Sevoflurane and propofol anaesthesia differentially modulate the effects of epinephrine and norepinephrine on microcirculatory gastric mucosal oxygenation

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Key points
- Catecholamines are routinely used in the intensive care setting.
- In dogs, the effects of epinephrine and norepinephrine vary depending on the type of anaesthetic.
- The local effects of the catecholamines (in the gastric mucosa) were not predictable from the systemic effects.

Background. Adequate gastrointestinal mucosal oxygenation is regarded to be crucial in the prevention and therapy of critical illness. Epinephrine and norepinephrine are used for perioperative haemodynamic support. However, their per se effects on gastromucosal haemoglobin oxygenation (μHbO2) remain unclear. Moreover, respective effects of epinephrine and norepinephrine may be affected by the type of underlying anaesthesia. Thus, we studied the effects of epinephrine and norepinephrine during anaesthesia with sevoflurane or propofol on regional gastromucosal μHbO2 and systemic O2-derived variables.

Methods. In a double-randomized cross-over study, chronically instrumented dogs (n=6 per group) were anaesthetized randomly with sevoflurane or propofol, ventilated, and then randomly received either epinephrine or norepinephrine (0, 0.05, 0.1, and 0.2 μg kg⁻¹ min⁻¹). We measured gastromucosal μHbO2, systemic haemodynamics, and O2-derived variables.

Results. During sevoflurane anaesthesia, norepinephrine markedly increased μHbO2 (P<0.0001) and systemic oxygen transport (DO2) (P=0.0006). In contrast, epinephrine failed to increase μHbO2, despite doubling DO2 (P=0.0002). During propofol anaesthesia, in contrast to sevoflurane, neither epinephrine nor norepinephrine affected μHbO2, although epinephrine, but not norepinephrine, again resulted in markedly increased DO2 (P<0.0001).

Conclusions. The effects of epinephrine and norepinephrine depended on the type of anaesthesia. In addition, regional effects (i.e. μHbO2) were not predictable from systemic effects (i.e. DO2).

Keywords: dog; epinephrine; mucosa, gastric; norepinephrine; propofol; sevoflurane

Accepted for publication: 28 May 2010

Adequate splanchnic oxygenation, particularly of the gastrointestinal mucosa, is regarded as being crucial for prevention and therapy of critical illness.1,2 However, splanchnic perfusion and oxygenation is impaired early in the course of reduced systemic oxygen transport,3 which may evolve during anaesthesia or surgery.4–6 Thus, perioperative therapeutic strategies to preserve or improve regional, splanchnic oxygenation are needed.

During anaesthetic procedures, depending on subpopulation or surgical procedure, systemic haemodynamics are frequently stabilized by the use of the natural catecholamines norepinephrine or epinephrine.7 In contrast to intensive care settings, where critically ill patients frequently present with profound inflammatory vasodysregulation (such as in sepsis), patients receiving norepinephrine or epinephrine for perioperative haemodynamic support during anaesthetic procedures often present without inflammatory vasodysregulation. However, in this latter group, the anaesthetics used may affect the cardiocirculatory system differently and alter the responsiveness to vasoactive drugs, such as catecholamines.8

Thus, we studied the systemic and regional gastric mucosal effects of epinephrine and norepinephrine under two classes of anaesthetics, the volatile agent sevoflurane and the i.v. anaesthetic, propofol, in healthy animals.

Methods

Animals

The data were derived from repetitive experiments on healthy dogs (foxhounds, n=6, male/female 1/5, 27–35 kg
bodyweight, obtained from the university animal experiment facility of Dusseldorf, Germany) that were treated in accordance with the National Institutes of Health guidelines for animal care and with approval of the local District Governmental Animal Investigation Committee (registration code 50.05-230-74/05). Each experiment on each dog was scheduled ≥2 weeks apart to exclude carry-over effects between the experiments. During this study period, the animals were under regular veterinary supervision at the university animal experiment facility.

For the continuous measurement of cardiac output (CO), ultrasonic flow transducers (20 mm S-series, Transonic, Ithaca, NY, USA) were chronically implanted around the pulmonary artery and calibrated, at least 4 weeks before the experiments. Before the experiments, food was withheld for 12 h with water ad libitum to ensure gastric depletion and to exclude gastric mucosal perfusion/oxygenation changes by digestive activity. The experiments were performed under general anaesthesia with either sevoflurane or propofol as described below, with mechanical ventilation formed under general anaesthesia with either sevoflurane and propofol both induced stable anaesthesia, allowing mechanical ventilation without response/movement of the animals. The animals were randomized using opaque envelopes to receive anaesthesia with sevoflurane or propofol. After induction (propofol 4 mg kg⁻¹ in both groups), catheters were inserted (right atrial position of the saline central venous catheter verified by fluoroscopy) and 30 min were allowed to establish steady-state conditions of the measured variables. Blood was sampled for baseline analysis, and thereafter, a second randomization using opaque envelopes was performed to allocate the dogs to the study groups, that is, epinephrine or norepinephrine. Each dog underwent each experimental combination.

**Measurements**

**Gastric mucosal oxygenation**

Gastric mucosal oxygenation was continuously assessed by reflectance spectrophotometry (EMPHO II, BGT, Friedrichshafen, Germany), as detailed previously. Briefly, light (502–628 nm) is transmitted to the tissue of interest via a micro light guide, and the reflected light is analysed for the percentage of oxygenated microvascular haemoglobin (μHbO₂). The flexible light guide probe (outer diameter 2.0 mm) was introduced into the stomach via an orogastric silicone tube (14 Charrière). During the experiments, the correct probe position was confirmed continuously by online evaluation of the signal quality (EMPHO II software, version 2.0) as detailed previously. The μHbO₂ values reported resemble the averaged μHbO₂ of the last 4 min (150 spectra, 1.6 seconds each) of each intervention under steady-state conditions.

**Systemic oxygen consumption**

Systemic oxygen consumption (VO₂) was measured continuously by indirect calorimetry (Deltatrac-II metabolic monitor, Datex, Helsinki, Finland) and thus was methodologically independent from determination of CO and systemic oxygen transport (DO₂), as detailed previously for anaesthetized dogs.

**Systemic haemodynamics and oxygenation**

We continuously measured heart rate (HR, ECG), mean arterial (aortic) and central venous (right atrial) pressures (MAP and CVP, respectively, using saline-filled sterile catheters and appropriate transducers, Gould-Statham, P231D, Elk Grove, IL, USA), and CO (ultrasonic transit-time flowmeter, T106, Transonic Systems, Ithaca, NY, USA). Intermittently, at the end of each intervention under steady-state conditions, we measured arterial blood gas tensions (Pao₂, Pco₂) and acid/base-related variables (pH, base excess (BE); ABL-700, Radiometer, Copenhagen, Denmark). Additionally, we intermittently measured arterial serum metabolites (glucose, lactate) and serum electrolytes (K⁺, Ca²⁺, Na⁺, Cl⁻; ABL-700). According to standard formulae, we calculated systemic vascular resistance (SVR), arterial oxygen content (CaO₂), and systemic oxygen transport (DO₂=CO CaO₂).

**Experimental programme**

The animals were randomized using opaque envelopes to receive anaesthesia with sevoflurane or propofol. After induction (propofol 4 mg kg⁻¹ in both groups), catheters were inserted (right atrial position of the saline central venous catheter verified by fluoroscopy) and 30 min were allowed to establish steady-state conditions of the measured variables. Blood was sampled for baseline analysis, and thereafter, a second randomization using opaque envelopes was performed to allocate the dogs to the study groups, that is, epinephrine or norepinephrine. Each dog underwent each experimental combination.

**Type of anaesthesia**

Anaesthesia was induced and maintained with anaesthetic agents alone, with no neuromuscular blocking agents. Anaesthesia was maintained with sevoflurane (Abbott, Wiesbaden, Germany) at an end-tidal concentration of 3.0 vol%, corresponding to ~1.25 MAC for dogs, or continuous i.v. infusion of propofol (~15 mg kg⁻¹ h⁻¹). To minimize lipid load and infused volume, propofol was administered as 2% (20 mg ml⁻¹) formulation (Fresenius Kabi, Bad Homburg, Germany). These dosages of sevoflurane and propofol both induced stable anaesthesia, allowing mechanical ventilation without response/movement of the animal. On the basis of previous experiments, the selected propofol dose and the selected sevoflurane concentration achieve the same baseline level of our key variable μHbO₂.

**Catecholamines**

The catecholamines norepinephrine and epinephrine were diluted and infused using a pressure-limited infusion pump (IVAC, M770, San Diego, CA, USA), via the central venous catheter. After a baseline period, epinephrine (Suprarenin, Aventis, Frankfurt, Germany) was administered with an initial dose of 0.05 μg kg⁻¹ min⁻¹, followed by a medium dose of 0.1 μg kg⁻¹ min⁻¹ and finally of 0.2 μg kg⁻¹ min⁻¹. Each step was maintained for 30 min, a time sufficient to reach steady-state conditions. Norepinephrine (Arterenol, Aventis, Frankfurt, Germany) was administered after a baseline period with an initial dose of 0.05 μg kg⁻¹ min⁻¹, followed by a medium dose of 0.1 μg kg⁻¹ min⁻¹,
and finally of 0.2 μg kg⁻¹ min⁻¹. Each step was again maintained for 30 min.

**Statistical analysis**

All data are presented as median [inter-quartile range (IQR)] for n=6 animals per group (total 24 experiments). Comparisons were performed between drugs (i.e. epinephrine vs norepinephrine) using the Mann–Whitney test, and within each group (i.e. baseline vs respective drug infusion steps) using the Friedman test, and corrected for multiple comparisons using Dunn’s post hoc test. Significance was assumed at P<0.05.

**Results**

The main result of our study is that norepinephrine, but not epinephrine, significantly increases microvascular gastric mucosal oxygenation (μHbO₂) during sevoflurane anaesthesia, whereas both catecholamines fail to increase μHbO₂ during propofol anaesthesia.

**Gastric mucosal and systemic O₂-related variables**

During sevoflurane anaesthesia, epinephrine elicited a dose-dependent, biphasic change in regional μHbO₂ (Fig. 1A, for the other O₂-related variables see Supplementary Table S1). Epinephrine decreased μHbO₂ at the low dose [from 58 (57–58) to 50 (40–57)%, P=0.026 vs norepinephrine], with a return to baseline at higher doses [back to 60 (47–63) and 59 (51–61)%, respectively]. However, epinephrine failed to increase μHbO₂ above baseline at any dose. In contrast, at the systemic level, epinephrine significantly increased DO₂ dose dependently (P=0.0002, Fig. 2), with a doubling of DO₂ at the highest dose, from 12 (10–14) (baseline) to 29 (16–34) ml kg⁻¹ min⁻¹. In contrast, norepinephrine during sevoflurane anaesthesia significantly (P<0.0001) increased regional μHbO₂ dose dependently from 57 (54–60) (baseline) to 67 (63–69)% (highest dose), and also significantly (P=0.0006) increased DO₂ [from 13 (11–14) to 21 (13–25) ml kg⁻¹ min⁻¹]. Thus, although DO₂ was lower with norepinephrine than with epinephrine at all dosages, only norepinephrine significantly increased μHbO₂.

In contrast to the significant and opposing effects of epinephrine and norepinephrine during sevoflurane anaesthesia, both catecholamines failed to significantly affect μHbO₂ during propofol anaesthesia (Fig. 1A): both epinephrine and norepinephrine maintained μHbO₂ stable at baseline values at all doses. However, similar to sevoflurane, in animals undergoing propofol anaesthesia, epinephrine resulted in a doubling of DO₂ (P<0.0001), while little effect was seen with norepinephrine on DO₂.

The relationship between regional (μHbO₂) and systemic oxygenation (DO₂) markedly differed between the groups. During sevoflurane anaesthesia, norepinephrine significantly increased μHbO₂ with only minor changes in DO₂, whereas epinephrine markedly increased DO₂ without increasing μHbO₂. In contrast, during propofol anaesthesia, despite marked changes in DO₂, there were no significant effects on μHbO₂. Thus, μHbO₂ cannot be deduced from DO₂ and vice versa.

Furthermore, the relationship between regional oxygenation (μHbO₂) and MAP markedly differed between the groups. During sevoflurane anaesthesia, only norepinephrine increased μHbO₂ pressure dependently, whereas in contrast during propofol anaesthesia, the marked and significant changes in MAP were not associated with changes in μHbO₂. Thus, μHbO₂ cannot be deduced from MAP.

**Systemic haemodynamics**

The haemodynamic data are shown in Supplementary Table S2. Epinephrine dose dependently increased CO, from 76 (65–82) to 120 (79–147) ml kg⁻¹ min⁻¹ (37%) during

![Image](https://via.placeholder.com/150)
sevoflurane anaesthesia ($P=0.002$), and from 85 (80–90) to 137 (118–156) ml kg$^{-1}$ min$^{-1}$ (38%) during propofol anaesthesia ($P=0.0015$). Epinephrine predominantly increased SVR and less consistently HR (Supplementary Table S2). At lower doses, epinephrine tended to decrease SVR, with a return towards baseline at the higher doses. In addition, epinephrine failed to increase MAP at the lowest dose, but increased MAP at higher doses. Thus, epinephrine at low doses acted as an inodilator, with accentuated vasoconstriction at the high doses. Norepinephrine, in contrast, acted predominantly as a vasopressor, increasing MAP even at the lowest dose, together with a reduction in HR. In parallel with this reduction of HR, norepinephrine also increased SVR at higher doses.

**Ventilation-derived variables**

Mechanical ventilation, targeted to maintain end-tidal CO$_2$ at 35 mm Hg, resulted in stable ventilation-derived variables. $P_{a\text{CO}_2}$, $P_{a\text{O}_2}$, and arterial oxygen saturation ($S_{a\text{O}_2}$) remained close to 37 mm Hg, 130 mm Hg, and 97%, respectively, for all groups and all interventions.

Arterial pH decreased slightly with both catecholamines and both anaesthetics, from $\sim$7.35 (baseline) to $\sim$7.30 (highest catecholamine dose) (Supplementary Table S3).

**Electrolytes and metabolites**

Arterial serum electrolyte concentrations were maintained in epinephrine- and norepinephrine-treated animals with both anaesthetics throughout the entire experiment (Supplementary Table S3). Epinephrine and norepinephrine both resulted in preserved arterial serum glucose concentrations between 90 and 130 mg dl$^{-1}$ with both anaesthetics (Supplementary Table S3). Epinephrine treatment significantly increased arterial lactate both during sevoflurane ($P=0.0028$) and propofol anaesthesia ($P<0.0001$), whereas norepinephrine resulted in maintenance of lactate under both sevoflurane and propofol anaesthesia (Fig. 3).

**Discussion**

**Experimental model**

Repetitive experiments were performed in a randomized fashion on healthy, chronically instrumented dogs with intervals of $\geq$2 weeks to exclude carry-over effects and minimize interindividual differences. Furthermore, the use of chronically instrumented animals avoided acute surgical instrumentation and thus confounders like stress responses to surgery, inducing elevated endogenous levels of epinephrine and norepinephrine. In addition, our model allowed us to study animals undergoing anaesthesia alone, without the need for analgesics$^{14}$ or other confounding drugs. Although this reduction of confounding factors appears advantageous in the present experimental study, it does not reflect the complexity of clinical anaesthesia, thus limiting extrapolation of our data to the clinical setting where epinephrine or norepinephrine may be used, for example, anaphylaxis, haemorrhage, sepsis, cardiac failure, burns, etc. All of these settings require specific animal models to extend our findings on the interaction between anaesthesia and catecholamine to the pathology of hypotension.

**Type of anaesthesia**

The dosages of the respective anaesthetics sevoflurane and propofol$^{9,12,15,16}$ resulted in a comparable, stable level of anaesthesia, as judged by toleration of mechanical ventilation (without need for any other drugs) and loss of pharyngeal and eyelash reflexes, respectively (Ramsay sedation score $\geq$4). In a recent study using a similar canine model,
the same dosages of sevoflurane and propofol were applied, with depth of anaesthesia monitored by the EEG-derived bispectral index. The anaesthetic dosages appear relatively high compared with clinical use, but are explained by increased anaesthetic requirements in dogs and deliberate avoidance of other confounding drugs in our mono-anaesthesia model, that is, no premedication and no analgesia.

Compared with the awake state, anaesthesia induces cardiovascular depression, depending on anaesthetic regimen applied. In our previous studies, we reported an awake MAP of ~100 mm Hg and CO of ~100 ml kg$^{-1}$ min$^{-1}$ in similarly instrumented dogs of comparable weight. Compared with these data, sevoflurane in the present study markedly depressed the cardiovascular system, whereas propofol had only moderate impact, although yielding the same level of anaesthesia. In addition, the selected sevoflurane and propofol dosages were also matched to achieve the same baseline levels in $\mu$HbO$_2$, as evident from the almost identical baseline $\mu$HbO$_2$ during sevoflurane and propofol anaesthesia.

Reflectance spectroscopy
Gastric mucosal $\mu$HbO$_2$ was continuously measured by reflectance spectrophotometry, a method previously detailed by us and others. As described before, the light guide was non-traumatically introduced via an orogastric tube into the stomach. Reflectance spectrophotometry allows direct determination of intracapillary haemoglobin oxygen saturation, representing microcirculatory oxygen availability. Furthermore, gastric endoluminal reflectance spectroscopy is reported to predominantly measure capillary haemoglobin oxygenation of the mucosa rather than of outer wall layers. Spectrophotometry reliably detects even clinically asymptomatic reductions in gastric mucosal oxygenation and correlates with the morphological severity and extent of gastric mucosal tissue injury. The values of $\mu$HbO$_2$ at baseline observed in our study are in accordance with previous studies on gastrointestinal mucosa oxygenation in dogs and pigs.

Interpretation of results
We found that norepinephrine, but not epinephrine, increases $\mu$HbO$_2$ during sevoflurane anaesthesia in dogs, whereas both catecholamines fail to increase $\mu$HbO$_2$ during propofol anaesthesia. In detail, epinephrine depresses $\mu$HbO$_2$ at low dosages during sevoflurane with only a return to baseline values at higher epinephrine dosages. Moreover, this biphasic response in regional $\mu$HbO$_2$ contrasts the observed, dose-dependent increase in systemic DO$_2$, suggesting interference from other factors such as vascular and metabolic effects. In line with activation of cardiac $\beta$- and vasodilatory $\beta$-adrenoceptors, epinephrine at low dose increased CO and DO$_2$ at stable MAP and tended to decrease SVR. Thus, epinephrine should increase $\mu$HbO$_2$ both via an increased systemic DO$_2$ and regional vasodilation, particularly at low doses where these $\beta$-effects are not counteracted by $\alpha$-adrenoceptor-mediated vasoconstriction. However, in line with our findings, activation of $\beta$-adrenoceptors by epinephrine decreases splanchnic blood volume, for example, by relaxing hepatic resistance vessels. Additionally, at the intramural level, our contrasting findings could result in part from a layer-specific adrenoceptor distribution within the gastrointestinal wall. Sympathetic nerve fibres with their adrenoceptors are predominantly located within the outer gut layers, that is, the muscularis and submucosa. Thus, low-dose epinephrine predominantly stimulates $\beta$-adrenoceptors and could thereby increase perfusion of outer gut layers, thus causing reduction of mucosal perfusion. At higher doses, however, epinephrine...
also stimulates vasoconstrictive $\alpha_1$-adrenoceptors, thus redirecting blood flow towards the mucosa and thereby restoring mucosal oxygenation. Compatible with this finding, a further increase in epinephrine dosage might eventually increase $\mu$HbO$_2$ above baseline, however, with aggravated systemic effects. This is supported by data from acutely instrumented pigs, demonstrating that higher epinephrine dosages increase mucosal oxygenation, with rather marked haemodynamic effects.

Norepinephrine markedly increased $\mu$HbO$_2$ during sevoflurane anaesthesia with only minor changes in DO$_2$. Again, this agrees with a preferential location of sympathetic nerve terminals within the outer gut wall. Since norepinephrine even at low doses predominantly activates $\alpha$-adrenoceptors, we suggest that norepinephrine induces an intramural redistribution of blood flow towards the gut mucosa, thereby increasing mucosal $\mu$HbO$_2$. However, our findings of increased $\mu$HbO$_2$ with norepinephrine, contrasts with experiments in dogs or rats, reporting a norepinephrine-induced depression of gut mucosal oxygenation and perfusion, respectively. Fuelled by those studies, norepinephrine was traditionally regarded only as a last resort vasopressor in hypotensive patients, leading to acceptance of lower arterial pressures to avoid norepinephrine and its assumed detrimental effects on splanchnic perfusion. However, this concept is currently challenged at least for septic patients, since septic vasodilatation may counteract a critical, norepinephrine-induced, splanchnic vasoconstriction. Our findings may extend this promotion of norepinephrine even to anaesthetized subjects without grossly impaired vasoregulation. In accordance with our propofol anaesthetized animals, norepinephrine also preserved mucosal $\mu$HbO$_2$ in acutely instrumented pigs anaesthetized with ketamine, midazolam, and fentanyl. In the present study, norepinephrine probably did not induce detrimental vasoconstriction in organs, necessitating the onset of anaerobic metabolism, since norepinephrine preserved (and even decreased) lactate levels. In striking contrast, epinephrine markedly increased arterial lactate levels, a finding also supported by others. Although increasing lactate levels are generally attributed to anaerobic metabolism, epinephrine may induce hyperlactataemia in the absence of anaerobic metabolism, by increasing glycolysis and glycogenolysis. In our study, the similar course of arterial pH at stable $\text{Pa}_\text{CO}_2$ with both epinephrine and norepinephrine, together with a hyper-glycaemic trend with epinephrine, is compatible with this concept.

Supporting the crucial role of splanchnic perfusion and oxygenation in critical illness, several studies have investigated the splanchnic effects of vasoactive drugs. However, the majority of studies did not compare the effects of epinephrine and norepinephrine, and were mostly performed in settings of severely impaired vasoregulation, such as sepsis, trauma, or after cardiac surgery, limiting a comparison of those data with our findings. Moreover, both animal and patient studies are highly inconsistent, with reports of beneficial and detrimental effects of epinephrine on splanchnic perfusion and oxygenation in sepsis. In contradiction to traditional clinical concepts, but in line with our findings, norepinephrine is reported to preserve or even improve tonometrically assessed splanchnic mucosal perfusion after cardiac surgery and in septic patients, respectively.

Summarizing these contradicting studies, it was concluded that effects of vasoactive agents on tonometrically assessed mucosal perfusion are unpredictable, necessitating further studies on this topic. Since tonometry is only an indirect estimate of mucosal perfusion complicated by multiple confounders, reflection spectrophotometry as used in our study may serve as a more direct method to measure mucosal oxygenation. Furthermore, in extension to the mentioned patient groups with severely impaired vasoregulation, the present study addresses the large population of patients without severely disturbed (inflammatory) vasoregulation undergoing anaesthesia.

**Type of anaesthesia**

Epinephrine and norepinephrine are used clinically for haemodynamic support, often in sedated or anaesthetized patients. As expected, sevoflurane and propofol per se induced different systemic haemodynamics. Limited reports suggest different microcirculatory effects, for example, within the cochlea, limb, or finger. Interestingly, although epinephrine and norepinephrine induced their expected systemic haemodynamic response similarly during either sevoflurane or propofol anaesthesia, significant regional effects only occurred in animals undergoing anaesthesia with sevoflurane and neither catecholamines significantly affected $\mu$HbO$_2$ during propofol anaesthesia. Thus, propofol appears to blunt the regional response to epinephrine and norepinephrine. This finding is compatible with others also reporting significant differences in regional (cerebral) catecholamine effects, depending on the type of anaesthesia.

The measured key modulators of vascular tone did not differ between the sevoflurane and propofol groups, suggesting that other, anaesthetic specific, mechanisms cause this difference in catecholamine response, with better preservation of regional metabolic or vascular autoregulation during propofol anaesthesia. A recent study comparing the effects of sevoflurane- and propofol-based anaesthesia on autonomic function reports that both agents elicit similar central, cardiac autonomic effects, but that sevoflurane induces a greater reduction in sympathetic nervous modulation of the peripheral vasculature. This may permit a more unmodulated peripheral response to exogenous catecholamines, in turn explaining stable $\mu$HbO$_2$ in response to epinephrine and norepinephrine during propofol anaesthesia. However, these explanations remain unproven.

**Clinical implication**

Extrapolation to the clinical setting suggests that norepinephrine may preserve or increase (depending on selected...
dose, and type of anaesthesia) microcirculatory mucosal oxygenation in anaesthetized subjects without disturbed vasoregulation. These beneficial regional effects appear to be associated with markedly less alterations in systemic circulation and metabolism, compared with epinephrine. Epinephrine in contrast failed to increase microcirculatory mucosal oxygenation, despite marked systemic effects in our study. Regional mucosal effects of norepinephrine and epinephrine are not predicted by their systemic effects and regional effects of vasoactive drugs depend on the type of baseline anaesthesia, for example, volatile or i.v. Further studies are required.

**Supplementary material**

Supplementary material is available at British Journal of Anaesthesia online.

**Conflict of interest**

None declared.

**Funding**

Departmental funding.

**References**


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