Effects of Dopexamine and Positive End-Expiratory Pressure on Intestinal Blood Flow and Oxygenation*

The Perfusion Pressure Perspective

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Objective: To evaluate the net effects of the concomitant use of positive end-expiratory pressure (PEEP) and dopexamine on intestinal tissue perfusion and oxygenation during predefined artificial reductions in intestinal perfusion pressure (IPP).

Design: Prospective, self-controlled, experimental study.

Setting: University hospital research laboratory.

Subjects: Seven female pigs.

Measurements: In barbiturate-anesthetized pigs, we measured mesenteric blood flow (QMES) [by transit-time ultrasonic flowmetry], jejunal mucosal perfusion (by laser Doppler flowmetry), and tissue PO2 (by microoximetry). Based on blood sampling, we calculated the intestinal net lactate production and oxygenation.

Interventions: These measurements and calculations were performed at three predefined and controlled IPP levels, which were obtained by an adjustable clamp around the superior mesenteric artery. At each IPP level, measurements were performed prior to and during PEEP (10 cm H2O), both with and without simultaneous dopexamine infusions (at 0.5 and 1.0 μg/kg/min).

Results: Within the IPP range of 77 to 33 mm Hg, intestinal perfusion and oxygenation were maintained irrespective of whether PEEP and/or dopexamine were applied or not. At IPP < 33 mm Hg, QMES and intestinal oxygenation deteriorated, resulting in regional net lactate production. At this IPP range, tissue oxygen perfusion was entirely pressure-dependent, and even small reductions in IPP led to prominent increases in intestinal net lactate production. Dopexamine did not modify this pattern.

Conclusions: We describe maintained intestinal tissue oxygen perfusion within a wide perfusion pressure range. Within this perfusion pressure range, PEEP did not induce any adverse regional circulatory effects. Below the perfusion pressure range for effective autoregulation, intestinal tissue oxygen perfusion deteriorated, and regional ischemia occurred. In this situation, dopexamine was unable to counteract IPP-dependent decreases in intestinal tissue oxygen perfusion. The regional ischemic threshold can be defined either as an IPP of < 33 mm Hg or as an intestinal tissue PO2 of < 45 mm Hg.

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Key words: dopexamine; lactate; oxygen uptake; positive end-expiratory pressure; splanchic circulation; swine

Abbreviations: CaO2 = systemic arterial oxygen content; CO = cardiac output; CVP = central venous pressure; HR = heart rate; IPP = intestinal perfusion pressure; LDF = laser Doppler flowmetry; MAP = mean arterial pressure; PEEP = positive end-expiratory pressure; PMES = mesenteric venous pressure; PSMA = superior mesenteric arterial pressure; PU = perfusion units; QMES = mesenteric venous blood flow; VO2 = oxygen uptake; VP-DO2 = mesenteric oxygen delivery; VP-lactate flux = mesenteric lactate flux; VP-VO2 = mesenteric oxygen uptake; ZEEP = zero end-expiratory pressure

Tissue hypoxia due to insufficient blood flow or low arterial oxygen content is not uncommon in critically ill patients. Oxygen delivery, tissue oxygen transport, and oxygen uptake (VO2) of the cells serve a functional entity (ie, tissue oxygen perfusion).1 The occurrence of tissue hypoxia during systemic circulatory failure and shock is presumed in the clinical...
setting. However, regional tissue hypoxia potentially can be present in patients who seem to be ade-

quately resuscitated or are without signs of circula-
tory shock, as far as systemic hemodynamic param-
eters are concerned. Such regional hypoxia is not
easily diagnosed, and the success of interventions to
increase tissue oxygenation might be hard to evalu-
ate. The assessment of regional tissue oxygen per-
fusion in clinical practice is usually based on indirect
indicators, including traditional systemic hemody-
namic indexes, and the evaluation of mixed venous
saturation and lactate levels in the systemic circula-
tion. Direct measurements of intestinal blood flow
and oxygenation (ie, tissue oxygen perfusion) are
invasive and time-consuming, and require special
skills and instruments that are not readily available at
the bedside.

The therapeutic interventions that frequently are
used in the clinical setting to improve tissue oxygen
perfusion include positive-pressure ventilation with
positive end-expiratory pressure (PEEP) to improve
arterial oxygen content and certain vasoactive drugs
(i.e., inodilators) to increase arterial blood flow. PEEP
ventilation improves pulmonary gas exchange
abnormalities by increasing pulmonary compliance
and functional residual capacity. Besides these de-
sirable respiratory effects, PEEP also may exert
adverse systemic and regional circulatory effects,
which are related both to PEEP-induced increases in
mean intrathoracic pressure and to the concurrent
intravascular blood volume status. The net
influence of PEEP on systemic oxygen transport is
therefore dependent on the balance between cardio-
vascular and pulmonary effects. We have reported
that PEEP decreased intestinal blood flow in pro-
portion to the applied PEEP level. This pattern was
also present when PEEP was applied at artificially
reduced intestinal perfusion pressures (IPPs).

The use of certain vasoactive drugs has been
suggested as an adjunct to adequate fluid resuscita-
tion in order to reduce the depression of cardiac
output (CO) and intestinal blood flow caused by
PEEP ventilation. However, data on the actual
efficacy of different vasoactive drugs to mitigate
PEEP-induced cardiovascular effects are sparse and
divergent. Dopexamine, a synthetic catechol-
amine that acts mainly through the activation of
dopaminergic (DA-1) and β₂-adrenoceptors is
frequently used to improve systemic circulation and
oxygenation, and appears to possess particular ben-
eficial effects on splanchnic perfusion. At
present, we are only aware of a few experimental
studies using dopexamine for such purposes. Thus, Steinberg and coworkers reported that
dopexamine, when used in conjunction with PEEP,
prevented the depression of mesenteric blood flow.
Further, Scheeren and coworkers showed that
dopexamine, but not dopamine, increased gastric
mucosal oxygenation during PEEP ventilation. How-
ever, it is unknown whether these findings were
dependent on alterations in IPP, or whether it is
possible to extrapolate the findings to situations of
hypotension. Analyses of the impact of regional
perfusion pressures, as stated above, require a model
with controlled perfusion pressures. Such study de-
signs have been used previously by our research
group and by others and this design eliminates
remote influences that may counterbalance intrinsic
blood flow control. With this perspective, the
present study was designed with the aim of evaluat-
ing the effects of PEEP and dopexamine on intesti-
nal tissue perfusion and oxygen kinetics during arti-
ficially controlled reductions in IPP.

Materials and Methods

Seven female pigs, with a mean (±SEM) weight of 39.6 ±
0.7 kg, were used with the approval of the University Animal
Experiment Ethics Committee. All procedures were carried out
according to the guidelines of the National Institutes of Health
guide for the care and use of laboratory animals.

Anesthesia

Animals were fasted overnight with free access to water. After
premedication with ketamine (12 mg/kg IM), atropine (2 mg/kg),
and atropine (0.05 mg/kg), anesthesia was induced by sodium
pentobarbital (15 mg/kg, followed by IV infusion at 15 to
20 mg/kg/h), with the addition of isoflurane during surgical
procedures. No muscle relaxants were used. After tracheostomy,
mechanical ventilation with oxygen in air (25 to 30% O₂) was
performed using a volume-cycled ventilator (model 900B; Siemens;
Elena, Germany), with a minute ventilation of 7 L/min at
a frequency of 20 breaths/min. A catheter at the proximal end of
the endotracheal tube was used for the continuous monitoring of
airway pressure, and PEEP was, in line with the protocol,
adjusted according to these airway pressure measurements.
Ventilation was initially adjusted to normocapnia (ie, 5.0 to
5.6 kPa), as judged by end-tidal CO₂ levels (Artema; Artema
Medical AB; Stockholm, Sweden) and intermittent arterial blood
gas analyses (ABL-5 autoanalyzer; Radiometer; Brunsboj, Den-
mark), and was then kept constant throughout the experiment.
Oxygen saturation was analyzed by a hemoglobin oximeter, using
the animal mode for pig hemoglobin (OSM-3 hemoximeter;
Radiometer). All blood gas data were within the normal range for
the pig. Blood samples for lactate concentration were analyzed by
an automated analyzer (Sport 2300 Stat Plus; Yellow Springs
Instruments, Inc; Yellow Springs, OH). End-tidal concentrations
of O₂, CO₂, and isoflurane were measured continuously by a gas
analyzer (Artema; Artema Medical AB) with the sampling site at
the proximal end of the endotracheal tube. All animals received
IV infusions of Ringer acetate (600 mL as a bolus, followed by
infusion of 20 mL/kg/h throughout the experiment). The core
temperature was kept between 37°C and 39°C using heating blankets. Urine outflow was diverted through a cystostomy catheter and was assessed hourly. A three-lead ECG was used for monitoring the heart rate (HR).

Instrumentation and Measurements

A schematic illustration of the experimental set up is depicted in Figure 1. All intravascular catheters were inserted via cut-downs to the appropriate vessels. The carotid artery and the external jugular vein were exposed through a right-sided neck dissection. Systemic arterial pressure was monitored continuously by a fluid-filled catheter with its tip in the proximal aorta. A flow-directed, thermodilution, pulmonary artery catheter (7F Swan-Ganz catheter; Baxter Medical; Kista, Sweden) was inserted via the right external jugular vein and advanced into a distal branch of the pulmonary artery for measurements of CO and core body temperature. CO was measured by the antegrade thermodilution technique (Wetenschappelijk Technische Instituut; Eindhoven, the Netherlands) at end-expiration with 5 mL iced 0.9% solution of NaCl as the indicator. CO data are presented as the mean of three consecutive measurements obtained within 2 min, not differing >10%. For continuous measurements of central venous pressure (CVP) and for the administration of fluids and drugs, a double-lumen central venous catheter was inserted via the left external jugular vein.

A long midline laparotomy was performed with the animal in the supine position. The proximal part of the superior mesenteric artery was freed, and an adjustable clamp for graded occlusion was attached to this vessel near the aortic origin. The portal and mesenteric veins were identified in the hepatoduodenal ligament. A transit-time ultrasonic flowmetry probe was applied around the mesenteric vein (type 8SB; Transonic Systems Inc; Ithaca, NY) for the measurement of superior mesenteric venous blood flow (QMES) [Transonic T206D; Transonic Systems Inc]. In the pig, the portal vein is formed by the confluence of the mesenteric and the gastric (splenic) veins. Only a negligible part of the gastric and splenic splanchnic perfusion therefore was included in the QMES measurements. The superior mesenteric artery was directly punctured and a polyethylene catheter with an outer diameter of 0.67 mm was introduced downstream to the clamp for BP measurements (ie, superior mesenteric arterial pressure [PSMA]). A direct puncture was used for introducing a polyethylene catheter (outer diameter, 1.0 mm) for pressure measurement (ie, mesenteric venous pressure [PMES]) and blood sampling in the mesenteric vein. All pressure transducers (System DPT-6000, PVB; Codan Triplus; Kungsbacka, Sweden) were calibrated to atmospheric pressure at the level of the right atrium by a saline solution column.

Jejunal mucosal perfusion was measured using laser Doppler flowmetry (LDF) with a specially designed catheter fitted with two laser Doppler optical fibers of equal length, terminating at the tip and facing the mucosa perpendicular to the axial line of the catheter (probe 415–134; Perimed AB; Järfälla, Sweden). The data are presented from the most consistent optical fiber recording. According to this technique, blood flow is expressed in arbitrary perfusion units (PU) and is described as being equivalent to the number of RBCs contained in the volume of blood through which the laser light is passing and at the speed at which these cells are moving. The catheter was inserted intraluminally through a small antemesenteric incision 2 m proximal to the iliocecal valve. The intestinal incision then was closed, and the laser Doppler catheter was secured by an additional suture. Each fiber had a core diameter of 150 μm and a fiber separation of 250 μm. The wavelength of the emitted laser light was 780 nm, and the Doppler shift frequency was 20 kHz. The probe was connected to a base unit (PeriFlux 4001 Master; Perimed AB). Calibration was performed according to the manufacturer at 0 PU on a plastic disk at optical zero and at 250 PU using motility standard provided by the manufacturer. The LDF technique has been thoroughly evaluated by several investigators at well-known circulatory physiology laboratories.

Tissue PO₂ in the jejunal wall, 2 m proximal to the iliocecal valve, was measured by a tissue probe (Licox CC 1.2; Gesellschaft
Für Medizinische Sondentechnik; Kiel-Mielkendorf, Germany), was inserted from the serosal side into the intestinal wall, and was connected to a tissue oxygen pressure monitor (Licox CMP; Gesellschaft für Medizinische Sondentechnik). A tissue temperature probe (Licox C 8.1; Gesellschaft für Medizinische Sondentechnik) that was connected to the tissue oxygen pressure monitor measured the temperature in the jejunal wall. Urine outflow was diverted through a cystostomy catheter and was assessed hourly. A three-lead ECG was used for the monitoring of HR.

All BP, ECG, blood flow, LDF, and tissue $P_{O_2}$ data were recorded continuously using a 16-channel recording system (model TA-5000; Gould Inc; Eastlake, OH), as well as a computer-based, multichannel signal acquisition and analysis system (Acknowledge III; Biopac Systems Inc; Santa Barbara, CA). The software (Acknowledge; Biopac Systems Inc), using a sampling frequency of 50 Hz, continuously collected all signals. The data were extracted from this system as mean values, which were established during registration sequences of 30 s duration.

Experimental Protocol

The study protocol is schematically depicted in Figure 2. Each data collection point included measurements of mean arterial pressure (MAP), HR, CVP, CO, PMES, PSMA, QMES, jejunal mucosal perfusion, and tissue $P_{O_2}$. Blood samples for blood gas analyses, oxygen saturation measurements, and lactate concentration analyses were drawn from the aortic and mesenteric venous catheters in conjunction with the hemodynamic recordings.

After the instrumentation was completed, the isoflurane supply was discontinued. A stabilization period of 1 h during basal sodium pentobarbital anesthesia was allowed to elapse before the first data collection point. The protocol included the following three subsequent stages: (1) "freely variable PSMA"—This refers to the first part of the study, when the adjustable superior mesenteric arterial clamp was entirely open and the prevailing systemic arterial pressure was allowed to serve unhindered as the intestinal arterial driving force; (2) "PSMA of 50 mm Hg"—At this stage, the superior mesenteric arterial inflow pressure was kept constant at a predefined level of 50 mm Hg (corresponding to an IPP of 33 to 42 mm Hg) by adjustments of the clamp around the superior mesenteric artery. The intestinal arterial inflow pressure also was maintained during the ongoing dopexamine infusions. Similarly, inflow pressure was kept at 50 mm Hg immediately before PEEP was applied. Subsequent changes in systemic arterial pressure during PEEP were, however, not met by further adjustments of the superior mesenteric arterial clamp; (3) "PSMA of 30 mm Hg"—Superior mesenteric arterial inflow pressure was kept constant at a predefined level of 30 mm Hg (corresponding to an IPP of 17 to 22 mm Hg). In all other aspects, this stage was the same as the sequence using the PSMA of 50 mm Hg.

The measurements were first done during zero end-expiratory pressure (ZEEP) [ie, the control measurements at each perfusion pressure level] and then, after a 10-min steady-state period, with PEEP at 10 cm H$_2$O. Thereafter, PEEP was discontinued and replaced by ZEEP. After a 5-min recovery period during ZEEP, dopexamine was administered at a rate of 0.5 µg/kg/min, and data collection was performed after a stabilization period of 15 min (still with ZEEP). A PEEP of 10 cm H$_2$O was then reinstalled, and measurements were repeated at the end of a 10-min steady-state period. Finally, PEEP was discontinued for 5 min before the rate of dopexamine infusion was increased to 1.0 µg/kg/min, and a similar ZEEP-PEEP measuring sequence was performed at this higher dopexamine dose. The duration of

![Figure 2](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21997/ on 06/17/2017)
the entire measurement sequence at each perfusion pressure level was 125 min, including a 45-min recovery period without controlled perfusion pressure or dopexamine infusion at ZEEP. The animals were killed during deepened sodium pentobarbital anesthesia with an IV bolus of potassium chloride. The correct positions of all catheters were verified, and flow probes were checked in situ for zero blood flow recordings.

Calculations

• Systemic vascular resistance = (MAP – CVP) × CO.
• Tissue PIP = PSMA – PMES.
• Systemic arterial oxygen content (CaO₂) = hemoglobin concentration (g/L) × arterial oxygen saturation × 1.39. Superior mesenteric venous oxygen content = hemoglobin (g/L) × mesenteric venous oxygen saturation × 1.39. The oxygen portion physically dissolved in blood was also taken into account.
• Mesenteric oxygen delivery (vp-DO₂) = (CaO₂) × QMES.
• Mesenteric VO₂ (vp-VO₂) = CaO₂ – superior mesenteric venous oxygen content × QMES.
• Mesenteric tissue oxygen extraction = vp-VO₂/vp-DO₂ × 100.
• Mesenteric lactate fluxes (vp-lactate flux) = mesenteric venous-arterial lactate concentration difference × QMES.

Statistical Analysis

All values are given as mean ± SEM (n = 7). Data were analyzed using repeated-measures analyses of variance. When significant main effects were found, simple contrasts were made using the Student two-tailed t test for paired data. A p value of < 0.05 was considered to be significant. The statistical analysis was performed with a statistical software package (SPSS, version 10.0; SPSS Inc; Chicago, IL).

RESULTS

Systemic Effects of Dopexamine and PEEP

For background information, systemic hemodynamic parameters are presented at ZEEP and PEEP, both with and without dopexamine (Table 1). These parameters are presented to understand better the systemic hemodynamic alterations that were induced by PEEP and/or dopexamine. However, we would like to emphasize that the alterations in systemic hemodynamics are of less importance for the interpretation of our results, since we used a controlled perfusion pressure model.

Regional Effects of Dopexamine and PEEP

At each applied IPP level, the situation at ZEEP was defined as the control and was used as the reference point.

Effects on IPP

At the stage of freely variable PSMA (see “Materials and Methods” section), the mean IPP was 77 ± 4 mm Hg at ZEEP (control point) and was significantly decreased by PEEP to 61 ± 4 mm Hg. Dopexamine dose infused at a rate of 0.5 μg/kg/min induced no significant change in IPP, while the dose infused at 1.0 μg/kg/min decreased the IPP to 53 ± 3 mm Hg. In comparison with the control, the concomitant use of dopexamine and PEEP decreased the IPP even further. Thus, the lowest IPP level (46 ± 3 mm Hg) was observed during PEEP and dopexamine infusion at 1.0 μg/kg/min (Fig 3).

At the stages PSMA of 50 mm Hg and PSMA of 30 mm Hg (see “Materials and Methods” section), the PEEP per se did not influence IPP significantly, while the combined use of PEEP and dopexamine induced a significant decrease in IPP at both dopexamine doses (Fig 3).

Effects on Intestinal Blood Flow

Within the IPP range 77 to 33 mm Hg (mean values, present during freely variable PSMA and PSMA of 50 mm Hg), there were, despite the wide IPP pressure range, only two significant alterations in QMES (compared to the initial control value at a mean IPP of 77 mm Hg). Thus, decreases were observed at the freely variable PSMA during PEEP alone (by about 215 mL/min) and during PEEP and dopexamine, 0.5 μg/kg/min (by about 165 mL/min). At an IPP < 33 mm Hg, QMES was, for all measuring points besides during dopexamine infusion at 1.0 μg/kg/min, significantly decreased compared to the initial control value at a mean IPP of 77 mm Hg.

| Table 1—Hemodynamic Effects of Dopexamine Infusion During ZEEP and PEEP at 10 cm H₂O at a Freely Variable PSMA* |
|-----------------|-----------------|-----------------|
| Variables       | Without Dopexamine | Dopexamine Infusion |
|                 | 0.5 μg/kg/min    | 1.0 μg/kg/min    |
| MAP, mm Hg      |                  |                  |
| ZEEP            | 87 ± 4           | 78 ± 5           | 66 ± 2†           |
| PEEP at 10 cm H₂O | 72 ± 4†          | 63 ± 4†          | 59 ± 2†           |
| HR, beats/min   |                  |                  |
| ZEEP            | 110 ± 6          | 116 ± 4          | 134 ± 5†          |
| PEEP at 10 cm H₂O | 102 ± 5†         | 123 ± 3†         | 141 ± 6†          |
| CVP, mm Hg      |                  |                  |
| ZEEP            | 5 ± 1            | 5 ± 1            | 5 ± 1             |
| PEEP at 10 cm H₂O | 8 ± 1†           | 8 ± 1†           | 8 ± 1†            |
| CO, L/min       |                  |                  |
| ZEEP            | 7.5 ± 0.6        | 8.4 ± 0.61       | 9.7 ± 0.5†        |
| PEEP at 10 cm H₂O | 5.5 ± 0.41‡      | 6.8 ± 0.41†      | 7.8 ± 0.41†       |
| SVR, mm Hg/L    |                  |                  |
| ZEEP            | 11.3 ± 0.7       | 9.0 ± 0.91       | 6.4 ± 0.2†        |
| PEEP at 10 cm H₂O | 11.9 ± 0.7‡      | 8.2 ± 0.51       | 6.7 ± 0.3†        |

*Values given as mean ± SEM; n = 7. SVR = systemic vascular resistance.
†Significant differences (p < 0.05) between measurements before vs during dopexamine infusion.
‡Significant differences between ZEEP and PEEP at 10 cm H₂O at respective dopexamine doses (ie, 0, 0.5, and 1.0 μg/kg/min).
Jejunal mucosal perfusion was maintained at IPP levels of 33 mm Hg but showed a pattern of gradual decrease that paralleled the reduction in IPP below this perfusion pressure level. This response was not influenced significantly by the dopexamine or PEEP interventions (Fig 4).

**Effects on Intestinal Oxygenation and Metabolism**

The vp-DO₂ level reflected the above mentioned QMES changes, with significant decreases observed only at freely variable PSMA during PEEP alone (by about 25 mL/min) and during the combined use of PEEP and dopexamine, 0.5 µg/kg/min (by about 19 mL/min). The overall pattern was thus an essentially maintained vp-DO₂ at IPP levels of > 33 mm Hg.

However, at an IPP < 33 mm Hg, the vp-DO₂ decreased significantly (Fig 5), while oxygen extraction increased (Fig 5). The vp-VO₂ was maintained as long as the IPP was > 33 mg Hg (Fig 5). Once the IPP decreased to < 33 mg Hg, the significant decrease in vp-DO₂ was associated with a gradually lowered vp-VO₂.

Intestinal tissue PO₂ decreased gradually in proportion to reductions in IPP (Fig 6). Furthermore, mesenteric lactate production occurred at an IPP of < 33 mm Hg (Fig 6). At this low IPP level, even minimal additional reductions in IPP (mean decreases, < 5 mm Hg) were associated with significant increases in lactate production (Fig 7). The relationship between intestinal tissue PO₂ and mesenteric lactate production (Fig 6) illustrates that the ischemic threshold in this study can be defined as either an approximate IPP of < 35 mm Hg or an approximate intestinal tissue PO₂ of < 45 mm Hg.

**Stability of the Model**

In this study, the stability of the intestinal preparation was examined repeatedly by control measurements. Such control measurements were performed prior to PEEP and at the end of a 45-min recovery period (with the arterial clamp fully released) following a data collection sequence at a freely variable PSMA and at a PSMA of 50 mm Hg. We observed no significant changes over time in intestinal PO₂ or in intestinal lactate flux (i.e., there was no net lactate production) among the control stages throughout the study protocol.
FIGURE 5. The relationship among vp-DO₂ and IPP (top), mesenteric oxygen extraction (vp-O₂ EXTR) and IPP (middle), and vp-Vo₂ and IPP (bottom). See the legend for Figure 2 for other abbreviations not used in the text. Values given as the mean ± SEM. For statistical comparisons, see text.

FIGURE 6. The relationship among intestinal tissue Po₂ (Po₂ TISSUE) and IPP (top), between vp-lactate flux and intestinal Po₂ TISSUE (middle), and between vp-lactate flux and IPP (bottom). See the legend for Figure 2 for other abbreviations not used in the text. Values given as the mean ± SEM. For statistical comparisons, see text.
The main finding of this study was that the prevailing perfusion pressure is the main determinant for intestinal tissue oxygen perfusion during the application of PEEP. Within the perfusion pressure range of 77 to 33 mm Hg, intestinal tissue oxygen perfusion was maintained despite the application of PEEP. In this situation, the regional vascular effects of dopexamine were minimal. Expressed differently, the need for pharmacologic vasoactive support of the intestinal circulation was nonexistent, probably due to the powerful autoregulation of this vascular bed. At IPPs of < 33 mm Hg, intestinal net lactate production was observed already at ZEEP, and even minimal reductions in IPP, as induced by PEEP, were associated with increased intestinal net lactate production. In this situation, dopexamine was unable to counteract the perfusion pressure-related oxygen debt. On the contrary, dopexamine was associated with increased regional net lactate production. Our data suggest that the regional ischemic threshold can be defined either as an approximate IPP of < 35 mm Hg or an approximate intestinal tissue Po2 of < 45 mm Hg.

Despite the wide IPP pressure range (i.e., 77 to 33 mm Hg) at freely variable PSMA and PSMA of 50 mm Hg, there were only two significant decreases in QMES, which indicates that autoregulation was active within this IPP range. This important local control of the blood supply probably was achieved by an interaction between myogenic and metabolic components. According to the myogenic theory, a decrease in perfusion pressure reduces transmural pressure and vascular wall tension, and consequently elicits a decreased arteriolar tone (i.e., vasodilation). The metabolic theory is based on the assumption that tissue metabolism and arteriolar smooth muscle constitute a local control system that provides the necessary coupling between blood flow and tissue nutritional requirements. According to this theory, decreased IPP induces arteriolar and precapillary sphincter relaxation to maintain blood flow to meet the need of the tissue for oxygen and nutrient delivery. Data from the literature indicate that increased oxygen extraction (i.e., capillary recruitment) is of greater quantitative significance than the myogenic aspect of blood flow autoregulation at severely depressed IPP levels. In line with this metabolic theory of autoregulation, we observed no significant alterations in VO₂, indicating adequate intestinal tissue oxygen perfusion at a PSMA of 50 mm Hg, compared to a freely variable PSMA.

The relationships among oxygen delivery, oxygen extraction, and VO₂ have been described in terms of blood flow dependence and independence. Normally, tissue VO₂ can be maintained during limitations in oxygen delivery due to an increased oxygen extraction ratio (i.e., flow-independent VO₂). However, if oxygen delivery is reduced below a critical level, VO₂ begins to decrease due to critical oxygen extraction, and VO₂ thus becomes flow-dependent. At this point, capillary density is maximized and local regulatory mechanisms cannot further increase oxygen extraction. In this study, at a PSMA of 50 mm Hg, intestinal tissue Po2

**Figure 7.** Changes in vp-lactate flux (top) and changes in IPP (bottom) at a PSMA of 30 mm Hg under different conditions. # = simple contrasts in comparison with the control at a PSMA of 30 mm Hg. See the legend for Figure 2 for other abbreviations not used in the text. Values given as the mean ± SEM, and p < 0.05 was considered to be significant.
was decreased but was still sufficient to maintain adequate intestinal oxygenation, indicating the presence of flow-independent VO₂.

With a PSMA of 30 mm Hg, a different pattern was observed. At this IPP level, which is below the perfusion pressure range for effective autoregulation, a significant drop in mesenteric blood flow was observed, and consequently the VO₂ decreased. The presence of mesenteric tissue net lactate production at this IPP level illustrates that oxygen extraction had reached a critical level of 45%, and, accordingly, VO₂ became flow-dependent. This oxygen extraction ratio could be compared with a mean oxygen extraction ratio of 33 ± 5% during normal conditions in the pig and an oxygen extraction ratio of 64% 30 min after hemorrhage to a MAP of 40 mm Hg. Furthermore, Heino and coworkers have reported, in a model of gradual splanchnic ischemia in the pig, increased splanchnic oxygen extraction from a mean 44 ± 3% at baseline to 60 ± 3% obtained after 30 min of total occlusion of superior mesenteric arterial blood flow. Our observed critical oxygen extraction ratio of 45% is lower than the above-described maximal oxygen extraction ratios, suggesting that maximal extraction may not have been reached in our model. However, our observation of significant net lactate production across the preportal vascular bed and a prompt decrease in intestinal tissue PO₂ suggests that oxygen extraction tended to reach maximal levels.

In addition to the above-described relationship between IPP and intestinal net lactate production, our measurements of intestinal tissue PO₂ allow us to further analyze the threshold, below which intestinal net lactate production occurs, that is indicative of regional ischemia. This threshold limit for intestinal tissue PO₂ has been reported previously to be 1.9 mm Hg in a study in which intestinal tissue PO₂ was correlated to histologically observed intestinal damage. We, on the other hand, have reported an intestinal tissue PO₂ limit of 45 mm Hg, which intestinal net lactate production occurs. When comparing our results with data obtained by Sheridan and coworkers, it must be emphasized that we used different species and also had different end points. The main focus of our study was the evaluation of the effects of alterations in IPP on intestinal tissue oxygen perfusion, while Sheridan et al focused on the histologic examination of the rat bowel. As illustrated in Figure 7, we have deepened our analyses of the relationship between IPP, below the threshold of 33 mm Hg, and intestinal tissue net lactate production. Below this critical limit, our data indicate that only minor decreases in IPP, such as 2 to 5 mm Hg, induced significant increases in net lactate production, irrespective of whether PEEP and/or dopexamine were used. Thus, the perfusion pressure is the main determinant for intestinal net lactate production.

The level of PEEP that was chosen in this study (10 cm H₂O) is in accordance with common clinical ICU practice. Several mechanisms have been suggested to explain the cardiovascular effects of PEEP. Thus, PEEP exerts direct effects on the heart, by reducing right and left ventricular function. Furthermore, PEEP increases intrathoracic pressure, thereby reducing venous return and CO. This increase in intrathoracic pressure results in the unloading of cardiopulmonary volume receptors, which usually elicits reflex sympathetic activation, increased norepinephrine release, and regional vasoconstriction. However, increased plasma norepinephrine levels, as well as unchanged systemic and regional norepinephrine levels, have been reported during PEEP ventilation.

Based on our observations, one could theoretically speculate whether vasoconstrictor therapy would be beneficial in a situation of severe intestinal hypotension similar to that produced in this study. If vasoconstrictor therapy does not increase perfusion pressure, and assuming that the vasocostriction also encompasses the intestinal vascular bed, it seems probable that a deleterious reduction in intestinal tissue oxygen perfusion would occur. On the other hand, if such vasoconstrictor therapy really increases IPP, our data indicated that the intestinal vascular bed would benefit from such therapy. However, one must bear in mind that the net effects of vasoconstrictor therapy on intestinal tissue oxygen perfusion are not easily deduced from systemic BP measurements. In this study, we also measured jejunal mucosal perfusion. In situations of reduced intestinal blood flow, it has been suggested that a redistribution of blood flow occurs, preserving intestinal mucosal perfusion better than serosal perfusion. It is noteworthy that our data show a somewhat different pattern, with less well-maintained jejunal mucosal perfusion. The mechanisms behind this discrepancy cannot be elucidated from the present results, meriting further investigation.

To conclude, we have described the maintenance of intestinal tissue oxygen perfusion within a wide perfusion pressure range. Within this perfusion pressure range, PEEP did not induce any adverse regional circulatory effects. At a PSMA of 30 mm Hg, which is below the perfusion pressure range for effective autoregulation, intestinal tissue oxygen perfusion deteriorated and regional ischemia occurred. In this situation, dopexamine infusion was unable to counteract perfusion pressure-dependent decreases in intestinal tissue oxygen perfusion. The regional ischemic threshold can
be defined either as an IPP of < 33 mm Hg or an intestinal tissue PO2 of < 45 mm Hg.

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