The physiological effects of thoracic epidural anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems

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ABSTRACT

Studies of regional anesthesia are increasing in popularity not only for the purpose of technical advancement, but also to better understand the effects of neural deafferentation on the function of various organs. Thoracic epidural anesthesia (TEA) is one of the most versatile and widely utilized neural deafferentation techniques. The aim of this article is to critically review published data regarding the most relevant effects of TEA on the cardiovascular, respiratory and gastrointestinal systems. In the cardiovascular system, TEA modifies the electrical activity of the heart in addition to ventricular function and wall motion. Improvements in regional blood flow and a reduction of the major determinants of cardiac oxygen consumption lead to less severity of the ischemic injury. Although TEA negatively affects the performance of intercostal muscles, it spares diaphragmatic function and, when it is limited to the first five thoracic segments, affects pulmonary volumes to a lesser extent. TEA can be safely used in patients with compromised respiration. Splanchnic sympathetic block is achieved when thoracic fibers from T5 to T12 are affected in a dose-dependent manner. Improved gastrointestinal blood flow and motility are clear in animals, and in clinical studies, TEA has been shown to improve recovery after major abdominal surgery. TEA thus presents a powerful tool available to anesthesiologists for perioperative intervention, but its use alone cannot prevent postoperative morbidity and mortality. It is therefore necessary to address its use in the context of multimodal intervention.

Key words: Anesthesia, epidural - Analgesia - Heart, physiology - Lung, physiology - Digestive system, physiology.

Regional anesthesia has enjoyed a tremendous increase in popularity over the past 20 years as the result of improved training, technological advances, and better understanding of the physiology of neural deafferentation on the function of various organs. Anesthesiologists have become increasingly involved in the treatment of acute, chronic and cancer pain, with a special emphasis on providing effective and efficient regional anesthesia. Despite its potential advantages, regional anesthesia only comprises 30-40% of anesthetic treatments in North America. Barriers to widespread practice of regional anesthesia include a lack of organized opportunities to perform and teach techniques without time constraints, the fear that a block might not work and a lack of experience.

Epidural anesthesia is one of the most versatile and extensively utilized regional anesthetic techniques. It is used not only for surgery, but also for obstetrics and trauma as well as acute, chronic, and cancer pain states. Thoracic epidural anesthesia (TEA) has been consistently shown to provide excellent pain relief, to facilitate early extubation, ambulation, oral intake of food and gastrointestinal function, to attenuate the stress response, and to improve postoperative pulmonary function. The clinical benefits of TEA can be explained to some extent by the physiological effects of neural deafferentation on various aspects of surgical patho-

physiology. The aim of this article is to critically review the current volume of published data regarding the effects of thoracic anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems, as these three systems have been thoroughly studied and are of particular importance to anesthesiologists practicing TEA on a daily basis.

Thoracic epidural anesthesia and the cardiovascular system

Effects on heart rate and rhythm

A significant portion of the chronotropic and inotropic control of the heart is mediated by afferent and efferent fibers carried through the reflex arch in the upper five thoracic spinal segments. Animal studies have confirmed a clear effect of TEA on cardiac electrophysiology. Hotvedt *et al.* showed increased ventricular effective and functional refractory periods and lengthened monophasic action potentials in dogs. Atrio-ventricular (AV) nodal conduction time and AV nodal functional refractory period were also markedly prolonged.[1] A further reduction of heart rate, prolonged AV nodal conduction time and refractoriness, decreased LV dP/dt max and decreased arterial blood pressure were found when TEA was added to intravenous injection of atenolol, suggesting a mechanism of decreased β-receptor stimulation.[2]

A TEA-mediated increase in vagal activity cannot be excluded because TEA did not attenuate epinephrine-induced dysrhythmias in the presence of halothane in bilaterally vagotomized anesthetized dogs.[3] It is not known whether the sympathetic nervous system functions directly as a cardioaccelerator or indirectly by modifying the parasympathetic tone. Meissner *et al.*[4] studied the effects of isolated cardiac sympathectomy by TEA in awake dogs and found lengthened repolarization and a prolonged refractory period in a ventricular site when compared to the atrium.

With TEA, a small but significant reduction in heart rate can be observed in healthy volunteers[5] and surgical patients.[6] In healthy volunteers, Takeshima *et al.* have documented that cervical epidural blockade induces only a slight impairment of the baroreflexes;[7] these results are similar to those described by Bonnet *et al.* in patients undergoing carotid artery surgery where blockade of cardiac sympathetic innervation reduced baroreflex reactivity without complete abolition.[8] High TEA (T1-T5) that spared the lower thoracic and the lumbar areas does not block the sympathetically-mediated cardiocirculatory response to various stresses such tracheal intubation[9] and hypercapnia.[10] Although the overall reduction of sympathetic tone and block of the cardiac accelerator fibers could reduced the risk of dysrhythmia as observed during cardiac surgery and cardiopulmonary bypass,[11, 12] a randomized controlled trial was not able to show decreased incidence of postoperative sustained atrial fibrillation despite a significant reduction in sympathetic activity.[13] Similarly, a direct temporal relationship between the presence or absence of TEA and the incidence of atrial arrhythmia could not be demonstrated.[14]

Myocardial function

The effect of TEA on myocardial function has been the subject of several experimental and clinical studies, but the results remain controversial.

Ventricular function

The reduction of cardiac sympathetic outflow by TEA may affect myocardial contractility, although the available data have yielded contradictory conclusions. In an animal study, TEA showed a beneficial effect with a significantly slower heart rate, decreased mean pulmonary artery pressure and central venous pressure, and significantly higher stroke volume index and oxygenation.[15] These data are not consistent with findings in dogs where TEA produced depression of both cardiac conduction and inotropy.[2]

In 48 patients, Goertz *et al.*[16] assessed left ventricular contractility using the end-systolic pressure-length relationship and cardiac dimensions determined by transesophageal echocardiography; they concluded that high TEA severely alters left ventricular contractility even in subjects without pre-existing cardiac disease. In healthy patients, Niimi *et al.*[17] found decreased cardiac output but not reduced left ventricular ejection or diastolic filling performance as assessed by transthoracic echocardiography. Neither impairments nor

improvements of segmental wall motion were demonstrated by transesophageal echocardiography in patients at risk for myocardial ischemia.[18] On the other hand, Kock *et al.* showed during exercise stress testing of patients with coronary artery disease (CAD) that left ventricular global and regional wall motion were better preserved after TEA.[19] Furthermore, significantly improved left ventricular function and reduced ischemia were demonstrated in patients undergoing coronary artery bypass grafting,[20] with a greater beneficial effect shown for patients with low ejection fraction.[21]

Coronary blood flow

Large coronary epicardial arteries and coronary arterioles are densely innervated by sympathetic adrenergic nerve fibers. Cardiac sympathetic stimulation results in vasoconstriction of both normal and diseased coronary segments in animals and in humans.[22-24]

In a canine model of experimentally-induced myocardial ischemia, cardiac sympathectomy by TEA has been shown to improve regional cardiac blood flow.[25, 26] High epidural blockade redistributes coronary blood flow to favor the endocardium in both normal and infarcted hearts.[25] Davis *et al.* confirmed this observation by also finding favorable alteration of the myocardial oxygen supply/demand ratio in addition to reduced hemodynamic correlates of myocardial O_2 consumption.[26]

In patients with severe CAD and unstable angina, high TEA relieved chest pain and was also found to beneficially affect the major determinants of myocardial oxygen consumption by lowering arterial systolic blood pressure and heart rate as well as pulmonary artery and pulmonary capillary wedge pressures, with no significant changes in coronary perfusion pressure.[27] These results were confirmed in a recent randomized controlled trial in which blockade with 5-10 mL of 0.3% ropivacaine increased myocardial oxygen levels prior to surgical revascularization without deleterious hemodynamic disturbances.[28]

Overall, TEA results in improvement of the oxygen supply/demand ratio without jeopardizing coronary perfusion pressure within ischemic myocardial areas. Moreover, cardioselective epidural blocks can increase the luminal diameter of stenosed segments of epicardial coronary arteries without affecting the diameter of non-stenotic segments[29] and without any effects on coronary resistance vessels.

Myocardial infarction and reperfusion injury

The effect of cardiac sympathetic blockade on myocardial infarction was studied in a canine experimental model. TEA resulted in substantially decreased severity of acute myocardial ischemic injury in open-chest dogs, mainly through reduction of myocardial mechanical activity,[30] and reduced infarct size as well as less postischemic hyperemia.[31]

After brief episodes of ischemic insult, recovery in awake dogs was significantly faster with high TEA,[32] whereas no additional protective effect on functional recovery from myocardial stunning was found in dogs anesthetized with sevoflurane[33] or propofol.[34]

In patients undergoing coronary artery bypass, TEA has been shown to reduce postoperative infarction as determined by reduced levels of troponin T[6] and cardiac troponin I, as well as after-reperfusion peak concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).[20]

In a recent randomized controlled study using a small sample, Kendall *et al.* did not find a significant difference in troponin T release at 24 hours after off-pump coronary artery surgery.[35] The use of TEA for abdominal surgery in patients at risk for coronary artery disease has been demonstrated to have no effect on perioperative plasma ANP and troponin T concentrations, and to reduce postoperative plasma concentrations of BNP.[36]

An overall reduction in the incidence of myocardial infarction has been indicated by two meta-analyses.[37, 38] Rodgers *et al.* concluded that patients receiving neuraxial anesthesia had fewer perioperative complications with a 33% reduction of myocardial infarction,[37] and Beattie *et al.*, who directly evaluated the effect of continued TEA on postoperative myocardial infarction, found a 3.8% lower incidence than in the control group.[38]

Hypotension and stress-related responses

Homeostatic responses to stress depend heavily on sympathetic efferent pathways, thus poor compensation for hypotension, hypoxemia and hypercapnia might be expected during the sympathetic blockade that accompanies TEA.

Thoracic epidural anesthesia and hypotension

In healthy volunteers, systolic and diastolic blood pressures are decreased after epidural anesthesia.[39] Hypotension is partly due to cardiodepressant activity and partly due to arterial and venous vasodilation. Peripheral vascular tone is controlled by α- and β-adrenergic receptors and indirectly by circulating catecholamines released from the adrenal medulla as the result of sympathetic outflow between segments T5 and L1. The range of depressant effects generated by high epidural blockade can be quite broad depending on the extent of spinal segment deafferentation. In a dog model, the upper thoracic roots demonstrated lateralized differences in their effects on homeostasis.[40] For example, blood pressure increased most when the upper four thoracic roots on the left side were stimulated, with T1 giving the greatest response followed by T2, T3 and T4. In contrast, T5 on the left gave an insignificant response, where T5 on the right side gave a strong response.[41] If these findings can be generalized to humans, the greatest suppression of blood pressure should occur when targeting the upper two thoracic segments on the left side.

Inhibitory effects of vasoconstrictor sympathetic outflow lead to functional hypovolemia. Epidural anesthesia *per se* does not affect intravascular volume or hemoglobin concentration. In 12 volunteers, Holte *et al*. investigated in detail the changes in plasma volume and intravenous fluid kinetics after TEA and with subsequent administration of vasopressors or plasma expanders, and found a significant decrease in hemoglobin concentration after hydroxyethyl starch administration.[42] Therefore, vasopressors may be preferable for treatment of hypotension after TEA, and not only for patients with cardiopulmonary diseases. Surgical patients can also benefit from a water restriction regimen.[43] Volume preloading to counteract decreased blood pressure after induction of TEA should therefore also be avoided.

If the sympathetic block is not extensive, the vasodilatation and sequestration of the blood are partly compensated by constriction of capacitance vessels in the remaining unblocked areas.[44] Furthermore, increased activity in remaining unblocked splanchnic nerve fibers can cause circulating catecholamines to be released from the adrenal medullary system, thereby contributing to increased sympathetic activity below the block.

The renin-angiotensin and vasopressin systems serve as important backup mechanisms for maintaining arterial blood pressure during circulatory challenge in both humans and animals.[45, 46] TEA interferes with the functional integrity of the renin-angiotensin system in healthy patients by blocking preganglionic sympathetic fibers innervating the kidney,[47] but it simultaneously increases the vasopressin concentration, most likely to compensate for decreased cardiac filling or arterial blood pressure when sympatho-adrenal responses are impaired.[48]

In spite of the overall hypotensive effect, some studies have even demonstrated a beneficial outcome for epidural anesthesia during hemorrhagic shock. Shibata *et al*. found that TEA initiated before hemorrhaging showed increased survival and decreased metabolic acidosis in dogs.[49] Survival was particularly improved when using upper level TEA. Similarly, Yoshikawa *et al*. concluded that hemodynamic and metabolic changes after hemorrhage were milder when dogs received segmental thoracic epidural analgesia as compared to thoraco-lumbar analgesia, confirming that widespread epidural administration weakens the response to hemorrhage.[50]

The survival benefit of upper TEA cannot simply be explained by differences in the levels of plasma catecholamines. In fact, Shibata *et al*. found no significant differences in catecholamine levels at any time point for TEA treatment after hemorrhage in dogs with or without intravenous infusion of epinephrine and norepinephrine. This implies that differences in catecholamine levels at the direct level of the nerve endings or other factors may be more important for survival effects.[51]

Cardiovascular response to hypoxemia and hypercapnia

TEA can modulate circulation during hypoxia in order to maintain arterial pressure. Two studies in canine models evaluated the cardiovascular response to hypoxia during epidural anesthesia.[48, 52] In awake dogs, Peters *et al.* reported that TEA blunted the changes in vital signs in response to short-term hypoxia (PaO_2 = 4.1±0.6 kPa for 10 min) while promoting vasopressin secretion and preservation of the ventilatory response.[48] Consistent with these results, Shibata *et al.* concluded that during longer periods of hypoxia (FiO_2 = 0.09 for 120 min) in anesthetized dogs, TEA could obscure the initial cardiovascular signs but also decrease myocardial oxygen requirements, increase O_2 extraction from the blood and attenuate the development of metabolic acidosis.[52]

Data regarding the influence of epidural blocks on the effects of hypercapnia are conflicting. In dogs, thoracic and thoraco-lumbar epidural anesthesia during hypercapnia depressed cardiac output and mean arterial blood pressure, although the physiological increase in circulating catecholamine levels was only abolished in the thoraco-lumbar epidural group.[53] However, a previous study in awake humans did not find significant changes in heart rate and blood pressure after cervico-thoracic epidural block in response to CO_2, and neither resting ventilation nor ventilatory response were affected.[54] Further studies are necessary to understand the physiological mechanism.

Summary

Thoracic epidural analgesia exerts a remarkable influence on the cardiovascular system. With regard to cardiac electrical activity in animal models, TEA was found to lengthen repolarization and the refractory period more at ventricular sites than at atrial sites. AV conduction and refractoriness were also prolonged. Human studies have documented a slight impairment in the sensitivity of the baroreflexes but sparing of sympathetically mediated responses to various stressors if TEA is limited to the first five thoracic vertebrae. Although it may reduce the overall risk of perioperative dysrhythmia, TEA does not decrease the incidence of postoperative atrial fibrillation.

Animal studies have produced contradictory results regarding the effect of TEA on ventricular function. In healthy patients, TEA seems to alter left ventricular contractility and reduce cardiac output, whereas it better preserves left ventricular global and regional wall motion in cardiac surgical patients.

TEA has been shown in canine models to improve cardiac regional blood flow to favor the endocardium, and in human patients to reduce the major determinants of cardiac oxygen consumption and even increase the luminal diameter of stenotic coronary segments without jeopardizing coronary perfusion pressure.

Thus, TEA can lessen the severity of acute myocardial ischemic injury and facilitate recovery after brief ischemic insult in experimental models. In patients, changes in the levels of troponin T and ANP are not consistent, but it is clear that TEA decreases the levels of brain natriuretic peptide as well as the overall incidence of myocardial infarction.

TEA produces functional hypovolemia by inhibiting vasoconstrictor sympathetic outflow; moreover, it interferes with the integrity of the renin-angiotensin system but incrementally increases the plasma concentration of vasopressin. Despite its hypotensive effect, TEA shows therapeutic benefit during hemorrhagic shock. The response to hypoxemia but not hypercapnia is blunted by TEA.

Thoracic epidural analgesia and the respiratory system

Respiratory muscles

Segmental blocks can impair the activity of respiratory muscles in the rib cage. The influence of TEA on the performance of parasternal intercostal muscles was investigated in anesthetized spontaneously breathing dogs,[55] and it was found that epidural injection of 0.1 mL/kg of 2% lidocaine completely abolished electromyographic activity and passive elongation of the parasternals during inspiration. It is thus likely that other respiratory muscles in the rib cage could be impaired as well.

In 6 healthy male volunteers, high TEA induced mechanical impairment of rib cage movements resulting in a decreased ventilatory response to carbon dioxide. Ventilatory impairment and

changes in the breathing pattern probably reflect the blockade of efferent or afferent pathways (or both) of the intercostal nerve roots.[56] TEA has been shown to decrease the percentage contribution of rib cage expansion during inspiration, and substantially increase the functional residual capacity (FRC) with a significant net caudal motion of the end expiratory position of the diaphragm.[57] Paralysis of the rib cage muscles did not increase the electrical activity of the unblocked muscles such as the scalenes.[58] Thus, if the diaphragm is capable of functioning normally, adequate ventilation should be maintained even with a reduction of the thoracic component of ventilation.

The diaphragm is the principal muscle of inspiration and is differentially innervated by the phrenic nerve (from C3 to C5), allowing the costal and crural sections to contract independently. Regional diaphragmatic shortening normalized by end-expiratory length has been measured by implantation of sonomicrometer crystals into the costal and crural regions of the diaphragms of awake lambs.[59] Improved postoperative tidal volume and diaphragmatic shortening were observed after TEA, probably due to changes in chest wall conformation and resting length, and intercostal muscle paralysis caused the effort of breathing to shift from the rib cage to the diaphragm. This improvement was not seen in patients after thoracotomy, despite increased values of other indices of respiratory function.[60] This difference in outcome may be species-related. These findings were confirmed in healthy subjects by Warner *et al.*, who demonstrated significantly decreased inspiratory volume as a result of the displacement of the rib cage after high TEA.[57] In contrast, other studies showed improved diaphragmatic activity by TEA after abdominal surgery by not only indirect measurement,[61] but also direct diaphragmatic electromyography using intramuscular electrodes.[62] Interruption of afferent input producing inhibition of diaphragmatic activity appears to be the most attractive hypothesis for these effects. In fact, TEA-related increases in diaphragmatic function appear to result from interruption inhibitory of motor impulses in the phrenic nerve that are either related to direct deafferentation of visceral sensory pathways or to diaphragmatic load reduction due to increased abdominal compliance.[63]

Response to hypercapnia and hypoxia

In 6 healthy male volunteers, Kochi *et al.* showed decreased hypercapnic ventilatory response following TEA with 9-12 mL of 2% lidocaine. Such decreases during spontaneous respiration were most likely due to the decreased contribution of the rib cage to tidal breathing, probably reflecting the blockade of efferent or afferent pathways of the intercostal nerve roots.[56] Different results were found by Sakura *et al.* in elderly patients.[64] Both lumbar analgesia and TEA (10 mL of 2% lidocaine) preserved the ventilatory response to hypercapnia and did not impair elements of the hypoxic drive, *e.g.* the ventilatory response to progressive isocapnic hypoxemia.[65]

Lung volumes

During epidural administration of local anesthetics some modifications in lung volume can be expected, depending on the extent of the neural blockade. It has been reported that TEA causes inspiratory capacity to significant decrease by approximately 11%, vital capacity (VC) by 13%, total lung capacity by 9% and FRC by 6%. Both forced expiratory volume in 1 s (FEV1) and forced VC (FVC) were decreased by 12%. PaO_2 and the alveolar-arterial oxygen tension difference were increased; PaO_2 decreased significantly at 25 min after the block, but not to a degree that would have clinical consequences.[66] Similar effects were observed for expiratory functions, *i.e.* expiratory reserve volume and expired minute volume. These results are consistent with findings of a previous study by Sjogren *et al.* that showed decreases in dynamic tests of ventilatory capacity.[67]

In 9 healthy volunteers, limitation of the thoracic block to dermatomes T1 to T5 decreased VC by 5.6% and FEV1 by 4.9%, probably as a result of intercostal motor blockade. Nevertheless, none of the volunteers complained of dyspnea or difficulties in breathing.[68]

The position of the patient can affect lung function measurements, resulting in decreased VC and FEV1.[69] Unfortunately, the previous study design did not take into account whether comparisons of treated conditions to the baseline were made in a sitting or supine position. Pulmonary function

tests are even less reliable when performed in the early postoperative period due to large technical errors that result from patient fatigue and lack of cooperation.[70]

Perioperative period

Thoracic and major abdominal surgery often induce postoperative pulmonary dysfunction with reduced FRC, FEV1 and VC. These changes can last for up to 14 days until complete recovery.[71]

TEA has been shown to blunt the reduction of FRC and VC after abdominal surgery.[72] Manikian *et al*. demonstrated that VC improved from 1380±115 mL to 1930±144 mL in patients after abdominal aortic surgery.[61] In patients undergoing cholecystectomy, Hendolin *et al*. found that TEA significantly prevented postoperative deterioration of respiratory function; FVC, FEV1 and PEF were decreased by 20% as compared to 55% for patients who received general anesthesia alone. This improvement continued for 48 h after surgery.[73]

Tenling *et al*.[74] obtained comparable findings for cardiac surgery. VC and FEV1 differed from baseline by about 10% on the 1st postoperative day; most interestingly, patients with TEA but not patients receiving systemic opioids were able to perform lung function measurements at 1 h after extubation. Considering that FEV1 well represents the ability of the patient to cough, this result might be more important than those of other functional pulmonary tests.

Many other factors can influence postoperative lung function including residual muscle relaxation, time of extubation and pain therapy. The use of muscle relaxation during general anesthesia seems to produce a type of "rest relaxation" characterized by a fading of muscle strength when maximal contractions are repeated. This could imply that FEV1 measurements "fade" as well.[75] Under epidural anesthesia, muscle relaxants are not always necessarily required, thus entirely excluding the fade effect.

In order to avoid the risk of pulmonary infections and other side effects linked to prolonged mechanical ventilation, early extubation is desirable even after major surgical procedures such as esophageal resection.[76] Several studies have shown that after these procedures, patients can be extubated directly at the end of surgery if regional blockades such as epidural and combined spinal-epidural anesthesia[77, 78] are used.

Pain impairs the ability of patients to deeply inspire and to cough, thus leading to increased risk of atelectasis. In a recent meta-analysis, Wu *et al*. found consistently significant benefits of epidural analgesia as compared to intravenous PCA morphine, particularly for alleviating pain upon activity. TEA resulted in pain-free ventilation and increased abdominal ventilation in the intra- and postoperative period after thoracotomy and major abdominal surgery.[61, 79] More profound postoperative analgesia has been advocated in order to improve the ability to cough, as this ability depends upon expiratory muscle strength.[74]

The induction of general anesthesia can also impair pulmonary gas exchange due to the development of intrapulmonary shunt and ventilation-perfusion (Va/Q) inequality. The degree of oxygenation impairment is directly correlated with the amount of atelectasis.[80] Muscle tone and cranial movement of the diaphragm play important roles in regional lung collapse; thus concern has been expressed about the role of TEA in ventilation/perfusion mismatch. Interestingly, Hachenberg *et al*. demonstrated that addition of TEA to general anesthesia in patients undergoing major abdominal surgery resulted in no additional effect on Va/Q distribution and gas exchange.[81]

Effects in respiratory compromised patients

In spite of the beneficial effects of TEA on organ function and postoperative pain relief, experimental and clinical experience suggests that motor blockade associated with TEA could lead to respiratory decompensation whereas sympathetic blockade could lead to increased bronchial tone and airway hyper-reactivity. For this reason, there has been some interest in elucidating the effect of TEA in specific groups of patients with compromised respiration.

Obesity

Obesity is a risk factor for postoperative pulmonary complications since it predisposes patients to the formation of atelectasis, which can then

lead to respiratory dysfunction thus contributing to pulmonary morbidity. A negative correlation between obesity and perioperative spirometric tests has been shown.[82]

Von Ungern-Sternberg *et al*. investigated the effects of TEA and conventional opioid-based analgesia on perioperative lung volumes as measured by spirometry in obese and non-obese patients. All perioperative spirometric values decreased significantly with increasing body mass index, and recovery was significantly faster for obese patients receiving epidural analgesia.[83]

Weight reduction surgeries show particularly interesting results in terms of the improvement of overall recovery. Following gastroplasty, the recovery of peak expiratory flow as well as the return of bowel function and mobilization were faster when postoperative epidural morphine was used instead of intramuscular morphine.[84] High thoracic epidural (T5) anesthesia in obese patients undergoing gastric bypass provided more satisfactory hemodynamic control than i.v. morphine (higher cardiac index, less left and right ventricular stroke work and lower systolic blood pressure-heart rate product) both during and after surgery.[85]

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by steady increases in airway obstruction due to a combination of inflammation and bronchoconstriction. Severe COPD markedly increases the mortality rate in elderly patients.[86] Patients suffering from severe COPD use their abdominal and intercostal muscles in order to generate sufficient flow. TEA might limit the ventilatory reserve and lead to insufficient spontaneous ventilation due to the blockage rib cage muscles. Groeben *et al*. addressed this concern by evaluating the respiratory effect of thoracic (C5-T8) epidural bupivacaine (6-8 mL, 0.75%) in 10 patients with COPD.[87] Despite a statistically significant reduction of VC and FEV1 (7.3% and 8.7%, respectively) and extensive sympathetic blockade, blood gases were not altered and there were no changes in airway resistance, FEV1/FVC, or FRC. Similarly, Gruber *et al*. demonstrated using bupivacaine (10-12 mL, 0.25%) that TEA did not adversely affect ventilatory mechanics, breathing pattern, gas exchange, or inspiratory muscle force in patients with severely limited COPD.[88] In a RCT involving 20 women with a history of severe COPD or asthma undergoing breast surgery, high thoracic segmental epidural anesthesia (C4-T9) in the supine position was found to slightly decrease FEV1 and VC as compared to the baseline. There was no difference between the effects of bupivacaine and ropivacaine, although the latter is believed to cause a more limited motor blockade.[89]

Asthma and airway hyper-reactivity

Asthma is characterized by airway inflammation with bronchial hyper-reactivity, which is also associated with hay fever, COPD, heavy smoking and viral infections. Undoubtedly, the use of regional anesthesia helps to avoid airway instrumentation which can cause markedly increased rates of intraoperative bronchospasm and even life-threatening postoperative complications.[57, 90] However, concerns about pulmonary sympathetic blockade and unopposed parasympathetic tone remain in cases where high thoracic epidural analgesia with spread up to the cervical dermatomes is used.[91]

Yuan *et al*. studied the effects of sympathetic denervation by TEA on basal airway resistance and airway reactivity in response to bronchoconstrictive stimuli in an experimental model. Acetylcholine or histamine was administered to anesthetized mongrel dogs before and after thoracic epidural anesthesia. No influence on basal peripheral airway resistance was found.[92] In humans, Groeben *et al*.[93] assessed whether sympathetic denervation by TEA influenced the threshold of bronchoconstriction with acetylcholine. Twenty patients with documented bronchial hyper-reactivity and scheduled for elective upper abdominal or thoracic surgery were assigned to receive either epidural bupivacaine (0.75%, 7-8 mL) or i.v. bupivacaine (1.2 mg/min) while two control groups received either epidural or i.v. normal saline. Compared to values obtained immediately before pulmonary sympathetic blockade, FEV1 and total respiratory resistance remained unchanged. The threshold concentration of acetylcholine for the hyper-reactive response increased

by three-fold after epidural as well as intravenous administration of bupivacaine. One possible explanation is that the systemic effect of the local anesthetic overrules any possible negative effect of the sympathetic block. In patients with airway hyperreactivity, high TEA does not alter airway resistance, suggesting that reported cases of severe bronchospasm during epidural anesthesia are unrelated to sympathetic blockade and may have been caused by mechanisms other than pulmonary sympathetic denervation.

Summary

TEA negatively influences the performance of the parasternal intercostal muscles and slightly impairs rib cage movement. Diaphragmatic function is not affected in healthy persons and can even increase postoperatively. The ventilatory response to hypercapnia and the hypoxic drive are preserved in elderly patients.

Static and dynamic pulmonary measurements may be reduced by TEA in healthy patients. When TEA is restricted to the first five thoracic segments, lung volumes are less affected. TEA reduces pulmonary dysfunction following thoracic or major abdominal surgery as the result of many factors; muscle relaxants are not always necessarily required, and there is a reduced need for mechanical ventilation that permits earlier extubation and pain-free ventilation. Adding TEA to general anesthesia does not generate additional impairment of the Va/Q distribution.

Concerns about using TEA in subjects with compromised respiration are unfounded; it can be safely employed in obese patients and those with COPD, asthma or airway hyper-reactivity.

Thoracic epidural analgesia and the splanchnic system

Splanchnic venous capacitance

Venous capacitance vessels contain about 80% of the regional blood volume, and changes in smooth muscle tone in these vessels can produce significant shifts in blood volume and alterations of venous return. Splanchnic veins play an important role in the active control of total body circulatory capacitance; interruption of their sympathetic innervation can disrupt this homeostatic balance.[94] Sympathetic withdrawal *via* preganglionic neural blockade is a principal cause of increased mesenteric capacitance. Hogan *et al.* studied the effect of extensive thoraco-lumbar epidural analgesia (injectate extended from T2 to L5) in rabbits using direct measurements of sympathetic efferent nerve activity and mesenteric vein diameter. Markedly decreased splanchnic sympathetic activity was observed, accompanied by splanchnic venous vasodilation.[95] Many factors could contribute to increased mesenteric capacitance with concomitant sympatholysis including intravascular pressure changes, catecholamine levels, neural input, and direct effects of lidocaine. In rabbits it has been demonstrated that splanchnic venodilation during TEA is an active process, and these changes cannot explained by direct effects of local anesthetics on the vessels, altered concentrations of circulating catecholamines, or passive response to increased transmural pressure.[96]

Hypotension, mesenteric venodilation, and interruption of sympathetic activity are dose-dependent[97] and related to the extent of the epidural blockade.[98] While these effects occur during both thoracic and thoraco-lumbar epidural blocks, epidural blockade limited to the lumbar segments shows mesenteric venoconstriction and less decrease in blood pressure due to baroreceptor stimulation-mediated increases in splanchnic sympathetic activity.

Neural blockades that interrupt sympathetic innervation to the abdominal vasculature produce mesenteric venodilation and more pronounced decreases in blood pressure. This indicates that splanchnic venous capacitance plays a pivotal role in determining the hemodynamic response to epidural anesthesia. Rabbit models, however, are not applicable to humans because humans due to great species differences in lower extremity mass; rat models may thus overestimate the importance of abdominal vascular changes.

In human subjects in a supine position, epidural anesthesia can lead to pooling of blood in the denervated lower extremities and reflex vasoconstriction in the innervated arms.[99] These results were confirmed in another study on healthy volunteers, which found that thoraco-lumbar epidural analgesia (up to T5) evokes the same reduction

of intrathoracic blood volume seen during orthostatic changes.[100] The overall decrease in regional blood volume corresponded to a 500- to 600-fold sequestration of blood in the legs. This shift was reversed by dihydroergotamine, an α1-agonist that preferentially constricts capacitance vessels of the skeletal muscle and skin; etilephrine, a mixed α- and β-agonist, selectively constricts the splanchnic vasculature and thus reverses the splanchnic pooling effects.[101]

Gastrointestinal perfusion

Gastrointestinal perfusion has become a major concern, especially in critically ill patients, since it has been associated with increased morbidity and mortality [102] and plays a role in the development of increased mucosal permeability, endotoxemia and organ failure.

Enhanced sympathetic nervous activity due to surgical manipulation, stress and pain can lead to gastrointestinal hypoperfusion with intestinal paralysis. Epidural blockade can blunt these responses, but segmental sympatholysis is still accompanied by increased sympathetic activity in the unblocked regions. In awake and propofol-anesthetized, chronically instrumented dogs, Meissner *et al.*[103] determined splanchnic blood flow using colored microspheres after TEA limited to the cephalad and T5 segments; they found that gastrointestinal perfusion was not compromised. No differences in intestinal oxygenation were found in pigs receiving T5-T12 TEA.[104] Different studies have even demonstrated improved gastrointestinal blood flow after thoracic epidural sympathetic blockade.

Using intracavital microscopy, Sielenkamper *et al.*[105] found that TEA increased the ileal mucosal blood flow and reduced intermittent flow in the villous microcirculation of rats; however, perfusion pressure was decreased. Significant improvement of microcirculation in the distal portion of the gastric tube was demonstrated in mongrel dogs undergoing esophagectomy.[106]

During progressive hypoxia, epidural anesthesia retarded intestinal acidosis and slowed the progression of intestinal ischemia in rabbits, thus preventing translocation of endotoxins through the gut mucosa.[107] These results are in line with the findings of Adolphs *et al.*, who studied the effect of TEA on hemorrhage-induced impairment of intestinal perfusion in rats.[108] On intracavital microscopy, the protective actions of TEA are evident even in spite of decreased microvascular perfusion and increased leukocyte-endothelium interactions.

Improved mucosal perfusion was advocated as a mechanism to explain the attenuated systemic response and improved survival during severe acute pancreatitis in rats.[109] However, results from clinical studies are conflicting. Splanchnic blood flow in patients is usually measured by indirect techniques such as gastric tonometry (gradient between arterial and gastric mucosal $PaCO_2$) due to the practical difficulties of assessing mucosal perfusion by using highly invasive direct techniques. Gastric pH has been shown to be a surrogate marker for the adequacy of intestinal perfusion and a determinant of outcome in critically ill patients.[110] TEA-mediated prevention of reduced intramucosal pH has been demonstrated intraoperatively [111] and postoperatively [112] in patients undergoing major abdominal surgery. In contrast, another study on patients undergoing colorectal surgery was unable to demonstrate a difference in splanchnic perfusion.[113]

In two randomized controlled trials (combined sample of 40 patients) evaluating TEA for aortic surgery, no beneficial effects on hemodynamic factors, intramucosal pH or release of circulatory regulators were demonstrated.[114, 115] By measuring the pCO_2 gap (the difference between intramucosal pCO_2 and arterial pCO_2) using gas tonometry in patients scheduled for elective laparoscopic cholecystectomy, Nandate *et al.*[116] found that the pneumoperitoneum showed significantly impaired submucosal gastric perfusion and metabolism that were unaffected by TEA.

Laser Doppler flow analysis of 15 patients during bowel surgery revealed an average colonic blood flow increase of 41% in patients receiving TEA. More recently, Gould *et al.* used the same technique to demonstrate a 65% reduction in mean colonic serosal red cell flux and an 80% reduction in inferior mesenteric artery flow; this was directly related to changes in mean arterial blood pressure. Moreover, the reduction of colonic flow did not respond to increased cardiac output by fluid resuscitation, but required the use of vasopressors.[117] Similar results were found in a previous

study by Lundberg *et al.* that found increased intestinal blood flow during TEA.[118]

Gastrointestinal motility

The contractile activity of the bowel is modulated by a variety of neural and humoral factors, with the parasympathetic and sympathetic systems stimulating and tonically inhibiting gastrointestinal motility, respectively.

Postoperative ileus is a common side effect after major abdominal surgery and consists of temporary inhibition of gastrointestinal function. The duration of postoperative ileus can be shortened by TEA because of the blockage of nociceptive afferent nerves and thoraco-lumbar sympathetic efferent fibers with functional maintenance of craniosacral parasympathetic efferent fibers.[119]

In a porcine model, Schnitzler *et al.*[120] found that epidural anesthesia accelerated colon transit time without affecting colon anastomotic healing after colorectal surgery. Udassin *et al.*[121] assessed the effects of epidural anesthesia on the recovery of gastrointestinal motility during the immediate postischemic period. After 30 min of bowel ischemia, epidural lidocaine treatment caused significantly more rapid resolution of postischemic adynamic ileus (60.3% of the bowel was filled with the marker meal *vs* 30.9% in saline-injected controls).

In studies on healthy human volunteers, Thoren *et al.* reported that TEA with morphine and bupivacaine did not affect esophageal peristalsis or lower esophageal sphincter pressure,[122] whereas epidural morphine but not bupivacaine delayed gastric emptying.[123] The same group evaluated the effect of epidural analgesia on gastric emptying, orocecal transit time, and small intestinal transit during application of painful stimuli (cold pain stress with intermittent immersion of the feet in ice-cold water). TEA did not affect these parameters.[124]

Many clinical trials have investigated the impact of TEA on postoperative gut function. In patients undergoing colorectal surgery, Carli *et al.* demonstrated not only a shortening of the duration of postoperative ileus and superior quality of analgesia,[125] but also a positive impact on out-of-bed mobilization and intake of food, with long-lasting effects on exercise capacity and health-related quality of life.[126] A recent review concluded that the administration of epidural local anesthetics to patients undergoing laparotomy can reduce gastrointestinal paralysis when compared systemic or epidural administration of opioids.[127] Earlier recovery of postoperative ileus and resumption of full diet have also been seen when TEA was used for laparoscopic colon resection.[128] After radical prostatectomy, combined epidural and general anesthesia has been shown to accelerate the recovery of bowel function.[129] The effect of epidural anesthesia on the recovery of gastrointestinal function after major abdominal surgery is particularly evident when the catheter is positioned above T12. In these cases bowel motility was found to be greater with the use of epidural local anesthetics as compared to epidural narcotics.[119] With epidural morphine, co-administration of naloxone into epidural space reduced intestinal hypomotility without affecting analgesia.[130]

Summary

Complete sympathetic block of the splanchnic region is achieved only if the spread of the local anesthetic includes the thoracic sympathetic nerve fibers that extend from T5 to T12. TEA sympatholysis and mesenteric venodilation are dose-dependent and related to the extent of the block. In animal models, TEA increases the gastrointestinal blood flow, improves microcirculation and slows the progression of intestinal ischemia. Clinical studies have shown more conflicting results, probably because splanchnic blood flow is usually measured by indirect techniques such as gastric tonometry.

TEA affects gastrointestinal motility in animals by accelerating colon transit after postischemic or postoperative ileus without affecting colon anastomotic healing. No effects were demonstrated in healthy volunteers whereas in patients undergoing major abdominal surgery, TEA has been shown to not only hasten the recovery of gastrointestinal function, but also to positively affect food intake and out-of-bed mobilization.

Conclusions

An attempt has been made to call the attention of the reader to the beneficial effects of TEA. Data

showing beneficial physiological effects of TEA on the cardiovascular, respiratory and gastrointestinal systems is solid, but several studies have questioned the efficacy of this technique on postoperative outcome by suggesting that major influences on postoperative morbidity and mortality cannot be exerted by a single modality. Instead, it is necessary to address the use of TEA in the context of multimodal interventions because the pathophysiology of surgical stress is derived from a constellation of different factors, all of which impact the recovery process. Although new discoveries are continuing to be made with regard to pain control, TEA currently remains the most powerful tool available to anesthesiologists for perioperative intervention within an integrated surgical environment aimed at reducing postoperative organ dysfunction and enhancing rehabilitation.

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