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The impact of endotoxin on jejunal tissue oxygenation

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Abstract

Objective: We examined the effects of systemic ETX on jejunal mucoal microcirculatory parameters in anesthetized pigs.

Methods: Jejunal mucosal tissue PO_2 was measured employing Clark-type surface oxygen electrodes. Oxygen saturation of jejunal microvascular hemoglobin was determined by tissue reflectance spectrophotometry. Jejunal microcirculatory blood flow was assessed by laser Doppler flowmetry. Microvascular conductance and rhythmical oscillation of the tissue PO_2 were calculated. Systemic hemodynamic variables, mesenteric venous and systemic acid base and blood gas variables, and lactate measurements were recorded. Measurements were taken at BL and after *Escherichia coli* LPS administration in 20 minutes intervals for 110 minutes.

Results: ETX infusion led to a significant ($P<.05$) decrease of PO_2muc (from 24±4 to 8±4 mm Hg) and microvascular HbO_2 (from 41±13 to 24±12%). Microcirculatory conductivity increased in ETX animals, microvascular blood flow remained unchanged (PU; from 228±45 to 232±58). ETX induced an increase in oscillation frequency of mucosal tissue oxygenation.

Conclusions: Endotoxinemia resulted in a significant depression of mucosal tissue oxygenation despite a constant microcirculatory blood flow. This impairment of tissue oxygenation resulted in an increase in the vasomotion pattern in a futile attempt to counteract the undersupply of oxygen to the jejunal tissue.

KEYWORDS

clark-type surface oxygen electrodes, microcirculatory flowmotion, mucosal oxygen tension, sepsis, vasomotion

1 | INTRODUCTION

In sepsis, microcirculatory dysfunction may play an important role in the pathophysiology of organ failure and consequently in patient outcome.[1] Especially in the intestinum, systemic inflammation alters intestinal microcirculatory function, leading to impairment of the mucosal and submucosal layer initiating a systemic inflammatory response.[2]

The impact of ETX on the microcirculation has provided interesting results in recent years. ETX reduces intestinal microvascular blood flow and in particular mucosal villus blood flow.[3,4] The density of perfused capillaries in the small intestinal villi seems to be reduced after ETX administration.[5] Furthermore, recent investigations demonstrated a poor correlation between systemic hemodynamic and microcirculatory parameters, rendering a vasopressor therapy for tissue resuscitation nearly senseless.[6]

Despite new investigations and in the light of the present theories, the exact pathophysiological answers of the microcirculation during acute systemic ETX emia are not yet given.[7] Basically the question regarding mucosal oxygenation in view of reduced microvascular blood flow, conductivity (reciprocal of flow resistance) of the microcirculation, and the phenomenon of vasomotion are still matter of investigations.

Abbreviations: ART, arterial; BL, baseline; CON, control; ETX, endotoxin; HbO_2, hemoglobin oxygen saturation; L mc, microvascular conductivity; LPS, lipopolysaccharide; PO_2muc, mucosal tissue oxygen tension; PU, perfusion units.

Vasomotion and flow motion have been observed and reported in animal and human microvascular studies with various techniques.[8] Vasomotion is characterized by two distinct frequency ranges: namely, alpha- or fast waves with a frequency of 10-20 cycles/min and beta- or slow waves with a frequency of 1-3 cycles/min.[9,10] It has been shown that induction of fast-wave vasomotion in terminal arterioles is associated with decreased perfusion pressure to the tissue below a specific local Art blood pressure and flow threshold, which is known to be the lower end of autoregulation in the microcirculation.[10] Furthermore, investigations in humans demonstrated a correlation between the oscillation frequencies and the outcome in patients suffering from multiple organ dysfunction.[11,12]

To address these questions, we conducted a prospective, randomized, experimental animal study. In an anesthetized pig model we measured direct effects of systemic ETX on microvascular blood flow, intestinal tissue oxygen supply, and, in particular, the jejunal PO_2muc. In contrast to other studies we investigated the oxygenation of the pathophysiologically and clinically most important cells of the gastrointestinal tract, the intestinal mucosal cells. Furthermore, L mc and the rhythmic oscillation of the oxygenation in the mucosa were investigated. The alternative hypothesis was that ETX impairs microcirculatory parameters and especially mucosal tissue oxygenation as a primary question in the jejunal mucosa in an anesthetized pig model.

2 | MATERIALS AND METHODS

2.1 | Anesthesia and animal instrumentation

The experimental protocol was approved by the Federal Ministry of Science and Research in Vienna, Austria. Animals were managed in accordance with the American Physiological Society institutional guidelines and the Position of the American Heart Association on Research Animal Use, as adopted on November 11, 1984. Anesthesia was used in all surgical interventions, all unnecessary suffering was avoided, and research was terminated if unnecessary pain or distress resulted. Our animal facilities meet the standards of the American Association for Accreditation of Laboratory Animal Care.

Nineteen domestic pigs (35-40 kg) of either sex were fasted overnight, but had free access to water. The animals were anesthetized with ketamine HCL (20 mg/kg) i.m. Tracheas of the animals were intubated and lungs were mechanically ventilated with a positive endexpiratory pressure of 5 mm Hg. Tidal volume and respiratory frequency were adjusted to maintain an Art PCO_2 of 35-45 mm Hg at BL; fractional inspiratory oxygen concentration was primary set at 0.3, and further adjusted to achieve an Art oxygen tension between 100 and 150 mm Hg. Anesthesia was maintained using a continuous infusion of midazolam (0.5 mg/kg/h) and fentanyl (10 μg/kg/h). If hemodynamic variables or clinical evaluation indicated an inadequate depth of anesthesia, additional bolus of midazolam (5 mg) and fentanyl (100 μg) was administered. Ringer's lactate and modified gelatine (MW: 22.600) were administered to keep central venous pressure between 10 and 12 mm Hg throughout the experiment, according to the Fank Starling curve measured with the pulmonary artery catheter. Following preparation of the right carotid artery and the internal jugular vein, an Art line and a 7.5-French pulmonary artery catheter (Baxter, Irvine, CA, USA) were inserted. Midline laparotomy was then performed, and a 16-gauge catheter was placed in the superior mesenteric vein for intermittent blood sampling. To expose part of the mucosa for tissue oxygenation and laser Doppler flow measurements, a 20-cm antimesenteric enterotomy was performed in the mid-jejunum. The boundary of the mucosa was sutured on a cork plate with an oval opening. The intestine was reintroduced into the abdominal cavity with the exception of the exposed mucosa. The temperature of the preparation was maintained at 38.5°C (normal porcine temperature), by covering the preparation with a plastic box, including a temperature sensor and a servo controlled heated water bath.

2.2 | Hemodynamic and blood gas measurements

Art, pulmonary artery, and central venous pressure were measured using three Statham P10EZ pressure transducers (Spectramed-Statham, Bilthoven, Netherlands). Cardiac output was determined in triplicate by the thermodilution method. Heart rate, blood pressure, and core temperature were continuously recorded. Zero reference for all pressures was the mid-chest position. Art, central venous, as well as mesenteric venous blood gases and acid-base status were determined using an automatic blood gas analyzer (AVL 995, AVL, Graz, Austria). HbO_2 was measured with a hemo-oximeter (Cooximeter, AVL). Hemoglobin concentration was assessed using the cyanmethemoglobin method. Art and mesenteric venous lactate was measured with a lactate analyzer based on reflectance photometry (Accusport, Boehringer, Mannheim, Germany).

2.3 | Measurements of jejunal mucosal tissue oxygenation and microvascular blood flow

PO_2muc was measured by two Clark-type multiwire surface electrodes (Eschweiler, Kiel, Germany). These electrodes were calibrated using pure nitrogen and room air in a water bath warmed to 38.5°C. One electrode consists of eight platinum wires, each of which has a diameter of 15 μm, representing an individual measuring point and one Ag-AgCl reference electrode. An Erlangen microlight guide spectrophotometer (EMPHO II, BGT, Überlingen, Germany) was used for determination of jejunal microvascular HbO_2. The measuring principle is based on the use of one illuminating, and six detecting, microlight guides (each 250 μm in diameter), and a rapidly rotating band-pass interference filter disk for the generation of monochromatic light in 2-nm steps, within the spectral range of 502-628 nm, representing 64 different wavelengths. Jejunal microvascular blood flow was assessed by laser Doppler velocimetry (LDF; Periflux 4001; Perimed, Järfella, Sweden). Laser Doppler measurements are based on the principle that light, scattered by moving red blood cells, undergoes a frequency shift that is proportional to the velocity of red blood cells. The Periflux 4001 uses laser light with a wavelength of 770-790 nm. A fiber-optic guidewire (PF407; Perimed) which conducts laser light to the tissue and carries backscattered light to a photodetector was placed on the mucosal surface. Jejunal microvascular blood flow was recorded in arbitrary PU.

Calibration of the laser Doppler flowmeter device was performed by using the manufacturer's original calibration kit (Perimed). Setting of zero value was conducted on the surface of a white compact synthetic material (PU=0). The second value of the calibration curve (PU=250) was derived by measurement in a motility standard fluid provided by the manufacturer (Perimed). The fraction of the scattered light that is Doppler shifted in this solution is exactly 250±5 PU. Each sensor was held in place by adhesion force, generated by a surrounding thin transparent silicon rubber patch, approximately 2 cm in diameter that was connected to the sensor via a small polyvinyl chloride cap.

2.4 | Experimental protocol

Following the initial part of surgery and a 90 minutes resting period, BL measurements of hemodynamics, blood gases, and intestinal tissue O_2 supply were performed (time (t)=0 minutes). Animals were randomly assigned to one of two experimental goups: *group con* (n=8) served as CON; *group etx* (n=11) received a bolus of 300 µg of *Escherichia coli* LPS (62 325 LPS from *E. coli* Serotype 011:B4; Fluca, Buchs, Switzerland) beginning after BL measurements followed by a continuous infusion of 0.2 µg/kg/min ETX throughout the experimental period. Further five measurements were made in 20-minutes intervals in both groups (*t*=30, 50, 70, 90, and 110 minutes). At the end of the experiments, deeply anaesthetized animals were euthanized by central venous bolus injection of 40 mmol potassium chloride.

2.5 | Oscillation frequency analysis

Fast Fourier transform analysis was performed for every single time series of PO_2muc (100 seconds) to obtain a quantitative description of main oscillatory frequency components (Figure 1). The frequency resolution of the fast Fourier transformation was 0.5 cycles per minute, which corresponds to 0.0083 Hz. After computing a power spectrum for each time point, median values were averaged to reflect the final power spectrum. Frequencies corresponding to heart rate or mechanical ventilation were discarded. Mean values of oscillation were used for statistical comparisons.

2.6 | Statistical analysis

Systemic oxygen delivery, oxygen consumption, and systemic and mesenteric oxygen extraction ratio were calculated according to standard formulas. PO_2muc and HbO_2 were recorded for periods of at least 100 seconds. Mean values of these variables were used for statistical comparison. Laser Doppler flowmetry measurements were taken for a period of 300 seconds. Mean values of the recorded PU were divided by mean Art blood pressure minus central venous pressure, giving the relative L mc in arbitrary units per mm Hg.[13]

Comparison between BL values was made using unpaired *t* test. Overall effects within and between groups were evaluated by repeated measurements of variance (ANOVA). In case of significant differences, further comparisons were made with paired *t* test (within group to BL) and unpaired *t* tests (between groups at individual time points). Global hypothesis was tested two-sided on a 0.05 significance level. The Bonferroni test was used for correction of multiple comparisons. Correlation coefficients were tested with Pearson's correlation if Gaussian distributed, and Spearman's correlation if non-Gaussian distribution was achieved. Data are presented as mean values±SD, if not indicated otherwise.

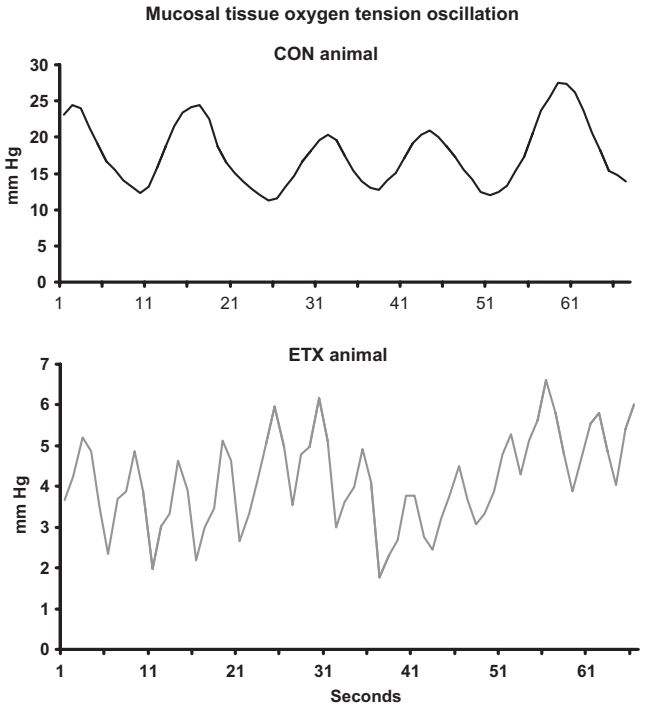

FIGURE 1 Examples of tissue oxygen tension oscillation in jejunal mucosa in a CON animal and an animal receiving ETX. Note the increased frequency of oscillation after administration of ETX

3 | RESULTS

A total of 19 pigs were used for statistical analysis (CON animals, n=8; ETX animals, n=11). Microcirculatory data of one animal in the ETX group were not included in statistical analysis because of failure in data recording. There was no statistically significant difference in BL variables between groups (Tables 1 and 2; Figures 2 and 3). ETX animals required significantly more crystalloid fluid (3740±235 mL vs 2833±236 mL; *P*=.004) to keep central venous pressure and pulmonary capillary occlusion pressure at BL levels compared to CON animals. No difference in colloidal volume administration could be documented (2820±479 mL vs 2667±236 mL; *P*=.670).

3.1 | Systemic variables during endotoxinemia

The initial response to infusion of *E. coli* LPS was characterized by an increase in mean pulmonary artery blood pressure (Figure 2). Furthermore, ETX infusion led to a decrease in mean Art pressure and increase in heart rate when compared to CON animals (Figure 2). Art

TABLE 1 Arterial and intestinal venous blood gases and pH in CON and ETX Animals

	0 min BL	30 min M1	50 min M2	70 min M3	90 min M4	110 min M5	Time effect (*P*)	Time-group interaction (*P*)
Art pH								
CON	7.44±0.06	7.43±0.04	7.45±0.04	7.44±0.03	7.45±0.04	7.45±0.04	.019	.006
ETX	7.45±0.03	7.37±0.05[a,b]	7.36±0.06[a,b]	7.37±0.05[a,b]	7.36±0.06[a,b]	7.36±0.06[a,b]		
Art PO_2 (mm Hg)								
CON	123±14	124±7	122±11	121±7	122±5	120±6	.008	.039
ETX	127±23	113±21	105±17	100±17[a,b]	100±17[a,b]	95±16[a,b]		
Art PCO_2 (mm Hg)								
CON	38±3	39±2	37±1	38±2	38±1	37±3	.590	.305
ETX	39±2	40±4	41±3	42±3	41±4	42±6		
Int ven pH								
CON	7.38±0.06	7.39±0.06	7.40±0.05	7.39±0.04	7.41±0.03	7.40±0.04	.013	<.001
ETX	7.41±0.04	7.33±0.04[a,b]	7.32±0.05[a,b]	7.33±0.05[a,b]	7.33±0.06[a,b]	7.31±0.06[a,b]		
Int ven PO_2 (mm Hg)								
CON	49±3	52±4	51±4	51±5	50±3	53±4	.485	.228
ETX	46±5	46±4	44±8	44±7	42±6	42±8		
Int ven PCO_2 (mm Hg mm Hg)								
CON	44±3	45±3	44±2	44±1	43±3	43±3	.295	.085
ETX	46±5	49±4	51±4	51±4	50±6	52±10		

M, measurement; art pH, arterial pH; art PO_2, arterial oxygen tension; art PCO_2, arterial carbon dioxide tension; int ven pH, intestinal venous pH; int ven PO_2, intestinal venous oxygen tension; int ven PCO_2, intestinal venous carbon dioxide tension. Values are mean±SD.

[a]Significant Bonferroni corrected post hoc BL comparison (*P*<.0031; significant vs BL).

[b]Significant Bonferroni corrected post hoc group comparison (*P*<.0031; significant vs CON).

pH decreased and Art lactate levels increased despite a slight increase in systemic oxygen delivery without a significant change in systemic oxygen consumption index in ETX animals (Tables 1 and 2; Figure 2). Art PO_2 decreased significantly more over time in ETX animals than in CON animals, despite adjustment of inspiratory oxygen fration (Table 1).

3.2 | Intestinal variables during endotoxinemia

Mesenteric venous pH decreased and mesenteric venous lactate concentration increased without an apparent increase in splanchnic lactate production in reference to Art lactate levels (Tables 1 and 2). No alterations in intestinal oxygen extraction ratio could be observed (Table 2).

3.3 | Jejunal microcirculatory alterations during endotoxinemia

Jejunal microvascular HbO_2 and mucosal tissue oxygenation decreased significantly after ETX administration (Figure 3). Although microcirculatory conductivity increased in ETX animals, microvascular blood flow remained unchanged throughout the study period (Table 2 and Figure 4). LPS infusion induced an increase in oscillation frequency of mucosal tissue oxygenation, which is nearly linear correlated with PO_2muc (Table 2 and Figure 5).

4 | DISCUSSION

In this porcine animal model, continuous intravenous *E. coli* LPS infusion resulted in pathologic alterations of the jejunal microcirculation. Despite an increase in microcirculatory conductivity and a consistent microcirculatory blood flow, endotoxinemia resulted in a significant impairment in PO_2muc and jejunal HbO_2. This deterioration was associated with a nearby linear increase in periodic oscillation frequency generated by microvascular vasomotion.

Administration of *E. coli* LPS led to pulmonary hypertension, a progressive increase in heart rate paralleled by a decrease in mean Art pressure, as expected and demonstrated in previous studies.[14-16] Despite an increase in the delivery of systemic oxygen, neither systemic nor intestinal oxygen extraction ratio increased in this early endotoxinemia model. Both systemic and intestinal lactate levels increased after exposition with ETX indicating the beginning of tissue hypoxia. The present animal model mirrors the pathophysiology of an acute systemic inflammatory process.

On the intestinal level this tissue hypoxia was evident by a decrease of PO_2muc and jejunal HbO_2. ETX effects on jejunal mucosal tissue oxygen supply have been reported to result from regional vasoconstriction and probably tissue damage mediated by some direct or indirect ETX effects.[16] In support of this concept, ETX has been shown to reduce microvascular mucosal villus blood flow and to reduce the

TABLE 2 Serum lactate, intestinal oxygen extraction, microcirculatory blood flow and conductivity, and oscillation frequency in PO_2muc in CON and ETX animals

	0 min BL	30 min M1	50 min M2	70 min M3	90 min M4	110 min M5	Time effect (*P*)	Time-group interaction (*P*)
Art lactate (mmol/L)								
CON	2.4±0.4	2.1±0.4	1.9±0.4	1.9±0.3	1.9±0.4	1.8±0.5	.196	<.001
ETX	2.3±0.5	3.0±0.7[b]	3.7±1.0[b]	3.4±0.7[b]	3.5±0.6[b]	3.7±1.4[b]		
Int ven lactate								
CON (mmol/L)	2.3±0.4	2.2±0.3	2.1±0.4	2.1±0.4	2.0±0.4	1.6±0.6	.297	.005
ETX	2.3±0.5	3.0±0.9[b]	3.5±1.1[b]	3.3±0.9[b]	3.4±0.8[b]	3.6±1.2[b]		
ER int (%)								
CON	28±4	32±6	32±7	30±9	31±9	30±8	.303	.574
ETX	33±9	35±12	38±11	37±11	39±11	41±13		
PU (Arbitrary units)								
CON	222±63	226±88	222±83	227±84	214±70	221±80	.177	.251
ETX	228±45	272±65	281±78	282±77	262±80	232±58		
L mc (PU/mm Hg)								
CON	2.55±0.62	2.55±0.92	2.50±0.82	2.52±0.78	2.31±0.68	2.27±0.75	.007	<.009
ETX	2.88±0.83	4.93±2.34[b]	4.9±2.3[b]	4.79±2.14[a,b]	4.65±2.04[b]	3.92±1.51[b]		
Oscillation PO_2muc (n/min)								
CON	3.8±1.2	4.4±1.7	3.6±1.0	3.5±0.7	3.0±1.2	3.5±0.9	.677	<.001
ETX	4.3±1.1	5.3±0.6	6.1±2.0[b]	6.1±1.1[b]	6.3±1.0[b]	5.8±0.5[b]		

M, measurement; Int ven, intestinal venous; ER int, intestinal oxygen extraction ratio. Values are mean±SD.
[a]Significant Bonferroni corrected post-hoc BL comparison (*P*<.0031; significant vs BL).
[b]Significant Bonferroni corrected post-hoc group comparison (*P*<.0031; significant vs CON).

density of perfused capillaries in small intestinal villi.[3,4] In the present study decreased tissue oxygen tension was present despite an increase in the conductance of microvasculature and, in addition, an increase in systemic oxygen delivery. The partial pressure of oxygen in a tissue is a function of (i) prevailing oxygen consumption, (ii) diffusion distances from nearby capillaries, and (iii) oxygen delivery.[17] Delivery of oxygen to the mucosal tissue layer in turn is a function of both blood flow and oxygen content of the supplied blood.

In our model, it can be assumed that oxygen consumption, diffusion distance, and the prevailing oxygen content was nearly consistent, the reason for the reduction in jejunal mucosal tissue oxygen supply is due to a decrease in jejunal microcirculatory blood flow to the mucosal tissue layer. This discrepancy to the measured blood flow detected by the laser Doppler flowmeter in the present study may be explained by the fact that the penetration depth and tissue volume derived blood flow determination reaches out of the mucosal layer. Measurements of light intensity demonstrated that the light emitted penetrates the entire intestinal jejunal wall, and is reflected by a mirror intermittently placed under the jejunal piece resulting in an increase in light intensity detected by the photomultiplier.[18] Similar results were obtained with the laser Doppler flowmeter in another study demonstrating a penetration depth of 3 mm in a segment of feline jejunum.[19]

It can be assumed that this ETX effect on jejunal mucosal oxygenation impairment may be mediated by a regional vasoconstrictive mechanism. In support of this concept, ETX has been reported to reduce intestinal microvascular blood flow and, in particular, mucosal villus blood flow.[3,4] In addition, the density of perfused capillaries in the small intestinal villi is reduced after ETX administration.[5]

Another mechanism for the decrease in mucosal tissue oxygenation might be a decrease in capillary density in association with an increase in heterogeneity of perfusion because of the presence of intermittently or not perfused capillaries in close proximity to well perfused microvessels.[20] Although not investigated in the present study these microcirculatory alterations in sepsis have been described in different organs and observed in rodents as well as in large animals.[21-24]

An interesting finding in the present study was the increase of the oscillation frequency of mucosal tissue oxygenation as an answer to a correlating decrease in oxygen partial pressure in the mucosal tissue. The oscillation of tissue oxygenation originates from rhythmical alterations in the flow pattern of the microcirculation named flowmotion or vasomotion. Vasomotion can be described as rhythmic oscillations in arteriolar vascular tone due to local changes in smooth muscle constriction and dilation.[8] This variation in vessel diameter induces alterations in red blood cell velocity, which affects microcirculatory transit times and facilitates gas exchange between microvessels and tissue.[25] The frequency of vasomotion is altered during abnormal conditions associated with low blood pressure, hypoperfusion, and decreased tissue oxygen tension.[25,26] It is speculated that vasomotion might serve

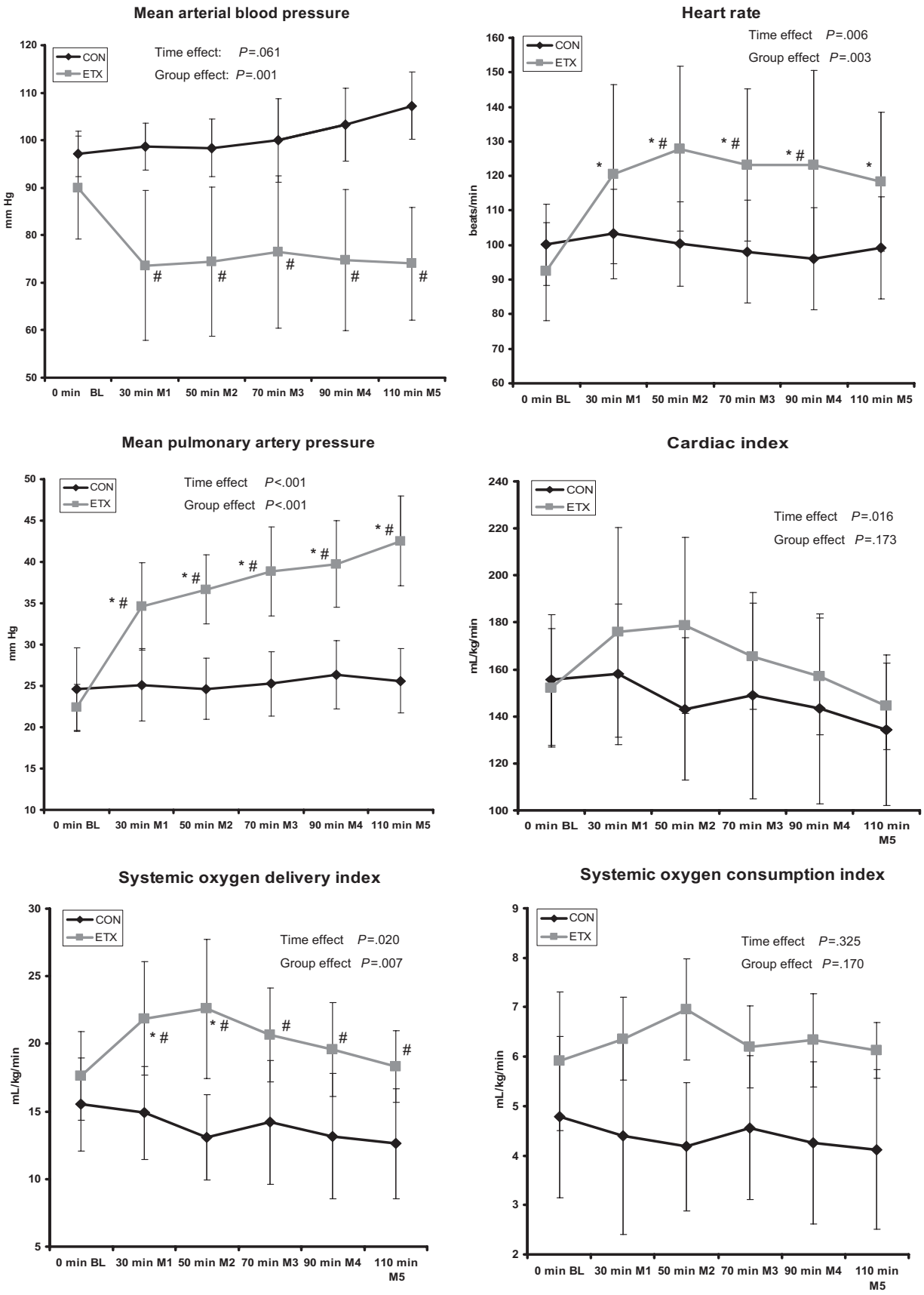

FIGURE 2 Hemodynamic and systemic oxygen parameters in CON and animals with acute ETX. There were no significant differences between groups at BL. #significant Bonferroni corrected post-hoc group comparison (*P*<.0031; significant vs CON). *significant Bonferroni corrected post-hoc BL comparison (*P*<.0031; significant vs BL)

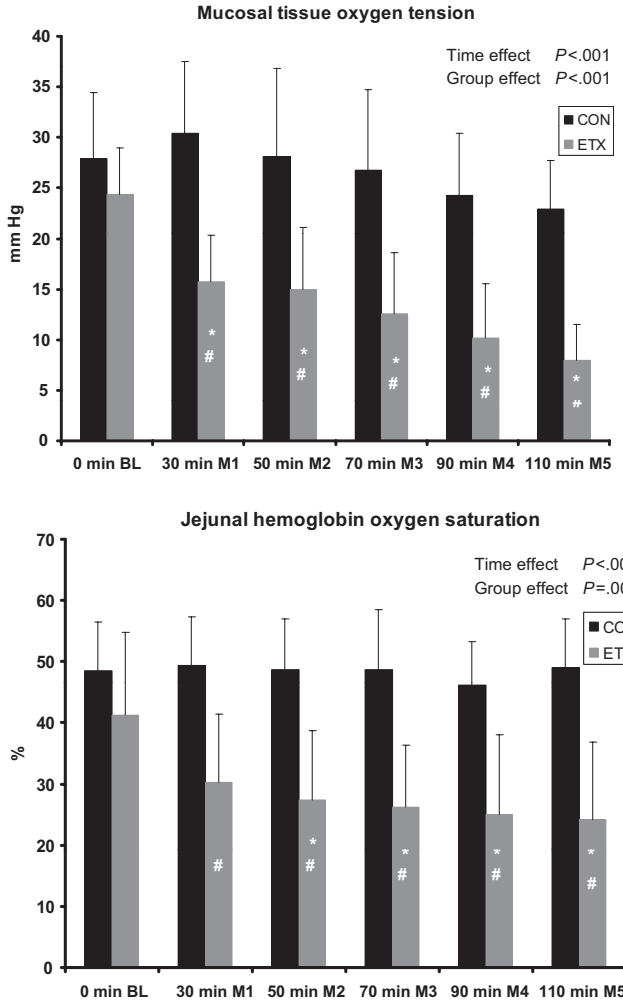

FIGURE 3 Mean PO_2muc and mean microvascular HbO_2 of the jejunum in CON and animals receiving ETX. There were no significant differences in PO_2muc and HbO_2 between groups at BL. Both, PO_2muc and HbO_2 decreased significantly after administration of *Escherichia coli* LPS compared to CON animals. #significant Bonferroni corrected post-hoc group comparison (P<.0031; significant vs CON). *significant Bonferroni corrected post-hoc BL comparison (P<.0031; significant vs BL)

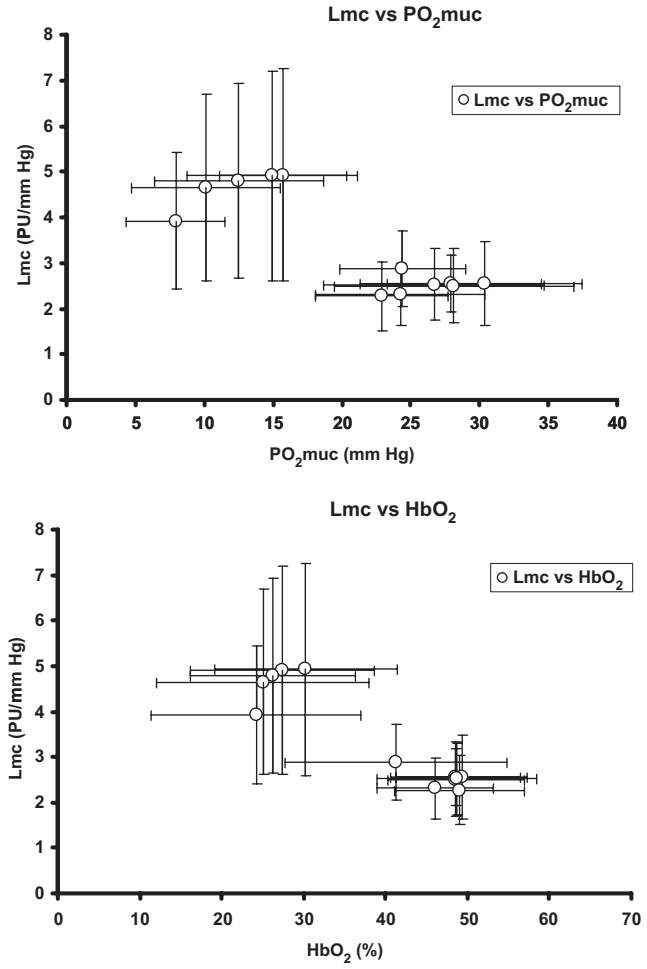

FIGURE 4 Correlation between L mc and PO_2muc (above) and microcirculatory HbO_2. The less the oxygenation of the mucosal tissue and the HbO_2 in the endotoxic animals the higher is the conductivity in the microcirculation

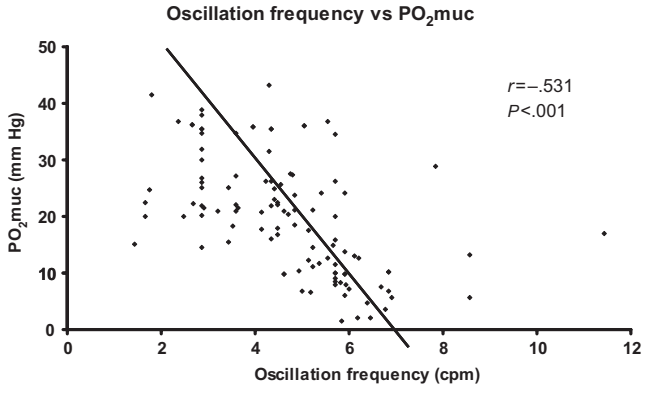

FIGURE 5 Correlation between oscillation frequency of mucosal tissue oxygenation (cycles per min, cpm) and jejunal PO_2muc. The less tissue oxygenation the higher the oscillation frequency indicating an increased vasomotion pattern of the jejunal microcirculation

as a protective mechanism for the supplied tissue under conditions of ischemia.[8,11,12]

The mechanisms responsible for the evolution of vasomotion during periods of limited oxygen supply are not well investigated. Hypoxia enhances the activity in the vasomotion pattern of terminal arterioles.[27] The oscillatory diameters cause reduced resistance in the microvascular networks compared with those in steady-state conditions.[28] Therefore, vasomotion still ensures an intermittent but adequate flow to the tissue.[27] Thus, it seems that the changes in the pattern of flowmotion contribute to the microvascular response to limited oxygen supply. This observation was supported by a study by Rücker and co-workers, investigating the metabolic state in perfused rat hind limbs by NADH fluorescence intravital microscopy indicating an improved blood flow to tissues due to increased vasomotion activity.[29] This theory of a correlation between an increased oscillation frequency in the flow-motion pattern of the microvasculature and a decreased oxygen utilization of the tissue may explain the observations in the present study. Due to a significant decrease in both,

PO_2muc and jejunal HbO_2, the oscillation frequency of the same microcirculatory bed increased, trying to compensate tissue hypoxia in this ETX animal model. A similar observation was made in the skin microvasculature in humans suffering from multiple organ dysfunction.[11] Oscillation frequency correlates well with the severity of multiple organ dysfunction and response of the microvasculature to hypoxia of the tissue within the skin.

Some limitations of our study should be noted: First, the decrease in cardiac index and concomitantly a decrease in systemic oxygen delivery were not corrected in this study, as the aim of this study was to investigate direct effects of ETX on jejunal mucosal oxygenation. As shown in a previous study, inotropic agents increase intestinal mucosal tissue oxygenation in a model of porcine endotoxemia.[30] Furthermore, fluid management may have an effect on tissue oxygenation. In the present study we have tried to keep normovolemia in CON and ETX animals. For reduction of edema formation in this acute setting of endotoxinemia we have administered dominantly colloidal fluids, minimizing the effect on mucosal tissue oxygenation as demonstrated in a previous study.[31]

A further general drawback of studies investigating microvascular function and dysfunction in animals and humans is the problem of the heterogeneity of regional blood flow and metabolic changes, not only when comparing different organs, but also within one particular organ system.[32] Therefore, measurements in the jejunal mucosa may not be representative for other organs.

In conclusion, administration of *E. coli* LPS intravenously in this porcine animal model resulted in a decrease in mean Art blood pressure, a progressive increase in heart rate, and an increase in both, systemic and intestinal lactate levels. On the microcirculatory level endotoxinemia resulted in an increase in vascular conductivity with a consistent microcirculatory blood flow in the jejunum. PO_2muc and jejunal HbO_2 were significant depressed. This impairment of tissue oxygenation resulted in an increase in the vasomotion pattern of the end-arterioles to counteract an undersupply of oxygen to the jejunal tissue.

5 | PERSPECTIVE

Impairment of mucosal tissue oxygenation is correlated with an increase in the vasomotion frequency of the microcirculation. This phenomenon may be of translational relevance in patients suffering from acute endotoxinemia in conjunction with tissue hypoxia and justifies further clinical trials.

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