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Sympathetic and Mesenteric Venous Responses to Baroreceptor or Chemoreceptor Stimulation during Epidural Anesthesia in Rabbits

Quinn H. Hogan, M.D., Alexander Kulier, M.D.,† Zeljko J. Bosnjak, Ph.D.,‡ John P. Kampine, M.D., Ph.D.§*

Background: **Baroreceptor and chemoreceptor reflexes maintain homeostasis through mechanisms that involve sympathetic activation. Because sympathetic control of the mesenteric veins plays a central role in hemodynamic responses to stress, the effects of epidural blockade on reflex responses to hypoxia and bilateral carotid occlusion (BCO) were examined by monitoring direct measures of splanchnic sympathetic neural traffic and mesenteric venous capacitance.**

Methods: **Rabbits were studied during α-chloralose anesthesia and mechanical ventilation. Sympathetic efferent nerve activity to the mesenteric vessels was measured by surgically placed electrodes, and mesenteric venous diameter was measured by videomicroscopy. Heart rate and mean arterial pressure were monitored by intraarterial cannulation. Intraluminal venous pressure was monitored by a servo-null micropressure technique. Responses were recorded during repeated administration of three different stresses, F_IO_2 = 0% for 40 s, F_IO_2 = 11% for 2.5 min, and BCO for 60 s. Animals received either thoracolumbar epidural blockade (0.4 ml/kg lidocaine 1.5%; n = 7) or 15 mg/kg intramuscular lidocaine (n = 7).**

Results: **Hypoxia and BCO produced sympathetic stimulation and active constriction of mesenteric veins. Epidural anesthesia accentuated the mean arterial pressure decrease from F_IO_2 of 0%, caused the 11% response to F_IO_2 to become depressor instead of pressor, and decreased the pressor effect BCO. Sympathetic efferent nerve activity and venous diameter responses to hypoxia and BCO were attenuated or eliminated.**

Conclusions: **The hemodynamic effects of hypoxia result from a combination of direct depression and reflex activation. Thoracolumbar epidural anesthesia in rabbits impairs compensatory reflexes invoked by chemoreceptor stimulation and eliminates response to baroreceptor stimulation. Loss of splanchnic control of mesenteric capacitance contributes to the inhibition of the hemodynamic response to hypoxia or BCO during epidural anesthesia in rabbits. (Key words: Anesthetic techniques: epidural. Anesthetics, local: lidocaine. Sympathetic nervous system: venous capacitance; efferent nerve activity. Complications: hypotension; hypoxemia.)**

SEVERE hypotension and hypoxemia are unavoidable risks during epidural anesthesia. Homeostatic responses to stress depend heavily on sympathetic efferent pathways, so deficient compensation for hypotension and hypoxemia might be expected during the sympathetic blockade that accompanies epidural anesthesia. Although the importance of general anesthetics in modulating reflex activity induced by hypoxemia and hypotension has been documented extensively,[1-3] there has been much less investigation into alterations that accompany regional anesthesia. In particular, the contribution of specific vascular beds has not been determined, and actual sympathetic activity has not been measured to identify accurately the effects of sympathetic neural blockade.

Previous investigations have examined homeostatic reflexes during epidural and spinal anesthesia without directly measuring vascular response or sympathetic activity. Neuraxial local anesthetic blockade blunts sympathetic activation[4-6] and hemodynamic compensation[7] that otherwise follow hypovolemia, and high blockade partially suppresses baroreceptor reactivity.[8-11] Sympathetic responses resulting from airway stimulation,[9,12,13] cold pressor test,[14] and intravenous ketamine[15] are also attenuated by high epidural anesthesia. Finally, the pressor responses to hypercapnia[16-19] and hypoxemia[20] are diminished or converted to a depressor response by extensive epidural blockade (but not by narrow thoracic segmental block[21]). Although these investigations have broadly defined the impediment to reflex control resulting from neural blockade, the mechanisms are un-

* Associate Professor, Department of Anesthesiology.

† Research Assistant Professor, Department of Anesthesiology.

‡ Professor, Departments of Anesthesiology and Physiology.

§ Professor and Chairman, Department of Anesthesiology; Professor, Department of Physiology.

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Address reprint requests to Dr. Hogan: Medical College of Wisconsin, Department of Anesthesiology, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226.

certain. Interference with both afferent pathways from peripheral sensors as well as efferent sympathetic motor fibers could contribute, and even blockade of efferent sympathetic traffic that modulates peripheral chemoreceptor[2] and baroreceptor[1] sensitivity could play a role, but the relative importance of each of these has not been elucidated. In addition, most previous studies have not tried to identify which vascular beds are of particular importance for hemodynamic control, although Jordan and Miller[7] highlighted the role of splanchnic innervation in conducting the response to hemorrhage. Finally, the indirect measures of sympathetic activation used in these studies, such as circulating catecholamines,[4,6,7,20] represent global changes and can only loosely indicate responses in specific tissue beds.

To determine more exactly the role of sympathetic activity and regional vascular responses during epidural anesthesia, we used direct measures of regional sympathetic neural traffic and vascular volumetric change.[22-24] These earlier studies showed that mesenteric venous dilatation contributes to hypotension during extensive epidural blockade, and that mesenteric venous constriction from increased splanchnic neural activity tempers hemodynamic changes in less-extensive blocks. Because abnormal reflex response to hypoxia and hypotension may contribute to catastrophic cardiovascular collapse during neuraxial anesthesia,[25,26] here we extend those previous observations to examine responses to stress during epidural anesthesia. We tested the hypothesis that splanchnic sympathetic blockade from thoracolumbar epidural anesthesia attenuates reflex venous capacitance changes, leading to diminished hemodynamic responses to hypoxemia and bilateral carotid occlusion.

Methods

Preparation

The basic preparation is the same as in a previous report,[22] where it is described in greater detail. After we received approval by our animal care and use committee, we induced anesthesia in male New Zealand White rabbits (weighing 1 to 2 kg) with 10 to 25 mg/kg thiopental *via* an ear vein and maintained by α-chloralose (25 mg/h). An epidural catheter (0.965 mm OD) was inserted *via* a small incision at the T12-L1 interspace. The trachea, femoral artery, and femoral vein were cannulated and the carotid arteries exposed. Subcutaneous lidocaine 0.5% was infiltrated at all incision sites. The study was performed during the infusion of 0.3 mg/kg/h vecuronium, and ventilation was controlled. An inspired oxygen concentration (F_IO_2) of 100% was administered except during hypoxia, as will be described. Heart rate and mean arterial pressure (MAP) were determined from the pressure trace from the femoral artery catheter. Normal baseline P_{CO_2} (35 to 40 mmHg) and pH (7.35 to 7.45) were maintained by ventilator adjustments and administration of $NaHCO_3$ guided by arterial blood gas determination; no correction was attempted while hypoxic gas mixtures were being given. Rectal temperature was maintained between 36.5 and 37.5°C by a warming pad.

Through a midline laparotomy, a postganglionic splanchnic nerve was dissected from the adjacent tissue, maintaining continuity proximally and distally. A bipolar recording electrode, composed of two single-strand stainless steel wires (0.25 mm OD) in Silastic tubing, was fixed to the nerve with Wacker silgel (Wacker-Chemie, Munich, Germany) to directly measure sympathetic efferent nerve activity.[27]

A loop of ileum was externalized through the laparotomy and mounted in a temperature-regulated plastic chamber. The diameter of the mesenteric vein (500 to 800 μm) was measured continuously *via* an on-line videomicrometer system.[28] The ileum and associated mesentery were superfused continuously with warmed physiologic salt solution formulated to simulate peritoneal fluid. This solution was maintained at a temperature of 37°C and a pH of 7.35 to 7.45 and continuously bubbled with a gas mixture of 5% oxygen, 5% carbon dioxide, and 90% nitrogen. The preparation was considered acceptable if the vein was responsive by contracting during hypoxia (F_IO_2 = 0% for 40 s); in about 70% of the animals, the first vein examined proved to be satisfactory.

The vertebral columns of the animals were dissected after they were killed to confirm epidural catheter placement and fluid distribution, indicated by staining of the dura and spinal canal by ink included in the injectate.

Protocol

After a rest period of 1 h and establishment of stable hemodynamic measurements, 25 ml/kg warmed normal saline was administered intravenously for 15 min. Animals were randomly assigned to the control group, which received 1 ml/kg intramuscular lidocaine 1.5% (n = 7), or to the study group, which received 0.4 ml/kg epidural lidocaine 1.5% (n = 7). These doses were

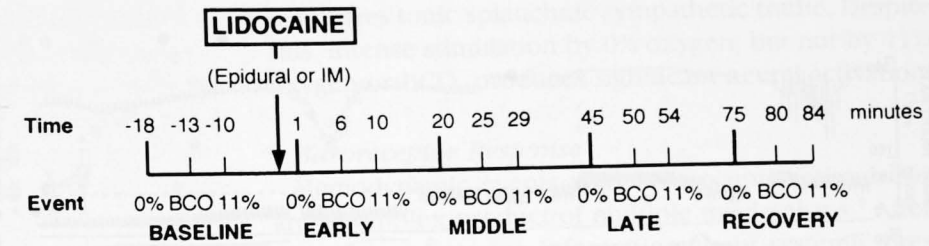

Fig. 1. Protocol for presentation of F_IO_2 of 0%, bilateral carotid occlusion, and F_IO_2 of 11%, before epidural or intramuscular lidocaine administration and four times later.

chosen to produce thoracolumbar blockade of all vertebral segments with preganglionic sympathetic outflow in the epidural group, and to produce comparable serum lidocaine concentrations (not measured in this study).[22] Normal saline was injected intramuscularly in the epidural lidocaine group and epidurally in the intramuscular lidocaine control group.

Each animal was repeatedly exposed to three different stress protocols (fig. 1). An F_IO_2 of 0% was administered for 40 s by substituting nitrogen for oxygen in the inspired gas mixture. After complete recovery of hemodynamic variables (280 s), bilateral carotid occlusion (BCO) was performed for 60 s using vascular clamps. After another recovery interval of 3 min, an F_IO_2 of 11% was administered for 2.5 min by switching fresh gas flow to a mixture of nitrogen and oxygen previously set at that level by an in-line polarographic oxygen analyzer (Instrument Laboratory model 408, Lexington, MA). Mechanical ventilation was maintained unchanged throughout the study, and intervals between hypoxia and BCO events were adequate for hemodynamic measures to return completely to prestress baseline levels. The set of three stresses were performed before lidocaine injection ("baseline"), immediately after injection ("early"), and three times subsequently ("middle," "late," and "recovery") to encompass the entire course of blockade. Hemodynamic changes from epidural blockade take about 5 min to evolve, so the F_IO_2 of 0% at the early time interval is during the incomplete onset of the block.

Blood gas determinations were performed in each animal during both hypoxic events just before termination of the hypoxic gas flow.

Intravenous Pressure

To determine whether vein diameter changes were active or a passive result of decreased vein pressure, intraluminal mesenteric vein pressure was monitored during an F_IO_2 of 11% (n = 3 animals), BCO (n = 3 animals), and an F_IO_2 of 0% (n = 6 animals) using a servo-null system.[29] Glass micropipettes, beveled to a 5- to 10-μm tip diameter, were filled with 2 M NaCl, inserted into the vein using a micromanipulator, and used as sensing electrodes with a servo-null pressure measuring system (model 900, World Precision Instruments, New Haven, CT). Observations were made both at baseline and after epidural or intramuscular lidocaine injection.

Statistics

Statistical analyses were performed on actual values before conversion to percentile figures. Univariate analysis of variance for repeated measures was used (Super ANOVA; Abacus Corporation, Berkeley, CA). On main effects or interactions with significant ($P < 0.05$) F values, denominator-adjusted t tests were performed. Significance of increment change during each stress event was also evaluated by analysis of variance. Results are reported as mean ± SE.

Results

The weights of animals in the intramuscular control and epidural study groups were comparable. F_IO_2 of 11% resulted in a Pa_{O_2} of 34 ± 1 mmHg, and F_IO_2 of 0% produced a Pa_{O_2} of 17 ± 2 mmHg. Epidural injectate spread of at least T1 through L3 was confirmed in all animals.

Figure 2‖ illustrates typical responses. Group mean data are graphed in figures 3, 4, and 5 (note that scales are not identical) and summarized below.

Heart Rate

Bilateral carotid occlusion caused a modest heart rate increase under baseline conditions, whereas both degrees of hypoxia produced bradycardia. Heart rate was decreased by epidural lidocaine but not by intramuscu-

‖ Kilbourne EM, Hageman GR, James TN, Urthaler F. Post-excitatory depression in thoracic sympathetic efferent neural traffic during a cardiogenic hypertensive chemoreflex. Basic Res Cardiol 1982; 77:423–30.

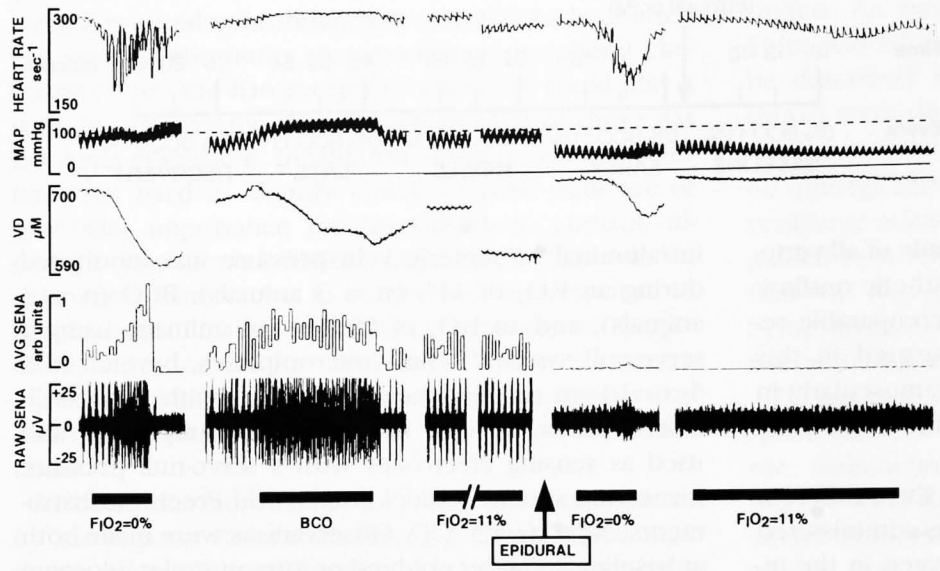

Fig. 2. Sample tracings of heart rate, mean arterial pressure (MAP), vein diameter (VD), averaged sympathetic efferent nerve activity (AVG SENA), and raw SENA, during F_IO_2 of 0%, bilateral carotid occlusion (BCO), and F_IO_2 of 11%. Before epidural lidocaine (*arrow*), F_IO_2 of 0% produces bradycardia and mild hypertension, accompanied by marked elevation in SENA and venoconstriction. Marked decrease of SENA after F_IO_2 of 0% is a consistent feature after intense sympathetic stimulation. Hypertension, slight tachycardia, sympathetic activation, and venoconstriction are induced by BCO. F_IO_2 of 11% results in hypertension and venoconstriction despite minimal sympathetic activation. One minute after epidural lidocaine injection, hypotension and venodilation are evident and SENA is almost eliminated, at which time F_IO_2 of 0% still produces bradycardia, sympathetic activation, and venoconstriction but with hypotension. During epidural anesthesia, F_IO_2 of 11% causes bradycardia and hypotension.

lar lidocaine. The small heart rate response to BCO was inconsistent after lidocaine injection in both groups, and no differences between groups were noted. F_IO_2 of 0% resulted in significantly less heart rate change during epidural anesthesia than after intramuscular lidocaine, although a bradycardic response persisted. Bradycardia from F_IO_2 of 11% was not affected by epidural anesthesia, and the bradycardia response in the epidural group decreased during recovery from the block. Intramuscular lidocaine may attenuate the heart rate response to F_IO_2 of 11%.

Mean Arterial Pressure

During baseline testing, MAP was increased by BCO. Mean arterial pressure was decreased by F_IO_2 of 0% and increased by F_IO_2 of 11%. Epidural anesthesia significantly decreased the pressor effect of BCO, amplified the MAP decrease from F_IO_2 of 0%, and caused the response from F_IO_2 of 11% to become depressor instead of pressor.

Sympathetic Efferent Nerve Activity

Increased sympathetic efferent nerve activity was caused by BCO and F_IO_2 of 0% at the baseline exposure, but no consistent response was seen with the more modest hypoxia of F_IO_2 of 11%. Epidural anesthesia eliminated the response to BCO and significantly attenuated the response to F_IO_2 of 0%. Whereas F_IO_2 of 11% produced sympathetic efferent nerve activity activation after intramuscular lidocaine, this was absent after epidural lidocaine.

Vein Diameter

Mesenteric venoconstriction was produced by BCO as well as by both hypoxic stresses under baseline conditions. Epidural anesthesia caused an increase in vein diameter and eliminated the slight BCO response. The response to F_IO_2 of 0% persisted during epidural anesthesia but was significantly lessened compared with the responses in the intramuscular control group. The response to F_IO_2 of 11% was eliminated by epidural anesthesia.

Intravenous Pressure

Insignificant micropressure changes were found during exposure to F_IO_2 of 0%, F_IO_2 of 11%, and BCO at baseline and after either epidural or intramuscular lidocaine.

Discussion

In accordance with our hypothesis, the data show that extensive epidural anesthesia in rabbits impedes hemodynamic compensation for hypoxia and BCO. Active mesenteric venoconstriction from moderate hypoxemia and BCO is eliminated by epidural anesthesia, and venoconstriction from severe hypoxemia is attenuated.

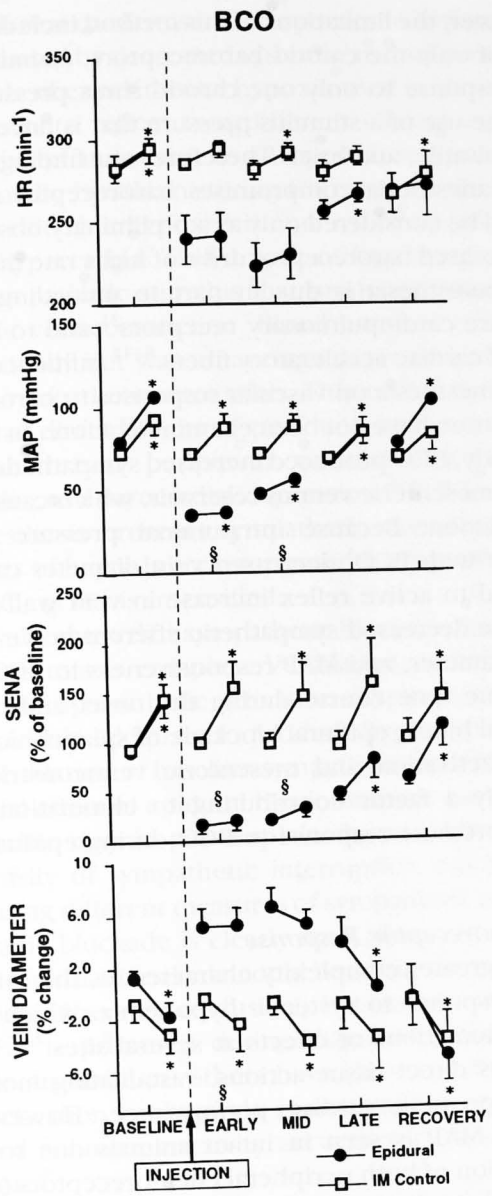

Fig. 3. Changes in heart rate (HR), mean arterial pressure (MAP), sympathetic efferent nerve activity (SENA), and vein diameter (VD) produced by bilateral carotid occlusion (BCO) before and four times after epidural or intramuscular injection of lidocaine (*arrow* and *dotted line*). Each pair of data points connected by a line represent the initial value immediately before BCO and the value during BCO. Baseline for SENA and VD are values just before injection. Values are means ± SE. *Significant change. §Significant difference between changes in epidural and intramuscular groups.

By interrupting reflex mechanisms, epidural anesthesia intensifies the direct hemodynamic depressant effects of severe hypoxemia, eliminates MAP correction during baroreceptor stimulation, and causes moderate hypoxemia to decrease MAP rather than increase it. As in earlier studies, epidural anesthesia almost completely eliminates tonic splanchnic sympathetic traffic. Despite this, intense stimulation by 0% oxygen, but not by 11% oxygen or BCO, produces significant neural activation.

Baroreceptor Response

Hemodynamic events after baroreceptor stimulation are a complex product of multiple mechanisms.[1] Afferent axons conveying information about systemic pressure originate not only in the carotid sinus but also in the aorta and heart. Effector mechanisms for blood

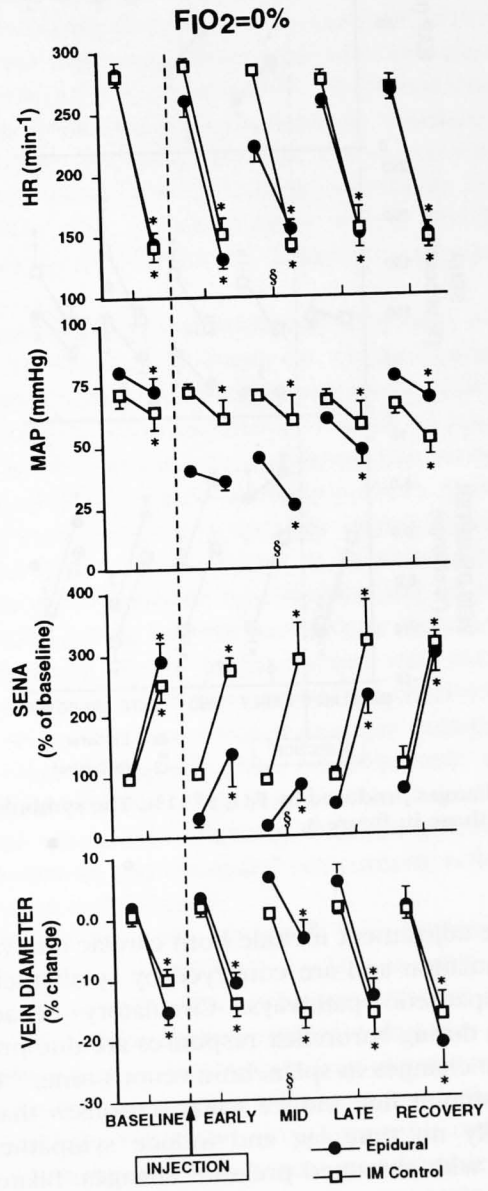

Fig. 4. Changes produced by F_IO_2 of 0%. The symbols are the same as those in figure 3.

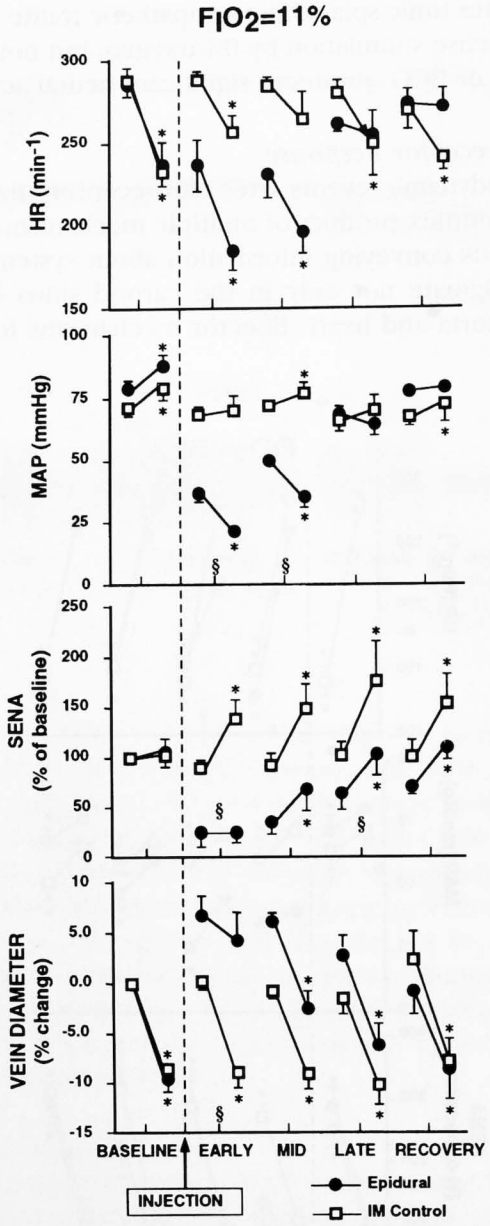

Fig. 5. Changes produced by F_IO_2 of 11%. The symbols are the same as those in figure 3.

pressure adjustment include both cardiac and vasomotor stimulation and are conveyed by sympathetic and parasympathetic pathways. Circulatory capacitance changes during baroreflex responses are due primarily to active changes in splanchnic venous tone.[30] Baroreceptor stimuli first induce vagal responses that have essentially no time lag and induce sympathetic responses with sustained pressure changes. Bilateral carotid occlusion is well established as a physiologic tool, principally because of the immediacy of the response. However, the limitations of this method include stimulation of only the carotid baroreceptors, examination of the response to only one carotid sinus pressure level, and the use of a stimulus pressure that is uncontrolled, nonpulsatile, and brief. Therefore, our finding that epidural anesthesia compromises baroreceptor response should be considered only as a preliminary observation.

Decreased baroreceptor drive of heart rate during epidural anesthesia is due in part to unloading of low-pressure cardiopulmonary receptors[31] and to interruption of cardiac acceleratory fibers.[8-11] Influences of epidural anesthesia on vascular responses to baroreceptor stimulation have not been examined before. In the present study, BCO produced increased sympathetic activity to the mesenteric venous reservoir, which caused vasoconstriction. Because intraluminal pressure did not change with BCO, decreased vein diameter can be attributed to active reflex increase in vein wall tension. Because decreased sympathetic efferent nerve activity, vein diameter, and MAP responsiveness to BCO follow the same time course during the onset and offset of epidural block, epidural blockade of splanchnic sympathetic activation and mesenteric venoconstriction is probably a factor contributing to elimination of the blood pressure response to BCO during epidural anesthesia.

Chemoreceptor Response

Even greater complexity characterizes the cardiovascular response to systemic hypoxemia, which results from interactions of effects at several sites.[2,32] Hypoxemia has direct tissue actions, vasodilating most beds and depressing cardiac performance. However, increased MAP is seen in intact animals due to reflex stimulation of both peripheral chemoreceptors (carotid and aortic bodies) and the central nervous system, each leading to increased sympathetic efferent activity. Neural controlled venous capacitance changes in the splanchnic circulation play a key role in supporting circulatory homeostasis during hypoxia.[33,34] The integrated cardiovascular response typically includes vasoconstriction and cardiac stimulation, with variable heart rate changes. When pulmonary stretch receptors are activated by hyperventilation in spontaneously breathing animals, an increase in heart rate is usually seen, but bradycardia is a more common consequence of hypoxemia during controlled ventilation. Further complexity is added by positive interactions of arterial baroreceptor input and peripheral chemoreceptor input[35] and baroreceptor augmentation of the central pressor ef-

fect,[36] such that cardiovascular responses to hypoxemia are accentuated by decreased systemic arterial pressure.

The levels of experimental hypoxia used in this study were chosen to reflect two different clinical circumstances. Abrupt and severe tissue hypoxia was modeled experimentally by administering 0% oxygen, which results in predictable hypoxemia and avoids added influences of hypercarbia. This degree of hypoxemia is an intense sympathetic stimulus that produces immediate mesenteric venoconstriction. Blood pressure often increased initially but was on average depressed after 40 s despite sympathetic excitation. This probably results from global direct effects of profound hypoxemia, including decreased peripheral vascular resistance,[37] bradycardia, and myocardial depression.[38,39] When epidural anesthesia prevents sympathetic stimulation, direct effects of hypoxia are unopposed and hypotension during F_IO_2 of 0% is intensified.

Our results show that sympathetic blockade from epidural anesthesia is complex. Ventilation with F_IO_2 of 0% provokes sympathetic activation despite local anesthetic blockade adequate to produce hypotension and near-total ablation of baseline sympathetic activity. This differential effect of epidural block on tonic and phasic neural traffic may in part explain the variable extent and intensity of sympathetic interruption reported in studies using different measures of sympathetic activity. Sympathetic blockade is clearly not "all or none," and it is doubtful that blockade could be achieved in which sympathetic fibers are exclusively but completely interrupted, as is proposed during diagnostic differential blockade. In addition, others have shown that sympathetic activation by hypoxia is not uniform, because decreased cutaneous activity accompanies splanchnic excitation.[40]

Ventilation with 11% oxygen allowed a sustained hypoxic exposure, during which hemodynamic variables reached a steady state. This pattern of hypoxia represents a severe but survivable degree of hypoxemia as might follow advanced pulmonary dysfunction. We documented active constriction of mesenteric veins as a component of the vasopressor response that follows presentation of 11% oxygen. Because average sympathetic efferent nerve activity was minimally changed, venoconstriction may be du in part to direct effects of moderate hypoxia on mesenteric veins.[41] Epidural anesthesia eliminates sympathetic activation evident in control animals and prevents the vasoconstrictor response. Profound sympathetic blockade after epidural anesthesia may block direct effects of hypoxia as well as neural effects because the direct venoconstrictor action of hypoxia depends on the presence of sympathetic activity.[41] The net result of epidural blockade is that this degree of hypoxemia becomes a depressor of MAP because the direct circulatory depression of hypoxemia[42] predominates in the absence of autonomic compensation.

Clinical Relevance

Reflex responses to chemoreceptor and baroreceptor stimulation depend on the details of the model, making generalization difficult.[2] For instance, although α-chloralose is minimally disruptive to sympathetic reflexes,[43] its use in our study may have potentiated the effects of epidural sympathetic interruption. Heart rate changes during hypoxemia differ in mechanically ventilated and spontaneously breathing animals,[44] but vascular responses are not affected.[45] Volatile anesthesia inhibits baroreceptor and chemoreceptor reflex activity[46,47] comparably to that which we observed with epidural anesthesia.

The importance of hemodynamic responses to hypoxia and hypotension is uncertain. Organ dysfunction such as myocardial ischemia or peripheral hypoperfusion may ensue from intense activation of stress responses, so that limiting these reflexes has become an anesthetic goal advocated by many authors. However, impaired compensatory responses during anesthesia might also lead to tissue injury or hemodynamic collapse. Loss of sympathetic mechanisms may be particularly harmful during hypoxemia because direct circulatory depressant effects of hypoxemia may then predominate. Hypoxia and hypotension are observed components of unexpected cardiopulmonary collapse that may develop during otherwise unremarkable clinical neuraxial anesthesia.[25] This may be due in part to the combined effects of circulatory depression from neuraxial anesthesia and obtunded sympathetic reflexes as documented in this study.

Sympathetic blockade interferes with intrinsic compensatory reflexes. Although caution is necessary in applying these observations to anesthesia for our human patients, these findings indicate that loss of adequate compensatory responses to hypoxia and hypotension erodes the margin of safety during extensive neuraxial anesthesia. Therefore, more aggressive correction of hypoxia and hypotension may be advisable during stable epidural block than when the sympathetic nervous system is unimpaired.

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