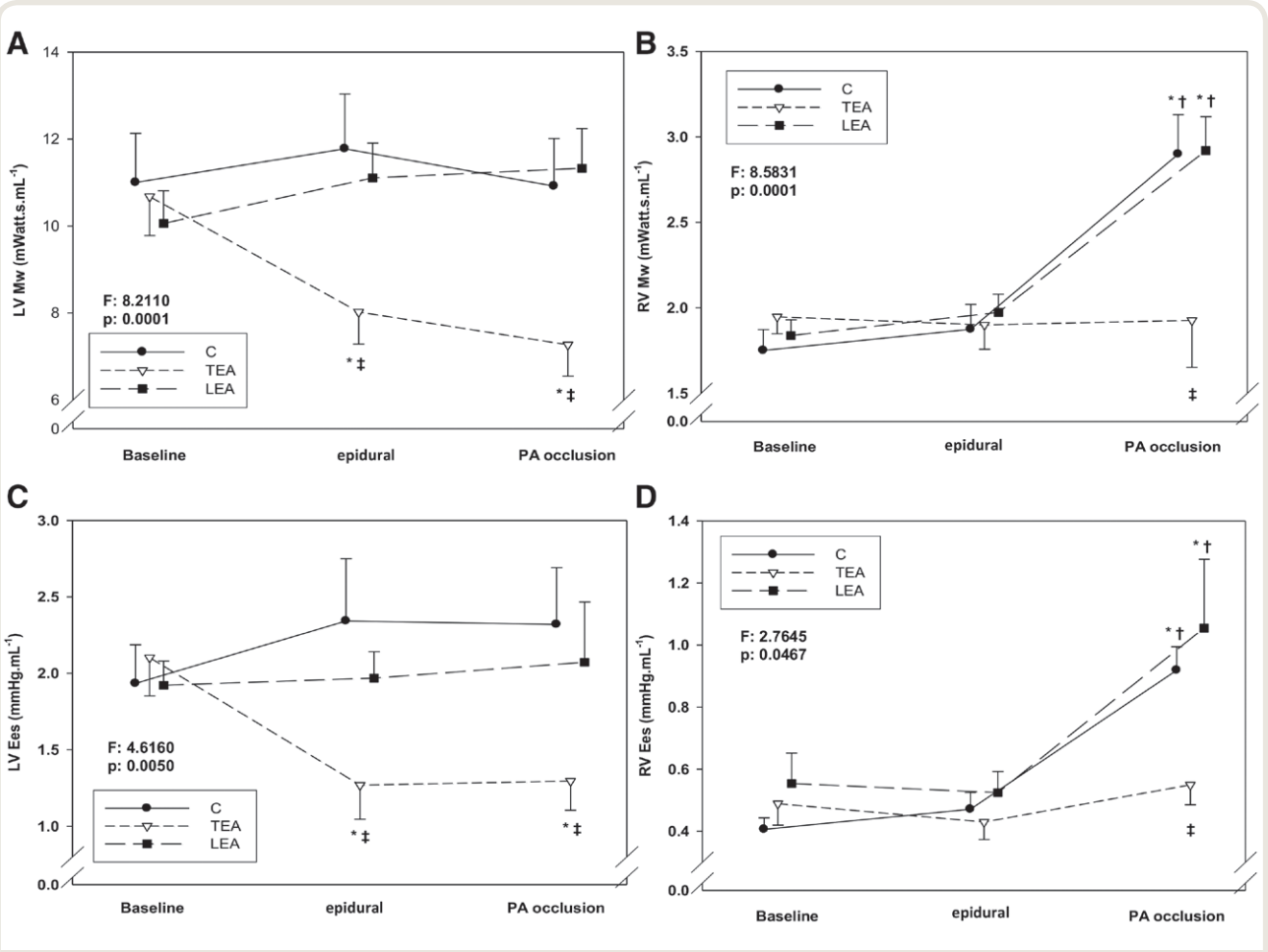


**Fig. 4.** Right and left ventricular contractility during baseline, epidural anesthesia, and acute pulmonary artery (PA) occlusion in control (C) animals and animals with a thoracic or lumbar epidural anesthesia (LEA). The effects of epidural anesthesia on the slope of the preload-recruitable stroke work relationship (Mw; *A* and *B*) and the slope of the end-systolic pressure–volume relationship (Ees; *C* and *D*) during baseline, epidural anesthesia, and during acute PA occlusion in the left ventricle (LV) and right ventricle (RV). The values are presented as means (SEM). **P* < 0.05 *versus* baseline; †*P* < 0.05 *versus* epidural; ‡*P* < 0.05 *versus* C. Reprinted with permission from Missant *et al.* (Missant C, Claus P, Rex S, Wouters PF: Differential effects of lumbar and thoracic epidural anesthesia on the haemodynamic response to acute right ventricular pressure overload. *Br J Anaesth* 2010; 104:143–9.) TEA, thoracic epidural anesthesia.

potent alternative analgesic techniques such as paravertebral blocks could also provide a solution.

### *Summary*

- Cardiac sympathetic blockade by thoracic epidural anesthesia directly reduces right ventricular contractility.
- The clinical importance of this effect is not known at present.

## Effect on Left Ventricular and Right Ventricular Diastolic Function

Ventricular relaxation and compliance are important determinants of diastolic function, an essential component of cardiac pump performance. Impaired relaxation and 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 thoracic epidural anesthesia on diastolic function, let alone the relevance of these temporary effects on clinical outcome, have not been well established. In normal conditions, contraction and relaxation are functionally coupled. Sympathetic stimulation of cardiac β-1 receptors causes a rise in cyclic adenosine monophosphate, 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 thoracic epidural anesthesia–induced cardiac sympathectomy causes a mild decrease in contractile performance, it would also decrease relaxation proportionally. However, most studies have reported unchanged left ventricular diastolic function after thoracic

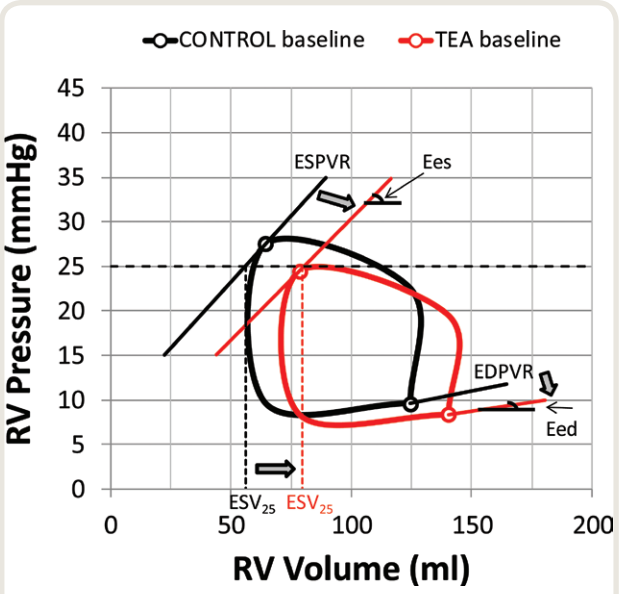


**Fig. 5.** Schematic right ventricle (RV) pressure–volume loops based on mean end-diastolic and end-systolic pressures and volumes during one-lung ventilation at baseline (*black loop*) and after induction of TEA (*red loop*). The increase in volume intercept of ESPVR at 25 mm Hg ($ESV_{25}$) and the rightward shift and more shallow slope of the end-systolic pressure–volume relationship (ESPVR) after thoracic epidural anesthesia indicate a decreased contractile performance. EDPVR, end-diastolic pressure–volume relationship; Eed, slope of the end-diastolic pressure-volume relationship, Ees, slope of the end-systolic pressure-volume relationship. Reprinted with permission from Wink *et al.* (Wink J, de Wilde RB, Wouters PF, van Dorp EL, Veering BT, Versteegh MI, Aarts LP, Steendijk P: Thoracic epidural anesthesia reduces right ventricular systolic function with maintained ventricular–pulmonary coupling. *Circulation* 2016; 134:1163–75).

epidural anesthesia in patients with normal cardiovascular status but used load-dependent parameters.[67,68] We recently studied the effect of thoracic epidural anesthesia on diastolic right ventricular and left ventricular 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 left ventricular and right ventricular diastolic function.[77] Baseline diastolic function was significantly lower in older patients, but thoracic epidural anesthesia 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 left ventricle and right ventricle remained unchanged after thoracic epidural anesthesia.[49] Using a similar technique in patients undergoing lung surgery, we found that the decrease in right ventricular inotropic state after thoracic epidural anesthesia was accompanied by a discrete reduction in right ventricular relaxation properties.[71,78] Thoracic epidural anesthesia effects on diastolic function are mild and well tolerated in healthy patients; whether this also applies to patients with established diastolic dysfunction remains to be investigated. This latter group of patients is particularly sensitive to preload changes and for that reason needs specific attention when thoracic epidural anesthesia is applied.

### *Summary*

- The direct effect of thoracic epidural anesthesia on diastolic function is minimal.
- Patients with diastolic dysfunction are extremely sensitive to changes in preload, which almost invariably occur with thoracic epidural anesthesia. Particular attention is required to prevent the hemodynamic consequences of preload reduction after thoracic epidural anesthesia 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 α-adrenoceptor–mediated coronary vasoconstriction has been demonstrated,[80,81] but adrenergic activation of the heart will also induce β-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 *et al.*[66] assessed thoracic epidural anesthesia effects on coronary circulation in healthy dogs. Coronary perfusion pressure, coronary blood flow, and systemic arterial pressure decreased after thoracic epidural anesthesia and lumbar epidural anesthesia. Interestingly, thoracic epidural anesthesia 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 thoracic epidural anesthesia as a consequence of a lower arterial pressure, HR, 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 thoracic epidural anesthesia.[84] Whether these thoracic epidural anesthesia–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 thoracic epidural anesthesia 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 thoracic epidural anesthesia group remained the same.[85] However, with a mean difference in increase of rate pressure product between the thoracic epidural anesthesia and control group of 2,215 (mm Hg/min), the increase in cardiac work and myocardial oxygen demand, if any, in the thoracic epidural anesthesia 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. Although unique for the fact that it is one of the only studies in men on this subject, the data should be interpreted with caution because myocardial contrast echocardiography is not an accurate technique to quantify myocardial perfusion.[86]

### *Summary*

Thoracic epidural anesthesia 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 thoracic epidural anesthesia are more pronounced during stress. Thoracic epidural anesthesia had no or minimal effect on HR in baseline conditions, yet the substantial increase of HR during raised right ventricular afterload was blunted after thoracic epidural anesthesia.[49,50,88,89] In addition, thoracic epidural anesthesia prevented the increase in contractility of the right ventricle and left ventricle to acutely raised right ventricular afterload, resulting in a decrease of CO and stroke volume (fig. 4).[49,50] 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 thoracic epidural anesthesia significantly reduced increases in blood pressure or HR after laryngoscopy and intubation,[91–93] whereas baseline values were only minimally changed by thoracic epidural anesthesia. In these studies thoracic epidural anesthesia involved blockade of the sympathetic innervation to the heart as well as to the adrenal glands. In a study by Dohi *et al.*,[94] cardiac sympathetic blockade by thoracic epidural anesthesia or adrenal sympathetic blockade by lumbar epidural anesthesia did not attenuate the circulatory response to laryngoscopy or intubation. These contrasting results suggest that sympathetic innervation both to the heart and adrenal glands contributes to the circulatory response after laryngoscopy and intubation. Kirnö *et al.*[95] also showed more pronounced effects of thoracic epidural anesthesia in humans during stress. They reported significant thoracic epidural anesthesia–induced reductions in the cardiac norepinephrine spillover compared with a control after, but not before, the surgical stress of sternotomy. Thoracic epidural anesthesia exercise studies in healthy volunteers showed that increases in HR during exercise were blunted after thoracic epidural anesthesia, and the decrease in HR appeared to be more substantial with increasing workloads.[52,96] Interestingly, thoracic epidural anesthesia did not completely abolish the HR response to stress or exercise, suggesting either incomplete cardiac sympathetic blockade by thoracic epidural anesthesia or involvement of the adrenal glands.

Ottesen[96] studied the effects of selective blockade of the sympathetic cardiac segments by thoracic epidural anesthesia in rest and during physical exercise in volunteers using a pulmonary artery catheter. During maximal exercise, stroke volume was maintained, and CO decreased only because of a reduction in HR after thoracic epidural anesthesia. The preservation of stroke volume does not indicate preservation of cardiac function, however, because higher end-diastolic volumes in the presence of reduced ejection fraction would also preserve stroke volume. Unfortunately, intrinsic ventricular function was not assessed in this study; hence comparisons between thoracic epidural anesthesia 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 thoracic epidural anesthesia are more pronounced during stress or exercise than in resting conditions. Data from thoracic epidural anesthesia 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 thoracic epidural anesthesia. 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 thoracic epidural anesthesia.

### *Summary*

- Thoracic epidural anesthesia 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 thoracic epidural anesthesia could interfere with this endogenous defense mechanism when hemodynamic challenges occur in the perioperative setting.

## Effects of Thoracic Epidural Anesthesia 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 HR. 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 thoracic epidural anesthesia 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, thoracic epidural anesthesia has been demonstrated to increase myocardial oxygen availability[103] and to improve myocardial oxygen balance by reducing HR, preload, and afterload, without affecting coronary perfusion pressure.[104] Reiz *et al.*[105] showed that in patients with coronary artery disease, thoracic epidural anesthesia reduces coronary vascular resistance and myocardial oxygen consumption. This cardioprotective role of thoracic epidural anesthesia is further supported by observations that thoracic epidural anesthesia compared with controls decreased loading conditions of the heart and myocardial oxygen demand after sternotomy.[95]

Coronary atherosclerosis and endothelial dysfunction are associated with an exaggerated response to coronary α-adrenergic activation that results in a reduced coronary blood flow response during sympathetic stimulation.[106–108] Cardiac sympathetic inhibition by thoracic epidural anesthesia might therefore improve coronary function in patients with coronary artery disease. Indeed, thoracic epidural anesthesia resulted in an increased luminal diameter in stenotic epicardial coronary arteries but not in the nonstenotic epicardial coronaries.[109] Whether this resulted in increased myocardial blood flow, a phenomenon referred to as reverse coronary steal, is unknown because myocardial blood flow was not measured in this study. In a more recent study by Nygård *et al.*,[110] the effects of thoracic epidural anesthesia on myocardial blood flow were assessed in patients with coronary artery disease. Whereas in patients without thoracic epidural anesthesia myocardial blood flow was unchanged during sympathetic stimulation, patients with thoracic epidural anesthesia 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 thoracic epidural anesthesia and decreased in stenotic and nonstenotic vessels with thoracic epidural anesthesia. Thoracic epidural anesthesia–induced changes in myocardial blood flow were less than 10% at rest, whereas 17 to 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]

Thoracic epidural anesthesia 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] In addition to improving myocardial oxygen balance, these thoracic epidural anesthesia–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 thoracic epidural anesthesia 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 thoracic epidural anesthesia.[116] These results were confirmed in patients with coronary artery disease during general anesthesia and thoracic epidural anesthesia. Despite lower coronary perfusion pressures after the induction of thoracic epidural anesthesia, 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] Thoracic epidural anesthesia significantly improved regional left ventricular wall motion and reduced ischemia and coronary risk in patients with coronary artery disease in another study.[118] Schmidt *et al.*[119] report improved diastolic and maintained systolic left ventricular function after thoracic epidural anesthesia in coronary artery disease patients. Another study using a derivative of tissue Doppler imaging demonstrated thoracic epidural anesthesia–induced improvements of diastolic and systolic left ventricular function in patients with ischemic heart disease.[120]

Clinical studies have been performed assessing the effect of thoracic epidural anesthesia on myocardial damage determined by the amount of postoperative troponin in coronary artery bypass graft patients. The potential myocardial protective effect of thoracic epidural anesthesia 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 thoracic epidural anesthesia on postoperative troponin as a marker of myocardial damage.[122–126] A potential influence of thoracic epidural anesthesia 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 *et al.*[130] found

no significant effect of thoracic epidural anesthesia on the incidence of perioperative myocardial infarction. Although 2,731 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 thoracic epidural anesthesia. In fact, the majority of meta-analyses available today failed to show a significant clinical impact of thoracic epidural anesthesia on cardiovascular outcome. This is in contrast with the well documented effects of thoracic epidural anesthesia 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 thoracic epidural anesthesia 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 thoracic epidural anesthesia and optimize its application in clinical practice.

### *Summary*

Thoracic epidural anesthesia 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 because pulmonary hypertension may result in right ventricular failure, and right ventricular function has been shown to be an important determinant of outcome.[10–12] Jahn *et al.*[88,89] demonstrated that in a model of ovine pulmonary embolism, induction of thoracic epidural anesthesia contrary to lumbar epidural anesthesia improves hemodynamic variables mainly as a result of a decrease in pulmonary vascular resistance. Effects of thoracic epidural anesthesia on right ventricular contractility were not measured, and extension of neural blockade was not assessed. Hemodynamic deterioration caused by pulmonary embolism was reduced by thoracic epidural anesthesia and aggravated by lumbar epidural anesthesia. The authors suggest that reduction of sympathetic outflow to the heart and lungs is the underlying mechanism for the beneficial results of thoracic epidural anesthesia during pulmonary hypertension. They also suggest that increased sympathetic tone in the unblocked thoracic spinal levels associated with lumbar epidural anesthesia is responsible for the hemodynamic aggravation during pulmonary hypertension. This is in contrast to the results of earlier experimental studies demonstrating that in respiratory distress syndrome, during pulmonary artery constriction and in pulmonary artery embolism, right ventricular contractility increases proportionally to an increase in right ventricular afterload (homeometric autoregulation). In anesthetized pigs, induction of thoracic epidural anesthesia has been shown to abolish this inotropic response to acutely raised right ventricular afterload (fig. 4). Combined with an increase in pulmonary vascular resistance, induction of thoracic epidural anesthesia resulted in a significant decrease in CO.[49,50] Moreover, lumbar epidural anesthesia had no effect on the hemodynamic response to pulmonary hypertension (fig. 4). Results indicate that the sympathetic nervous system might have an important role in the described inotropic response of the right ventricle to pulmonary hypertension. In humans, however, thoracic epidural anesthesia did not affect the native positive inotropic response of the right ventricle to increased afterload (fig. 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 thoracic epidural anesthesia was prevented, and cardiovascular effects might have been more profound without pacing. Overall, cardiac sympathetic blockade by thoracic epidural anesthesia reduces right ventricular contractile performance. The clinical importance of this finding is unknown. The role of the right ventricle has been neglected for a long time, and it has never been investigated whether temporary changes in right ventricular 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 right ventricular afterload, thoracic epidural anesthesia might interfere with the capacity of the right ventricle to adapt to increases in afterload, resulting in decreases in CO and cardiovascular collapse.

### *Summary*

High-thoracic epidural anesthesia limits cardiac reserve and the capacity of the right ventricle to adapt to increases in right ventricular afterload, which can decrease CO.

## Conclusions

There has been renewed interest in the cardiovascular effects of thoracic epidural anesthesia since the latest review on this subject was published 10 yr ago.[9] The beneficial hemodynamic effects and cardioprotective properties of thoracic epidural anesthesia, demonstrated in a number of experimental studies, did not translate in better cardiac outcome for patients undergoing surgery who were treated

with thoracic epidural anesthesia. More recent exploratory studies even suggested that thoracic epidural anesthesia was associated with increased cardiovascular problems in high-risk patients. Mechanisms underlying such a potential harmful effect and characteristics of high-risk populations, however, remain speculative.

Recent experimental and clinical studies have added information on the complex interaction between thoracic epidural anesthesia–induced sympatholysis and cardiovascular homeostasis. Using more advanced methodology, they clearly demonstrate that cardiac sympathetic blockade by high-thoracic epidural anesthesia reduces left ventricular and right ventricular contractility. This direct effect of thoracic epidural anesthesia is well tolerated in healthy subjects because concomitant arteriolar vasodilation and the subsequent decrease in left ventricular afterload facilitate cardiac ejection. Hence overall pump performance and CO 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 right ventricular inotropic state can have more impact on pump performance.

The cardiovascular effects of thoracic epidural anesthesia 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. Thoracic epidural anesthesia 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 thoracic epidural anesthesia.

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

In conclusion, the conviction that thoracic epidural anesthesia has beneficial hemodynamic effects may not apply to all patients. Although protective in particular pathophysiologic conditions such as ischemic heart disease, cardiac sympatholysis may also attenuate the capacity of the heart to respond to hemodynamic challenges in particular subgroups. This should be considered whenever patients treated with thoracic epidural anesthesia develop hemodynamic instability in the perioperative setting.

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## Competing Interests

The authors declare no competing interests.

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