Thoracic Epidural Anesthesia with Ropivacaine Does Not Compromise the Tolerance of Acute Normovolemic Anemia in Pigs

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ABSTRACT

Background: The initial treatment of an acute blood loss with acellular fluids leads to the dilution of the red cell mass remaining in the vasculature, that is, to acute normovolemic anemia. Whether the compensation and, thus, the tolerance of acute anemia, are affected by sympathetic block induced by thoracic epidural anesthesia has not yet been investigated.

Methods: Eighteen anesthetized and mechanically ventilated pigs were instrumented with thoracic epidural catheters and randomly assigned to receive an epidural injection of either 5-ml ropivacaine 0.2% (n = 9) aiming for a Th5–Th10 block or saline (n = 9) followed by continuous epidural infusion of 5 ml/h of either fluid. Subsequently, acute normovolemic anemia was induced by replacement of whole blood with 6% hydroxyethyl starch solution until a "critical" limitation of oxygen transport capacity was reached as indicated by a sudden decrease in oxygen consumption. The critical hemoglobin concentration quantified at this time point was the primary endpoint; secondary endpoints were hemodynamic and oxygen transport parameters.

Results: Thoracic epidural anesthesia elicited only a moderate decrease in mean arterial pressure and cardiac index and a transient decrease in oxygen extraction ratio. During progressive anemia, the compensatory increases in cardiac index and oxygen extraction ratio were not compromised by thoracic epidural anesthesia. Critical hemoglobin concentration was reached at identical levels in both groups (ropivacaine group: 2.5 ± 0.6 g/dl, saline group: 2.5 ± 0.6 g/dl).

Conclusion: Thoracic epidural anesthesia with ropivacaine 0.2% does not decrease the tolerance to acute normovolemic anemia in healthy pigs. The hemodynamic compensation of acute anemia is fully preserved despite sympathetic block, and the critical hemoglobin concentration remains unaffected. **(Anesthesiology 2014; 121:765-72)**

THORACIC epidural anesthesia (TEA) has become an integral part of the anesthetic management of major surgery (*e.g.*, abdominal, thoracic, or urologic surgery). The initial treatment of surgical blood loss usually consists of the infusion of acellular fluids to maintain normovolemia. The consequence is a dilution of the red cell mass remaining in the vascular system (acute normovolemic anemia). In this context, the term "anemia tolerance" refers to (1) the patient's physiologic potential to tolerate even profound stages of acute anemia, and (2) the anesthesiologist's intention to accept low hemoglobin concentrations to avoid premature and unnecessary transfusions of allogeneic blood products.[1]

As a result of the organism's tolerance to anemia, tissue oxygenation is maintained, although oxygen transport capacity decreases progressively with dilutional anemia. At physiologic hemoglobin concentrations, oxygen supply to the tissues (D_{O_2}) exceeds total body oxygen demand—reflected by oxygen consumption (V_{O_2}) under rest conditions—by the factor three to four.[2] Therefore, oxygen supply to the tissues is sufficient to meet demand over a wide range of hemoglobin concentrations. As a consequence, V_{O_2} remains constant, even when D_{O_2} decreases with falling hemoglobin concentrations (supply independency of V_{O_2}, see fig. 1). Acute anemia is essentially compensated by increases in cardiac output and arteriovenous oxygen extraction,[3] the latter occurring to a variable extent within different organs.[4] When these compensatory mechanisms are exhausted (*i.e.*, when cardiac output and oxygen extraction cannot be further increased), the amount of oxygen delivered to the tissues becomes insufficient to meet demand and V_{O_2} starts to decline (supply dependency of V_{O_2}).[5,6] The hemoglobin concentration corresponding with the sudden decrease in

What We Already Know about This Topic

- Thoracic epidural anesthesia produces a marked reduction in sympathetic tone
- The effect of reduction in sympathetic tone on the tolerance to acute anemia is unknown

What This Article Tells Us That Is New

- Thoracic epidural anesthesia does not decrease the tolerance to acute normovolemic anemia in healthy pigs
- The hemodynamic compensation of acute anemia is fully preserved, despite sympathetic block

Submitted for publication February 27, 2014. Accepted for publication May 13, 2014. From the Department of Anesthesiology, Intensive-Care Medicine and Pain Therapy, University Hospital Frankfurt, Frankfurt am Main, Germany (A.P., C.F.W., M.L., M.S., S.K., O. Horn); Clinic of Anesthesiology, Ludwig Maximilians University Hospital, Munich, Germany (B.Z.); and Clinic of Anesthesiology, Surgical Intensive Care Medicine and Pain Management, Krankenhaus Nordwest, Frankfurt, Germany (O. Habler).

 Anesthesiology 2014; 121:765-72

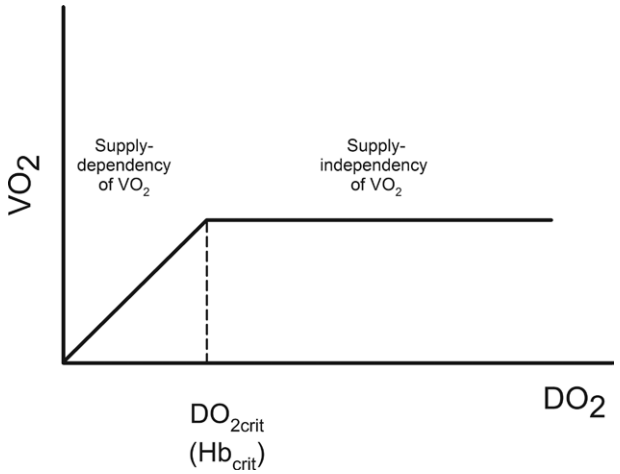

Fig. 1. Schematic representation of the relationship between oxygen consumption (Vo_2) and oxygen delivery (Do_2). Physiologically, Do_2 amounts the three- to four-fold of Vo_2. Over a long period, Vo_2 remains independent on Do_2 despite the anemia-related decrease in Do_2. A critical hemoglobin concentration (Hb_{crit}) is reached, when Do_2 falls short of the actual oxygen demand and the compensation of acute anemia (*i.e.*, increases in cardiac output and oxygen extraction) begins to fail. As a consequence, Vo_2 begins to decrease (onset of supply dependency of Vo_2).

Vo_2 is referred to as the "critical" hemoglobin concentration (Hb_{crit}) and reflects the individual limit of an organism's tolerance to anemia.[7]

Aside from analgesic effects, sympathetic block produced by TEA has been demonstrated to optimize myocardial and splanchnic oxygen balances and is therefore purported to be cardioprotective, particularly in high-risk patients.[8] On the contrary, thoracic sympathetic nerve block may result in bradycardia, vasodilation, and hypotension and, thus, in reduced cardiovascular performance. Hence, we hypothesized that (1) the sympathetic nerve block elicited by TEA might compromise hemodynamic compensation and, therefore, the tolerance to acute anemia, and (2) Hb_{crit} would be met at higher hemoglobin levels than in individuals not subjected to TEA.

Materials and Methods

After approval by the local governmental review board (Department for veterinary affairs/V54, Regional Council Darmstadt, Germany), experiments were carried out in 18 healthy farm-bred pigs of either sex (body weight 23.8 ± 1.9 kg). All animals received care in compliance with the Guide for the Use of Laboratory Animals.

Anesthesia and Ventilation

Twelve hours prior to the experiments, animals were denied food but had free access to water. After intramuscular premedication with ketamine (10 mg/kg) and midazolam (1 mg/kg), anesthesia was induced by intravenous injection of propofol (3 mg/kg) and fentanyl (30 μg/kg) and maintained by continuous infusion of propofol (160 $\mu g \cdot kg^{-1} \cdot min^{-1}$), fentanyl (0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and midazolam (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$). To facilitate intubation and mechanical ventilation, muscular paralysis was achieved with pancuronium bromide (bolus injection 200 μg/kg followed by continuous infusion of 130 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Estimated fluid losses were replaced with Ringer's solution (3 $ml \cdot kg^{-1} \cdot h^{-1}$). The trade names of all anesthetic drugs applied are listed in the appendix.

Animals were orotracheally intubated and ventilated with a Servo 900B ventilator (Siemens-Elema, Solna, Sweden; F_{IO_2} 0.21, 14 cycles/min, positive end-expiratory pressure 5 cm H_2O). Tidal volume was individually adjusted to provide arterial normocapnia and was then maintained throughout the entire protocol.

Instrumentation and Monitoring

Epidural Catheter Insertion. After induction of anesthesia, animals were placed in the prone position for insertion of an epidural catheter. The fifth and the tenth thoracic vertebrae and the eighth interspace (Th8/9) were identified using fluoroscopy, and the borders of the dermatomes Th5 and Th12 were marked. The eighth interspace was surgically dissected under sterile conditions (resection of the interspinal ligaments and the spinal process of the eighth vertebra). The ligamentum flavum was visually identified, an 18-G Tuohy needle (Braun, Melsungen, Germany) was carefully advanced into the epidural space, and a 20-G epidural catheter was inserted for 5 cm. The catheter was fixed in this position before the incision was closed.

Hemodynamic Monitoring. Subsequently, animals were placed in the supine position, and a five-lead electrocardiogram (II, V5) was placed. A central venous catheter (Arrow, Reading, PA) was inserted into the cranial vena cava, and a Swan-Ganz catheter (Baxter, Irvine, CA) was floated into a pulmonary arterial branch for monitoring of pulmonary arterial pressures and withdrawal of mixed venous blood samples. A 6-F introducer sheath was inserted into the right femoral artery and vein, respectively. A thermodilution catheter (Pulsion, Munich, Germany) was placed into the left femoral artery for continuous measurement of arterial blood pressure and cardiac output. Ambient temperature was kept constant at 23°C, and body core temperature was monitored during the entire protocol.

Experimental Protocol

After completion of instrumentation, a 60-min stabilization period was allowed to elapse to achieve stable baseline conditions. Upon recording the first data set ("Baseline"), animals were randomized to receive an epidural bolus injection of either 5ml ropivacaine 0.2% or normal saline (ROP group, n = 9 *vs.* SAL group, n = 9). The investigator remained blinded until the completion of the epidural injection.

The intended spread of sympathetic block was Th5-10. If necessary, additional 1-ml boluses of ropivacaine were injected to establish this degree of sympathetic block; animals of the SAL group did not receive further epidural bolus

injections. For maintenance of the TEA level, a continuous epidural infusion of ropivacaine (5 ml/h) was initiated (animals of the SAL group received the corresponding volume of normal saline) and the second data set ("TEA") was recorded.

As a measure of sympathetic block, skin temperature was assessed before and 30 min after epidural injection by infrared thermometry, a method that has been described elsewhere.[9] Using a handheld infrared thermometer (Micro-Epsilon Messtechnik, Ortenburg, Germany), skin temperature was measured along the right and left anterior axillary lines in the dermatomes Th5–Th10 and on two reference points on the surface of the lower abdomen below Th12. Within each dermatome, a difference in temperature of at least 0.5°C compared to the reference points was considered to indicate a sympathetic block.

Subsequently, a hemodilution protocol was initiated with replacement of whole blood for hydroxyethyl starch (6% HES 130/0.42) in a 1:1 ratio. For precise synchronization of blood withdrawal with the HES infusion rate (1 $mL \cdot kg^{-1} \cdot min^{-1}$), a bidirectional precision pump (Harvard Apparatus, Holliston, MA) was used. Target parameter was the animal's individual Hb_{crit}, which was assessed in an automated and investigator-independent manner (see the next section, "Assessment of Hb_{crit}").

When Hb_{crit} was reached, skin temperature was again scanned to verify the final level of the sympathetic block. Thereafter, the final data set was collected ("Hb_{crit}") and animals were sacrificed by intracardiac injection of potassium chloride.

Assessment of Hb_{crit}

Hb_{crit} correlates with critical limitation of Do_2 and marks the onset of total body oxygen supply dependency (see fig. 1). Using specific software (Delta-Crit-System),[10] the corresponding Vo_2 decrease was detected by analysis of the Vo_2 values obtained every 60 s. Vo_2 was assessed with a metabolic monitor (Delta-Trac II, Datex-Engstrom, Helsinki, Finland). During the stabilization period, Delta-Crit-System incorporated the Vo_2 values into a regression analysis and calculated the mean and SD for this baseline value. During the subsequent hemodilution period, Vo_2 values were compared with the mean value baseline calculated by Delta-Crit-System. When three subsequent Vo_2 values fell below a predefined level (three times the SD of the baseline regression line), a significant Vo_2 decrease was signaled by visual and acoustic computer alerts and recorded.

Measurements

Intravascular blood volume was determined at baseline using "whole-blood" dilution of the indocyanin green.[11] Measurements of hemodynamic and oxygen-derived parameters were performed at "Baseline," "TEA," and at "$Hb_{crit.}$"

Cardiovascular catheters were connected with pressure transducers and linked with a multichannel recorder (Hugo-Sachs, March-Hugstetten, Germany). All measurements were recorded with a personal computer. Arterial and mixed venous blood samples were withdrawn for blood gas analyses and assessment of hemoglobin concentration (GEM-3000 and 682 CO-Oxymeter; Instrumentation Laboratory, Lexington, MA). Derivative parameters were calculated as described in the appendix.

Statistics

Statistical analysis was performed with the SAS 9.3 software package (SAS Institute, Cary, NC). All data are presented as mean ± SD. The sample size was estimated according to our experience with previous studies using a similar experimental protocol. Distribution of data was assessed with the Shapiro-Wilk test. In the case of normal distribution, time effect on the different variables as well as differences between groups at the investigated time points were tested by a two-way repeated-measures ANOVA. *Post hoc* analysis of differences detected with ANOVA was performed with the Student–Newman–Keuls test. In the case of non-normal distribution, time effect on the parameters as well as between-group differences were tested by ANOVA on ranks. *Post hoc* analysis of differences detected with ANOVA on ranks was performed with the Tukey test. For all parameters, statistical significance was accepted at P value less than 0.05.

Results

Baseline Characteristics

There were no significant differences between the groups regarding body weight and all investigated parameters observed at baseline (see table 1).

Effects of TEA

As a measure of sympathetic block, skin temperature was measured along the left and right anterior axillary lines within the dermatomes Th5–Th10 (see fig. 2). While the epidural injection of normal saline was void of any effects (see fig. 2, B and D), TEA with 0.2% ropivacaine elicited a sympathetic block of the segments Th5–Th10, which was reflected by an increase in skin temperature (see fig. 2, A and C).

As a consequence of sympathetic block, systemic vascular resistance index decreased by 34% (P = 0.06), which was accompanied by decreases in mean arterial pressure (MAP) by 17% (P = 0.07) and coronary perfusion pressure by 19% (P = 0.056) and a moderate increase of cardiac index (P = 0.32). Moreover, mixed venous oxygen saturation (Svo_2) increased by 33% (P = 0.006), while oxygen extraction ratio (O_2-ER) decreased by 45% (P = 0.002).

Primary Endpoint: Hb_{crit}

The induction of critical normovolemic anemia required the exchange of 106 ± 40% of circulating blood volume in the ROP group and 99 ± 31% in the SAL group. In both groups, Hb_{crit} was met at 2.5 ± 0.6 g/dl (difference of means: −0.05, 95% confidence interval: −0.64, 0.53), so that no differences between the groups could be observed (P = 0.86).

Table 1. Hemodynamic and Oxygen-derived Parameters Assessed at Baseline, After Institution of TEA and at the Individual Hb_{crit}

	Baseline	TEA	Hb_{crit}
BVI, ml/kg			
ROP	79 ± 17		
SAL	74 ± 12		
Temp, °C			
ROP	38.2 ± 1.0	38.1 ± 1.0	37.8 ± 1.1
SAL	38.2 ± 0.7	38.1 ± 0.6	37.9 ± 0.6
HR, 1/min			
ROP	78 ± 13	87 ± 14	122 ± 33*†
SAL	68 ± 13	70 ± 12	118 ± 22*†
MAP, mmHg			
ROP	91 ± 16	75 ± 9	57 ± 14*†
SAL	91 ± 13	82 ± 10	73 ± 16*‡
MPAP, mmHg			
ROP	18 ± 4	18 ± 4	21 ± 3*†
SAL	16 ± 3	18 ± 4	25 ± 4*†‡
PCWP, mmHg			
ROP	5 ± 3	3 ± 2	6 ± 3
SAL	4 ± 1	4 ± 1	6 ± 2
CPP, mmHg			
ROP	66 ± 14	53 ± 9	31 ± 12*†
SAL	69 ± 10	58 ± 8	44 ± 15*†
CI, $l \cdot min^{-1} \cdot m^{-2}$			
ROP	3.1 ± 1.0	3.8 ± 1.0	6.6 ± 1.5*†
SAL	3.0 ± 0.6	3.5 ± 0.6	7.1 ± 0.8*†
SVI, ml/m^2			
ROP	40 ± 9	43 ± 7	57 ± 15*†
SAL	44 ± 3	50 ± 4	61 ± 10*†
SVRI, $dyn \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$			
ROP	4,499 ± 1,560	2,967 ± 906	1,147 ± 339*†
SAL	4,213 ± 1,048	3,194 ± 747	1,377 ± 418*†
PVRI, $dyn \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}$			
ROP	674 ± 243	618 ± 224	405 ± 224
SAL	617 ± 144	614 ± 249	393 ± 90
Cao_2, ml/dl			
ROP	10.4 ± 1.0	9.8 ± 0.9	3.7 ± 0.8*†
SAL	10.5 ± 0.8	10.6 ± 0.9	3.7 ± 0.8*†
Pao_2, mmHg			
ROP	94 ± 8	97 ± 17	103 ± 18
SAL	95 ± 7	95 ± 6	92 ± 19
Svo_2, %			
ROP	43 ± 7	57 ± 8	43 ± 10†
SAL	47 ± 8	51 ± 8	41 ± 8
Do_2I, $ml \cdot m^{-2} \cdot min^{-1}$			
ROP	320 ± 95	363 ± 78	237 ± 57*†
SAL	319 ± 78	372 ± 67	257 ± 38*†
Vo_2I, $ml \cdot m^{-2} \cdot min^{-1}$			
ROP	211 ± 31	208 ± 36	176 ± 26
SAL	195 ± 20	202 ± 23	184 ± 18
O_2-ER, %			
ROP	61 ± 16	42 ± 7*	59 ± 19†
SAL	52 ± 8	48 ± 9	61 ± 7†
pH			
ROP	7.54 ± 0.04	7.54 ± 0.06	7.47 ± 0.06*†
SAL	7.54 ± 0.05	7.54 ± 0.04	7.44 ± 0.05*†
BE, mmol/l			
ROP	6.9 ± 3.0	7.1 ± 2.9	2.2 ± 3.5*†
SAL	5.3 ± 2.9	6.3 ± 3.8	1.6 ± 3.2*†
Lac, mmol/l			
ROP	2.0 ± 1.0	1.5 ± 0.5	2.0 ± 1.1
SAL	1.8 ± 0.7	1.7 ± 0.8	1.5 ± 0.9

BVI, CI, Do_2I, PVRI, SVI, SVRI, and Vo_2I are indexed to body surface area (see appendix).

*P < 0.05 *versus* baseline. †P < 0.05 *versus* TEA. ‡P < 0.05 ROP *versus* SAL.

BE = base excess; BVI = blood volume index; CaO_2 = arterial oxygen content; CI = cardiac index; CPP = coronary perfusion pressure; DO_2I = oxygen delivery index; Hb_{crit} = critical hemoglobin concentration; HR = heart rate; Lac = lactate concentration; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; O_2-ER = oxygen extraction ratio; PaO_2 = arterial oxygen tension; PCWP = pulmonary capillary occlusion pressure; pH = pH value; PVRI = pulmonary vascular resistance index; ROP = ropivacaine group (n = 9); SAL = saline group (n = 9); SVI = stroke volume index; SvO_2 = mixed-venous oxygen saturation; SVRI = systemic vascular resistance index, TEA = thoracic epidural anesthesia; Temp = body core temperature; VO_2I = oxygen consumption index.

Hemoglobin concentrations are displayed at baseline, TEA, and Hb_{crit} in figure 3.

Secondary Endpoints: Hemodynamic and Oxygen-derived Parameters

During hemodilution, arterial oxygen content decreased proportionally with falling hemoglobin concentrations (P < 0.001 *vs.* TEA in either group). To compensate for acute anemia, cardiac index (CI) and O_2-ER increased significantly in both groups. The increase of CI (P < 0.001 *vs.* TEA in either group) was achieved by increases in heart rate and stroke volume. Systemic vascular resistance index decreased by 61% and 56%, respectively (P < 0.001 *vs.* TEA in either group), as MAP decreased by 24% in the ROP group (P = 0.012) and by 11% in the SAL group (P = 0.33). Coronary perfusion pressure decreased by an average of 41% in the ROP group (P < 0.001) and by 24% in the SAL group (P = 0.039). At Hb_{crit}, animals subjected to TEA were more hypotensive than controls, as indicated by lower values of mean arterial and pulmonary arterial pressures (P = 0.011 and P = 0.009 *vs.* SAL group, respectively).

Despite the compensatory increase of CI, oxygen delivery (Do_2) decreased significantly (ROP group: P = 0.002, SAL group: P = 0.005) during progressive anemia. Hence, O_2-ER increased by 40% in the ROP group (P = 0.03 *vs.* TEA) and by 27% in the SAL group (P = 0.037 *vs.* TEA). While base excess decreased in both groups (P = 0.018 and P = 0.017, respectively), lactate concentration was not yet elevated at Hb_{crit} in either group.

Discussion

The main finding of the present study is that sympathetic block (Th5–Th10) induced by TEA with 0.2% ropivacaine has no effect on the limit of tolerance to anemia. This was reflected by identical values of Hb_{crit} in animals subjected to TEA compared to those that received epidural saline.

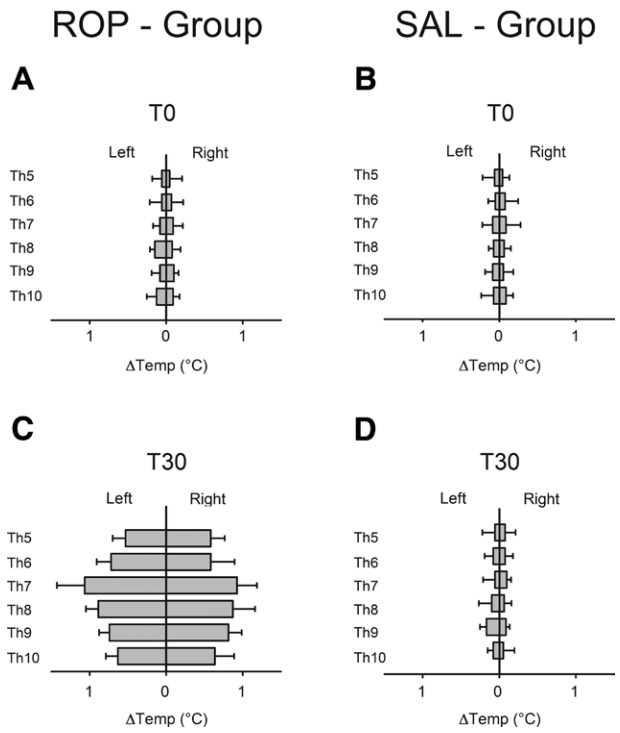

Fig. 2. Skin temperature measured along the left and right anterior axillary lines within the dermatomes Th5–Th10 in animals receiving epidural ropivacaine (ROP group; *A* and *C*) and saline (SAL-group; *B* and *D*), respectively. Data are presented as ΔT relative to a reference point on the surface of the lower abdomen. Measurements were performed immediately after epidural injection of either fluid (T0, *A* and *B*) and after 30 min (T30, *C* and *D*).Within the different dermatomes, the injection of ropivacaine elicited a relative increase of skin temperature (*B*). In contrast, skin temperature was not altered after epidural injection of normal saline (*D*).

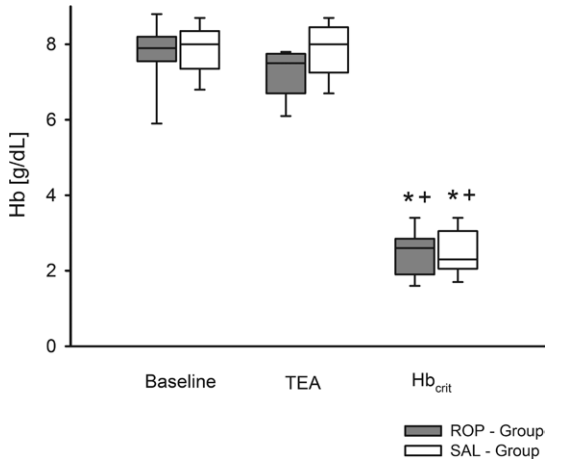

Fig. 3. Hemoglobin concentration assessed at baseline, after institution of thoracic epidural anesthesia (TEA), and at the individual critical hemoglobin concentration (Hb_{crit}). The ropivacaine group (ROP, n = 9) is displayed by gray boxes, the saline group (SAL, n = 9) by white boxes. Beginning with a hemoglobin concentration of 7.7 ± 0.8 g/dl (ROP group) and 7.8 ± 0.6 g/dl (SAL group) at baseline, Hb_{crit} was met at 2.5 ± 0.6 g/dl in both groups. *P < 0.05 *versus* baseline. +P < 0.05 *versus* TEA.

Hb_{crit} represents the ultimate limit of tolerance to anemia at the level of the whole organism.[5,12] In previous experimental studies, we could demonstrate that this critical limitation of oxygen supply was associated with 100% mortality, if no treatment (*e.g.*, elevation of F_{IO_2}, transfusion of red blood cells, or infusion of artificial oxygen carriers) was initiated at Hb_{crit}.[13–15] Hb_{crit} has been chosen as the primary endpoint in a variety of studies investigating the impact of interventions on the limit of tolerance to acute anemia. As reflected by reduced values of Hb_{crit} (listed in table 2), tolerance to anemia was found to be increased by (1) hypothermia (moderate reduction of body core temperature reduces total body oxygen demand),[16] (2) hyperoxic ventilation (excellent bioavailability of oxygen physically dissolved in the plasma),[13,17–19] (3) infusion of norepinephrine (stabilization of coronary perfusion pressure during hemodilution)[20] or infusion of artificial oxygen carriers (maintenance of arterial oxygen content despite reduced hematocrit),[15,21,22] (4) deep neuromuscular block (lowering skeletal muscular oxygen demand),[23] and (5) use of colloidal rather than crystalloid fluids for volume replacement (maintenance of microvascular perfusion due to reduced extravasation rate).[24] In contrast, tolerance to anemia was reduced by (1) hypovolemia (reduction of microcirculatory oxygen supply), (2) profound anesthesia (pharmacologic reduction of cardiac output),[25] and (3) coronary artery disease (reduced coronary flow reserve).[26]

TEA today has become an integral part of perioperative care during and after major surgery, as it provides an effective analgesia.[27] TEA-related effects beyond analgesia (*i.e.*, sympathetic block) have been demonstrated to improve

Table 2. Synopsis of Experimental Studies Investigating the Impact of Several Interventions on the Value of Hb_{crit}

Author	Species	Intervention	Hb_{crit}, g/dl	Endpoint
Perez-de-Sá[16]	Pig	Hypothermia	2.3 ± 0.2	Value of Hb_{crit}
Pape *et al.*[17,19]	Pig	Hyperoxia (F_{IO_2} 0.6)	2.4 ± 0.4	Value of Hb_{crit}
		Hyperoxia (F_{IO_2} 1.0)	1.3 ± 0.3	
Meier *et al.*[13]	Pig	Hyperoxia (F_{IO_2} 1.0)	3.1 ± 0.4	Survival time after Hb_{crit}
Meier *et al.*[20]	Pig	Norepinephrine	2.6 ± 0.4	Survival time after Hb_{crit}
Pape *et al.*[15]	Dog	Artificial O_2 carrier	2.7 ± 0.5	Survival time after Hb_{crit}
Meisner *et al.*[22]	Pig	Artificial O_2 carrier	Hct 1.2%	Value of Hb_{crit}
Pape *et al.*[23]	Pig	Neuromuscular blockade	2.4 ± 0.5	Value of Hb_{crit}
Pape *et al.*[24]	Pig	Varying plasma substitute	2.1 ± 0.4	Value of Hb_{crit}
Van der Linden[25]	Dog	Varying depth of anesthesia	2.5 ± 0.6	Value of Hb_{crit}

Hb_{crit} = critical hemoglobin concentration; O_2 = oxygen.

clinical outcome in patients undergoing cardiac and noncardiac surgery.[8] Some meta-analyses[28,29] suggest a reduction of cardiopulmonary morbidity and mortality after major surgery performed with TEA. Moreover, TEA might improve intestinal perfusion and tissue oxygenation,[30–32] gut motility,[33] and anastomotic patency.[34] In experimental studies, hepatic[35] and intestinal[36] perfusion remained unaltered despite significant hypotension elicited by TEA.

However, experimental data regarding cardiovascular performance in pigs subjected to TEA are equivocal: While the hemodynamic response to cross-clamping of the thoracic aorta was not affected by sympathetic block,[37] the inotropic reserve of the right ventricle was compromised by TEA.[38]

We hypothesized that TEA might impair the hemodynamic compensation to acute normovolemic anemia resulting in a compromised tolerance to anemia. If so, this should lead to caution in use of TEA in high–blood-loss surgery to reduce transfusion.

Our data do not confirm this hypothesis. The assumed hemodynamic depression (*i.e.*, hypotension and limited cardiac output) was predominantly observed in experimental studies using higher concentrations of local anesthetics for TEA.[31,35,36,39] Contrary to our expectations, the present data suggest that hemodynamic compensation for acute anemia (*i.e.*, increase of cardiac output) was fully maintained during TEA with 0.2% ropivacaine.

Although the decrease in MAP was moderate after injection of ropivacaine, MAP and, thus, coronary perfusion pressure were significantly lower at Hb_{crit}, indicating that hypotension was more severe in animals subjected to TEA combined with profound anemia than in those experiencing acute anemia alone.

Our findings obtained in healthy pigs may not apply to patients with cardiovascular comorbidity (*e.g.*, coronary artery disease). In the presence of coronary arterial sclerosis, a decrease in coronary perfusion pressure may result in a critical limitation of myocardial oxygenation even at higher hemoglobin concentrations.

The spread of sympathetic block was assessed by measurement of skin temperature, which is an indirect method to assess sympathetic nerve activity. In contrast to direct techniques (*e.g.*, microneurography), thermometry is a simple and noninvasive method that allows a good chronological and spatial resolution of measurements.[40] Moreover, skin temperature assessed by infrared thermometry has been validated as a surrogate parameter of sympathetic activity in clinical[9,40] as well as in experimental[38,41] studies.

In the present study, Hb_{crit} was derived from mean total body oxygen consumption. The Delta-Trac II metabolic monitor provides a reliable method of V_{O_2} measurement, which has been validated.[10,42] Although the assessment of Hb_{crit} at the level of the whole organism has been used to investigate the impact of interventions on tolerance to anemia, this approach neglects the limits of anemia tolerance on the cellular and the organ-specific level. While the present study was not designed to address this point, results of a recent experimental study suggest that in the kidneys and in the intestine signs of tissue hypoxia occur before the critical limit of systemic oxygen supply is reached in anesthetized pigs subjected to acute normovolemic hemodilution.[4] In contrast, hepatic,[35] gastric,[31] and intestinal[36] tissue oxygenation were found unaltered despite significant systemic hypotension elicited by high-dose TEA.

Clinical data suggest that TEA improves myocardial oxygen balance in patients undergoing coronary bypass surgery, resulting in increased myocardial contractility.[27,43] This finding could have had a positive effect on tolerance to anemia by improving the cardiac response to acute anemia. In the present study, however, the institution of low-dose TEA did not affect CI, but elicited a decrease in O_2-ER and systemic vascular resistance index while V_{O_2} remained constant, which may reflect improved tissue perfusion. Theoretically, this finding could also have contributed to an augmentation of tolerance to anemia, for example, due to augmentation of splanchnic tissue oxygenation.

Despite these potentially positive effects of TEA on anemia tolerance, the values of Hb_{crit} were identical in both groups, indicating that TEA did neither improve nor diminish tolerance to anemia. In particular, the compensatory increases in O_2-ER and CI during progressive anemia were unrestricted despite the presence of a sympathetic block.

In summary, our data indicate that the limit of tolerance to anemia was not compromised by TEA using 0.2% ropivacaine in healthy pigs. In clinical practice, however, blood transfusion should be initiated before this limit is reached, that is, before Hb_{crit} is reached, particularly since comorbid cardiovascular diseases or critical illness may severely restrict an individual's tolerance to acute anemia. Yet, a blood transfusion may occasionally be impossible, for example, having to "bridge" an acute blood loss until compatible blood products are available or refusal of blood transfusion for religious reasons. Even in these situations, where extremely low hemoglobin concentrations must be tolerated, essential compensatory mechanisms of acute anemia were maintained over a wide range of hemoglobin values despite sympathetic block.

Conclusion

TEA with ropivacaine does not compromise the tolerance of acute anemia in healthy pigs, as essential compensatory mechanisms were fully preserved despite sympathetic block. Thus, TEA appears to be a reasonable choice even in major blood-loss surgery. However, whether the threshold for transfusion should be altered in those receiving TEA—particularly in the presence of cardiovascular comorbidity—remains to be elucidated.

Acknowledgments

The authors thank Alf Theisen (D.V.M.), Waldemar Daut, and his team for their excellent animal care and Heinz Winkelmeier for his valuable technical assistance.

Dr. Theisen, Mr. Daut, and Mr. Winkelmeier are employed at the Central Research Facility, Goethe University, Frankfurt/Main, Germany. Sincere thanks are given to Hans-Joachim Wilke, D.E.A.A. (Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Frankfurt/Main, Germany), for language-editing the present manuscript.

Support was provided soley from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

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Appendix. Drug-list and Calculated Parameters

For induction and maintenance of anaesthesia, the following drugs were applied:

Ketamine (Ketavet, Parke-Davis, Berlin, Germany)

Midazolam (Midazolam, Ratiopharm, Ulm, Germany)

Propofol (Brevimytal, Braun, Bad Melsungen, Germany)

Fentanyl (Fentanyl, Janssen, Neuss, Germany)

Pancuronium (Pancuronium, Curamed, Karlsruhe, Germany)

Balanced electrolyte solution (Tutofusin, Pharmacia, Erlangen, Germany)

6% HES 130/0.42 (Tetraspan, Braun, Melsungen, Germany).

For epidural anesthesia, ropivacaine (Naropin, AstraZeneca, Wedel, Germany) was applied.

Body surface area (BSA) was calculated according to Holt *et al.*[44]:

$$BSA = k \cdot BW^{\frac{2}{3}} \left(m^2\right),$$

where BW = body weight (in kg) and k = 9 (constant for the species pig).

Cardiac index was calculated as:

$$CI = \frac{CO}{BSA}\left(\frac{l}{m^2}\right),$$

where CO = cardiac output.

Stroke volume index was calculated as:

$$SVI = \frac{CI}{HR}\left(\frac{l}{m^2}\right),$$

where HR = heart rate.

Systemic and pulmonary vascular resistance indices were calculated as :

$$SVRI = \frac{(MAP - CVP)\cdot 79.9}{CI}\left(\frac{dyn \cdot s}{cm^5 \cdot m^2}\right) \text{ and}$$

$$PVRI = \frac{(MPAP - LVEDP)\cdot 79.9}{CI}\left(\frac{dyn \cdot s}{cm^5 \cdot m^2}\right),$$

where MAP = mean aortic pressure, CVP = central venous pressure, $MPAP$ = mean pulmonary arterial pressure, and $LVEDP$ = left ventricular end-diastolic pressure.

O_2 extraction ratio (O_2-ER) as calculated as follows:

$$O_2ER = \frac{CaO_2 - CvO_2}{CaO_2}\cdot 100(\%)$$

where Ca_{O_2} and C_{VO_2} are arterial and mixed venous oxygen content.

Coronary perfusion pressure was calculated as

$$CPP = DAP - PCWP,$$

where DAP = diastolic arterial pressure and $PCWP$ = pulmonary capillary occlusion pressure.

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