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Effect of Supplemental Oxygen versus Dobutamine Administration on Liver Oxygen Tension in dPP-Guided Normovolemic Pigs

G. Pestel[a] K. Fukui[a] H. Hager[b] A. Kurz[c] L. Hiltebrand[d]

[a]Department of Anesthesiology, Johannes Gutenberg University, Mainz, Germany;
[b]Department of Anesthesiology, Medical University of Vienna, Vienna, Austria;
[c]Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio, USA;
[d]Department of Anesthesiology, Bern University Hospital (Inselspital), Bern, Switzerland

Key Words
Dobutamine · Difference in pulse pressure · Liver · Monitoring · Oxygen · Tissue oxygen tension

Abstract
Background: Difference in pulse pressure (dPP) confirms adequate intravascular filling as a prerequisite for tissue perfusion. We hypothesized that both oxygen and dobutamine increase liver tissue oxygen tension (ptO_2). ***Methods:*** Eight anesthetized pigs received dPP-guided fluid management. Hepatic pO_2 was measured with Clark-type electrodes placed subcapsularly, and on the liver surface. Pigs received: (1) supplemental oxygen (F_iO_2 1.0); (2) dobutamine 2.5 μg/kg/min, and (3) dobutamine 5 μg/kg/min. Data were analyzed using repeated-measures ANOVA followed by a Tukey post-test for multiple comparisons. ptO_2 measured subcapsularly and at the liver surface were compared using the Bland-Altman plot. ***Results:*** Variation in F_iO_2 changed local hepatic tissue ptO_2 [subcapsular measurement: 39 ± 12 (F_iO_2 0.3), 89 ± 35 mm Hg (F_iO_2 1.0, p = 0.01 vs. F_iO_2 0.3), 44 ± 10 mm Hg (F_iO_2 0.3, p = 0.05 vs. F_iO_2 1.0); surface measurement: 52 ± 35 (F_iO_2 0.3), 112 ± 24 mm Hg (F_iO_2 1.0, p = 0.001 vs. F_iO_2 0.3), 54 ± 24 mm Hg (F_iO_2 0.3, p = 0.001 vs. F_iO_2 1.0)]. Surface measurements were widely scattered compared to subcapsular measurements (bias: –15 mm Hg, precision: 76.3 mm Hg). Dobutamine did not affect hepatic oxygenation. ***Conclusion:*** Supplemental oxygen increased hepatic tissue pO_2 while dobutamine did not. Although less invasive, the use of surface measurements is discouraged.

Introduction

Patients with hepatic dysfunction are at high risk for perioperative complications [1]. Cells distant from the terminal afferent vascular branches (zone 3 cells) have a tissue oxygen tension (ptO_2) close to the venous pO_2, [2], and are thus prone to hypoxia and consecutive damage when systemic pO_2 decreases below normal. Therefore, an adequate oxygen supply is crucial to maintain liver function.

Several therapeutic options exist to maintain tissue pO_2. Supplemental oxygen increases the oxygenation of regional vascular beds and improves the patient's outcome [3–5]. However, oxygen availability in the tissues critically depends on adequate tissue perfusion [6]. Thus, fluid administration is a therapeutic mainstay as long as both ventricles operate on the ascending portion of the

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Gunther J. Pestel, MD
Department of Anesthesiology, Johannes Gutenberg University
Langenbeckstrasse 1
DE–55131 Mainz (Germany)
Tel. +49 6131 17 7117, Fax +49 6131 17 6649, E-Mail gunther.pestel@gmx.net

Frank-Starling curve (biventricular preload dependence). To ascertain this condition of fluid responsiveness, adequate monitoring is mandatory. Static indicators such as central venous pressure, pulmonary artery occlusion pressure, or left-ventricular end-diastolic area have been shown to be poor predictors of fluid responsiveness [7]. Dynamic indicators like difference in pulse pressure (dPP) that rely on heart-lung interaction have consistently been demonstrated to be excellent predictors of fluid responsiveness during mechanical ventilation, with a linear relationship between dPP values and hypovolemia [8–11]. However, once normovolemia is achieved, additional fluid fails to increase blood flow in the celiac trunk [12]. Therefore, augmenting cardiac output, e.g. by adrenergic inotropes, might be another option to optimize blood flow in regional vascular beds.

Assessing liver pO_2 by inserting probes into the parenchyma is an accepted methodology [13, 14]. Noninvasive approaches to measure liver tissue pO_2 either did not get wide acceptance [15] or were inconclusive [16, 17]. Polarographic tissue oxygen sensor probes have been shown to give stable and reliable tissue pO_2 measurements [18, 19]. To the best of our knowledge, a comparison between polarographic tissue oxygen sensors placed on the liver capsule (noninvasive) and polarographic tissue oxygen sensors placed under the liver capsule has not been done yet.

The goal of this trial was to study the effects of an oxygen and a dobutamine challenge on liver tissue pO_2 in an experimental setting with goal-directed fluid management to ensure normovolemia. We hypothesized that both oxygen and dobutamine improve tissue pO_2. The secondary goal of our study was to compare two measurement sites of liver tissue pO_2, i.e. an intraparenchymal site versus a surface site. Our hypothesis was that both measurement sites can be used interchangeably.

Materials and Methods

This study was performed according to the National Institute of Health guidelines for the use of experimental animals. The protocol was approved by the Washington University Animal Studies Committee. Eight domestic pigs weighing 23–25 kg were fasted overnight but were allowed free access to water. The pigs were sedated with intramuscular telazol (2 mg/kg), ketamine (1 mg/kg) and xylazine (1 mg/kg). Anesthesia was induced and maintained by inhalation of isoflurane (1.5–2.0%). All pigs were orotracheally intubated and ventilated with oxygen in nitrogen [inspired oxygen fraction (F_iO_2) = 0.3]. The animals were ventilated in volume-controlled mode, with the tidal volume kept at 10–15 ml/kg and the respiratory rate adjusted (11–14 breaths/min) to maintain end-tidal carbon dioxide tension between 35 and 40 mm Hg.

Surgical Preparation

Catheters were inserted into the femoral artery and vena cava inferior by femoral cut down. A balloon-tipped catheter was inserted into the pulmonary artery through the left femoral vein. The location of the catheter tip was monitored by observing the characteristic pressure trace on the monitor as it was advanced through the right heart into the pulmonary artery. With the pig in supine position, a midline laparotomy was performed. A urinary catheter was inserted into the bladder.

Tissue pO_2 was measured with a polarographic tissue oxygen sensor (Licox CC 1.2, Gesellschaft für Medizinische Sondentechnik, Kiel, Germany). The oxygen sensor is a flexible micro catheter probe used for long-term monitoring of partial tissue pO_2 and body fluid. A thermistor (Licox 8.1, Gesellschaft für Medizinische Sondentechnik) placed in close proximity provided accurate temperature compensation. The device was calibrated before insertion. Calibration remains stable (within 8% in room air) in vivo for at least 8 h. Oxygen sensors were calibrated in room air (ambient pO_2, 154 mm Hg). All pO_2 values measured before insertion were within 8% of 154 mm Hg.

To measure liver tissue pO_2, oxygen probes were inserted subcapsularly through 20-gauge cannulae from the liver surface through the liver capsule. Another probe was placed on the liver surface between the right and the left lobe. Dressing (Tegaderm®, 3M, St. Paul, Minn., USA) of the probe to insulate it from the ambient atmosphere was taken out with great care.

The body temperature of the animals was maintained at 37.0 ± 0.8°C using a warming mattress and a patient air warming system (Bair Hugger, Arizant Healthcare Inc., Eden Prairie, Minn., USA).

After induction of anesthesia, the animals received an initial bolus of 10 ml/kg of lactated Ringer's solution, followed by continuous infusion at the rate of 15 ml/kg/h. Intravascular volume was optimized by a goal-directed fluid management approach using dPP as described previously [9]. Briefly, dPP was calculated by determining the maximal and minimal values of pulse pressure (PP_{max} and PP_{min}) over one respiratory cycle. dPP is the difference between PP_{max} and PP_{min} divided by the mean of the two values and is expressed as a percentage. In addition to the continuous infusion of lactated Ringer's solution, boluses of 100 ml of lactated Ringer's solution were given to decrease dPP to below 13%. This cutoff point was chosen because it accurately distinguishes [8] volume responders (dPP > 13%) from nonresponders (dPP < 13%).

The animals were allowed to stabilize after induction of anesthesia and insertion of the catheters and probes for 60 min. We considered an animal to be stable when its mean arterial pressure was above 60 mm Hg, cardiac output was above 2.0 liters/min, and dPP was below 13% for 30 min without intervention. To achieve that condition, pigs received additional fluid boluses (median 6, range 4–8) during and shortly after the surgical phase; there was no need for vasopressors, inotropes or vasodilators.

Experimental Design

All animals were subjected to 3 treatments in the following order: (1) oxygen challenge (F_iO_2 1.0); (2) dobutamine 2.5 μg/kg/min, and (3) dobutamine 5 μg/kg/min. At least 30 min were allowed to pass between treatments. Treatment periods also lasted 3 min to provide sufficient time for establishment of steady-state conditions. An F_iO_2 of 0.3 was reestablished after the oxygen challenge.

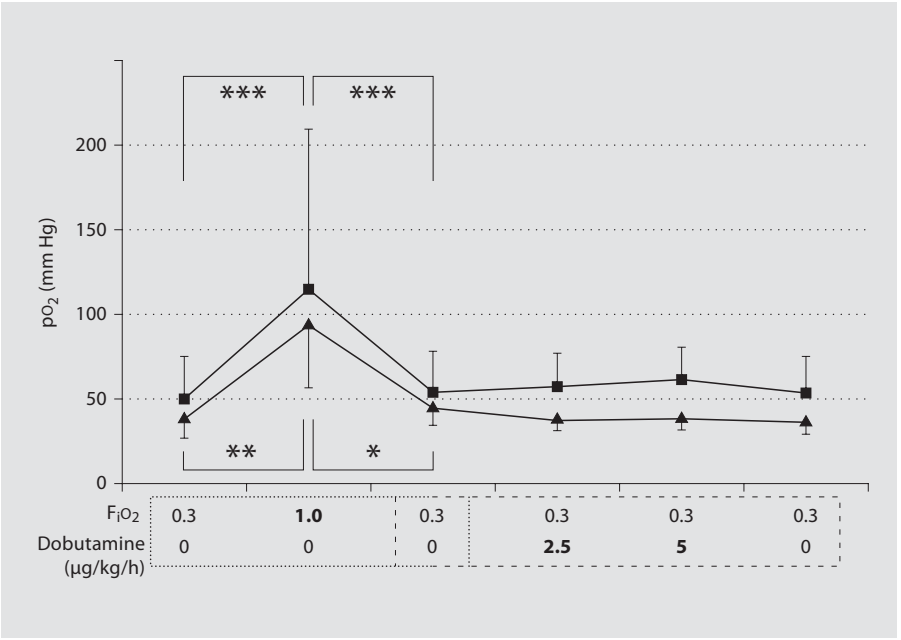

Fig. 1. Liver tissue pO_2 of 8 pigs measured at the subcapsular level (▲) and at the liver surface (■) during an oxygen and a dobutamine challenge. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Systemic hemodynamics were recorded every 5 min. Cardiac output measurements were taken during each experimental condition with ice-cold saline in triplicate. Arterial and a mixed venous blood gas analyses were performed during each condition.

Statistical Analysis

All data were tested for normal distribution with a Kolmogorov-Smirnov test. A one-tailed paired ANOVA for repeated measurements followed by the Tukey-Kramer post-test for multiple comparisons were used to describe differences between interventions. Absolute values were used for all calculations. Comparisons of liver tissue pO_2 measurements at the subcapsular site and at the liver surface were performed by the Bland-Altman plot. $p < 0.05$ was considered statistically significant. Data are presented as means ± standard deviations (SDs).

Table 1. Vital signs of pigs at baseline (n = 8 animals)

	Mean ± SD
Mean arterial pressure, mm Hg	83.4 ± 10.6
Cardiac output, liters/min	2.28 ± 0.68
Central venous pressure, mm Hg	11.1 ± 1.3
Pulmonary artery occlusion pressure, mm Hg	9.5 ± 2.1
dPP, %	6.6 ± 1.6
Temperature, °C	36.8 ± 0.5
F_iO_2	0.3 ± 0
Arterial pO_2, mm Hg	111.6 ± 21.7
End-tidal carbon dioxide tension, mm Hg	37.3 ± 1.7

Results

At baseline, all pigs were hemodynamically stable, normothermic and adequately ventilated. Vital signs of the pigs at baseline are shown in table 1.

Supplemental oxygen administration increased local hepatic tissue pO_2 from 38 ± 11 to 93 ± 36 mm Hg at the subcapsular site ($p = 0.01$) and from 51 ± 24 to 114 ± 94 mm Hg at the liver surface ($p = 0.001$). Accordingly, the reduction in F_iO_2 to 0.3 decreased local hepatic tissue pO_2 to 44 ± 10 mm Hg ($p = 0.05$), and to 54 ± 24 mm Hg at the liver surface ($p = 0.001$). Conversely, dobutamine had no significant effect on local hepatic tissue pO_2 (fig. 1).

Systemic hemodynamics were unaffected by different F_iO_2. Heart rate ($p < 0.001$), cardiac output ($p < 0.001$), and stroke volume ($p < 0.001$) increased significantly after starting dobutamine 2.5 µg/kg/min. At a dose of 5 µg/kg/min, dobutamine led to a further increase in heart rate ($p < 0.001$) and cardiac output ($p < 0.01$), but not in stroke volume, compared to measurements following a dobutamine dose of 2.5 µg/kg/min (fig. 2).

The oxygen challenge (switching F_iO_2 from 0.3 to 1.0) increased arterial pO_2 ($p < 0.01$); administration of F_iO_2 at 0.3 brought pO_2 levels back to baseline. The oxygen challenge did not affect arterial oxygen content. System-

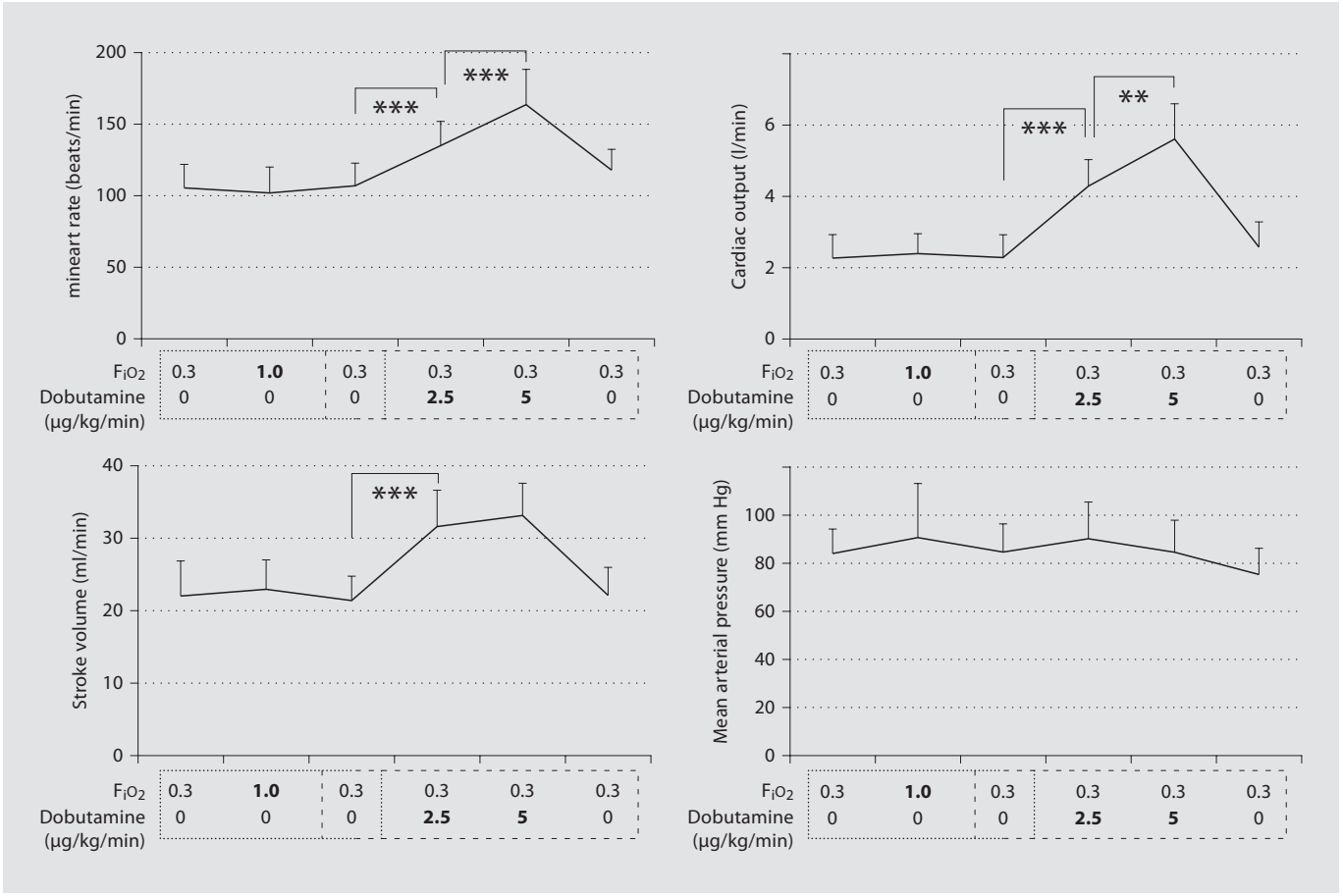

Fig. 2. Hemodynamics of 8 pigs during an oxygen and a dobutamine challenge. ** $p < 0.01$; *** $p < 0.001$.

ic oxygen delivery increased with dobutamine ($p < 0.001$ for dobutamine 2.5 µg/kg/min compared to baseline) due to increases in cardiac output. The oxygen challenge had no impact on systemic oxygen delivery. Neither the oxygen challenge nor the administration of dobutamine had an effect on systemic oxygen consumption compared to baseline. However, switching F_iO_2 from 0.3 to 1.0 reduced systemic oxygen consumption (fig. 3).

Tissue pO_2 at the liver surface and the subcapsular level showed similar trends as a response to treatment. However, when comparing data obtained by measuring liver tissue pO_2 at the liver surface with data obtained at the subcapsular site, the Bland-Altman plot showed a large bias of –15 mm Hg, and a precision of 76.3 mm Hg (fig. 4).

Discussion

We studied the induction of (a) hyperoxia and (b) the administration of dobutamine in an experimental setting with goal-directed fluid management by dPP to ensure normovolemia. Supplemental oxygen (F_iO_2 1.0) increased local hepatic tissue pO_2. When F_iO_2 was decreased to 0.3, local hepatic tissue pO_2 decreased to baseline levels. Dobutamine administration did not affect local hepatic tissue pO_2.

Hyperoxia is considered to be beneficial, as it has been shown to lower mortality in an experimental setting [20]. Hemorrhagic shock was induced in 14 pigs; then the animals were partially fluid-resuscitated with hydroxyethyl starch. Additionally, the study group was ventilated with 100% oxygen and showed lower mortality, and higher muscular pO_2. In a clinical study enrolling 51 patients, it was shown that tissue pO_2 is increased by ventilation with 100% oxygen after cardiac surgery whereas two different

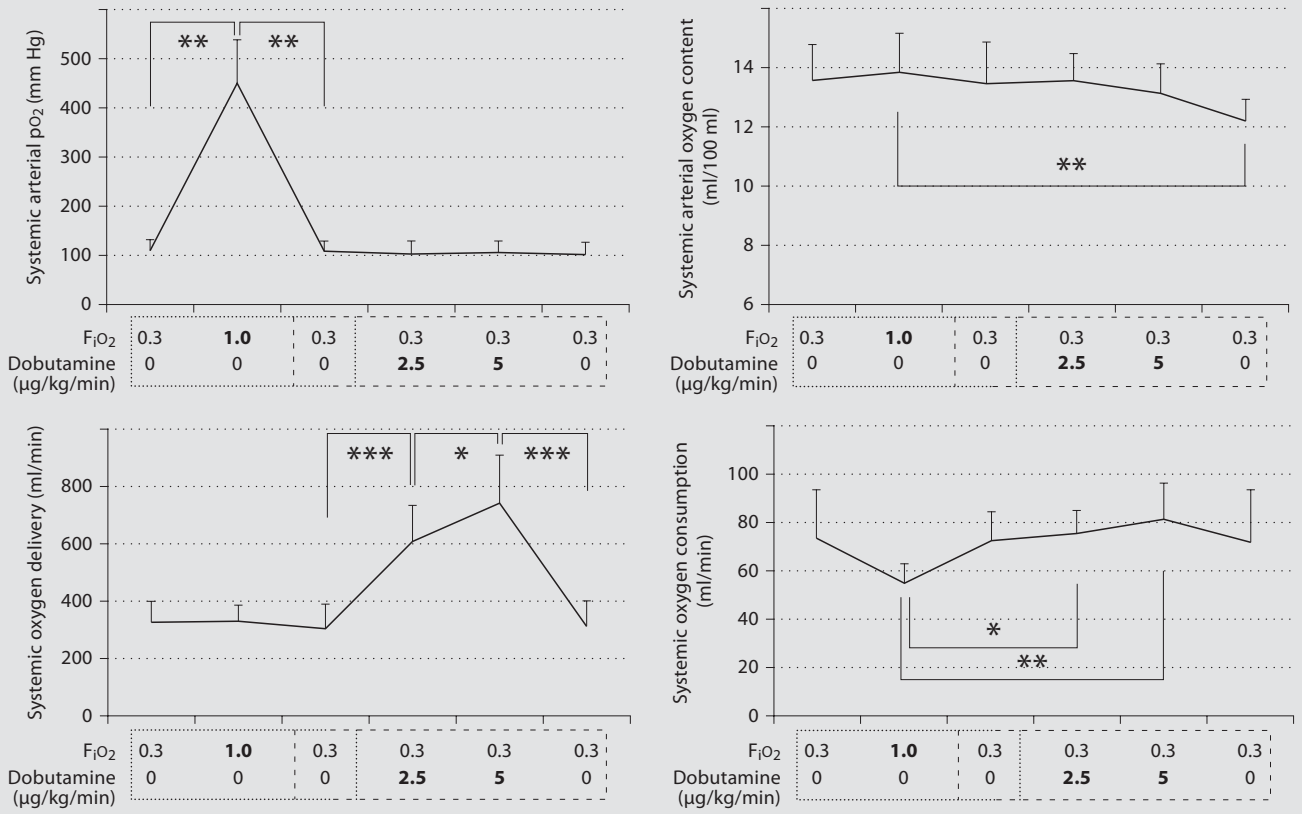

Fig. 3. Oxygenation measurements in 8 pigs during an oxygen and a dobutamine challenge. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

transfusion regimens had no impact on tissue pO_2 [21]. These findings are in accordance with our results showing an increase in liver tissue pO_2 during ventilation with an F_iO_2 of 1.0.

However, ventilation with 100% oxygen is not without hazards. An F_iO_2 of 1.0 favors the formation of atelectasis [22], and is capable of inducing the formation of reactive oxygen species [23]. A high F_iO_2 may lead to vasoconstriction in tissue beds, e.g. coronary vasoconstriction [24]. Hyperoxia may cause maldistribution of blood flow and deterioration of blood flow at the level of the distribution vessels as a protective mechanism against high pO_2, leading to decreased oxygen uptake in spite of unchanged O_2 delivery [25]. This would be in accordance with our findings, which showed a reduced oxygen uptake when the animals were ventilated with 100% oxygen.

The effect of an F_iO_2 of 0.3 versus an F_iO_2 of 1.0 on liver tissue oxygen tension was studied in 11 anesthetized patients undergoing hepatic resection [26]. Measurements were taken by a multi-analyte sensor (Paratrend®, Diametrics Medical, UK) inserted under the liver capsule. Baseline hepatic tissue pO_2 was in the same range as in our study and in a study assessing intrahepatic tissue pO_2 with a pO_2 histogram derived from consecutive measurements using a pilgrim step method with a polarographic pO_2 needle electrode [27]. The multi-analyte sensor (Paratrend) showed an increase in liver pO_2 with an F_iO_2 of 1.0, but statistical significance was not reached [26]. The authors point out that some data were lost due to fragile probes. However, in the last 6 of 11 patients studied they obtained 95% of possible data points. In our study, we noted a marked increase in liver tissue pO_2 when ventilating with 100% oxygen, and no effect when administering dobutamine. An interpretation of the different findings of these two studies remains highly speculative: After inserting a thoracic epidural catheter, Brooks

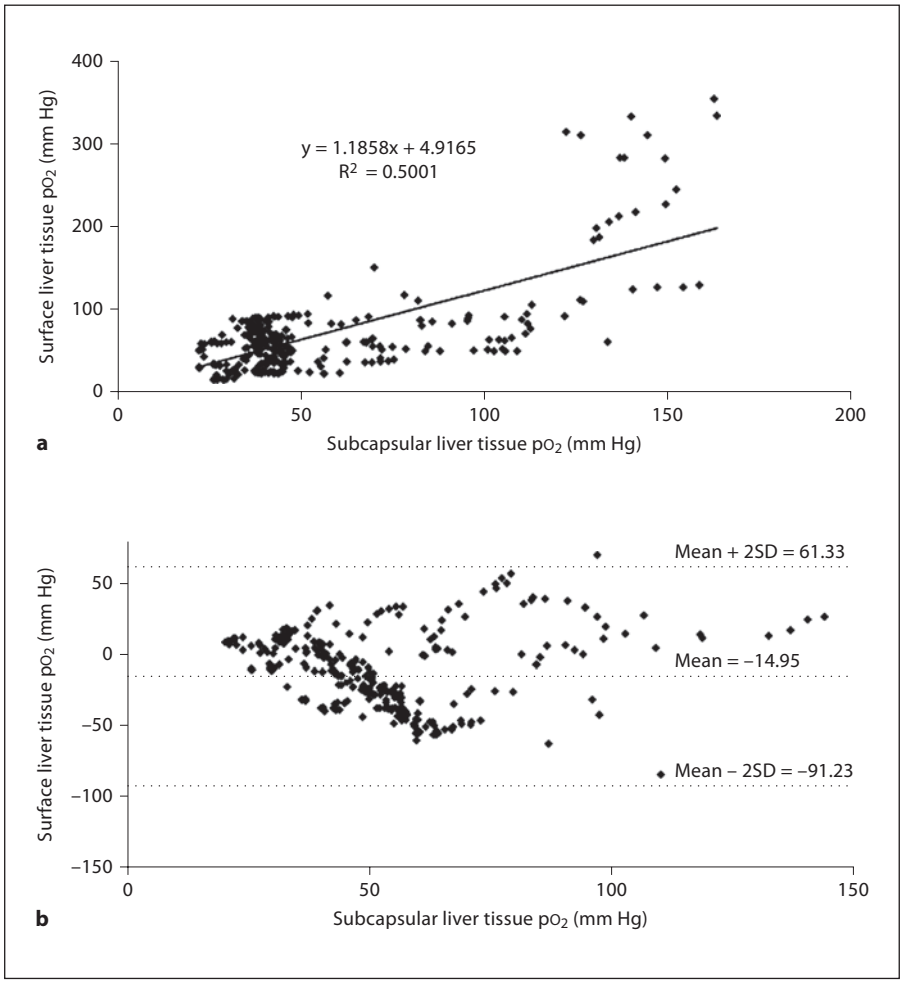

Fig. 4. Linear regression (**a**) and Bland-Altman plot (**b**) of measurements of liver tissue pO_2 at the subcapsular level and at the liver surface.

et al. [26] used an ephedrine infusion to keep blood pressure within preoperative values ± 20%. To our knowledge, only one study assessed the impact of ephedrine on liver pO_2 [28], describing an increase in hepatic oxygen consumption after administering ephedrine to restore central hemodynamics after epidural block at a level of T1–T2 in dogs. Maybe, this mechanism in conjunction with a restrictive fluid management (Brooks et al. kept central venous pressure between 0 and 5 mm Hg in their patients) prevented sufficient perfusion of the liver, and thus pO_2, even at a high F_iO_2 level.

Restrictive fluid management has been considered to be useful to minimize blood loss during hepatic surgery [29, 30]. However, this approach has been challenged, as fluid restriction led to an increased rate of renal failure and 30-day mortality [31] in liver transplantated patients. We consider a functional approach, i.e. monitor-guided and goal-directed fluid therapy when fluid responsiveness can be expected, to be most promising to avoid risks from both too restrictive and too liberal fluid administration. Therefore, we monitored dPP, and gave additional fluid when dPP increased to values above 13% [8].

The effect of additional oxygen and dobutamine on hepatic hemodynamics, and oxygen and lactate metabolism during hepatic artery occlusion and reperfusion was studied in 18 dogs [32]. At the beginning of hepatic artery occlusion, the animals received either 100% oxygen or dobutamine 5 μg/kg/min. The marked increase in portal venous pO_2 with additional oxygen but not with dobutamine resembles our findings of a marked increase in tissue pO_2 with hyperoxia but not with dobutamine.

In our study, dobutamine at a dose of 2.5 μg/kg/min almost doubled cardiac output, and increased heart rate and stroke volume. A rate of 5 μg/kg/min of dobutamine further increased cardiac output and heart rate but not stroke volume. Mean arterial pressure remained unaffect-

ed with both dosages of dobutamine, as did local hepatic tissue pO_2. This is in accordance with Nordin et al. [33], who even saw a deterioration of liver pO_2 with dobutamine in a hemorrhage-crystalloid resuscitation model.

Dobutamine is supposed to increase tissue pO_2 by dilating previously vasoconstricted small vessels due to a β_2 effect, thus leading to a more even flow distribution and higher oxygen uptake [34]. Hemodynamic and metabolic disturbances in the splanchnic area can be counteracted by dobutamine administration [35]. We saw an increase in oxygen delivery with both doses of dobutamine. Oxygen consumption increased with dobutamine 5 μg/kg/min; however, this increase did not reach statistical significance. Oxygen consumption increased in a study with 8 pigs [36], when dobutamine was given at a dose of 10 μg/kg/min. In a rat model [37], an infusion of dobutamine 5 μg/kg/min caused a pronounced increase in mean arterial pressure; tissue pO_2 in skeletal muscle remained unaffected even at higher doses. Hepatic tissue pO_2 was unaffected by dobutamine in our study as well.

To investigate a site for measuring liver tissue pO_2 that does not need a puncture of the liver capsule, we compared measurements obtained from a neatly sealed liver surface probe with a measurement performed with a probe inserted under the liver capsule. Obviously, a noninvasive measurement technique would be helpful for studies of liver pO_2. In an experimental hemorrhage-resuscitation model in 6 dogs, transcutaneous pO_2 was assessed as well as pO_2 on the liver surface, measured with a second transcutaneous pO_2 probe [38]. A correlation coefficient of 0.79 was found regarding the two pO_2 measurements; however, no specific comparisons between the two measurement sites of pO_2 were reported. To the best of our knowledge, only one Japanese group assessed liver pO_2 by attaching a Clark-type electrode on the liver surface [15]. Additionally, pO_2 in the kidney and femoral muscle was measured, but no comparisons of measurements of the 3 sites were reported.

When we compared measurements on the liver surface with subcapsular tissue pO_2 measurements, we found comparable trends to treatment with 100% oxygen. However, tissue pO_2 measurements on the liver surface were widely scattered. In contrast to measurements in the gut, we consider the liver capsule to impair tissue pO_2 measurements with electrodes sealed on the liver surface. Thus, we recommend subcapsular measurements of liver pO_2 to assess tissue oxygenation of the liver.

The fact that we did not use the direct Fick method or an ultrasonic flow probe on the aorta to measure hemodynamic parameters constitutes a limitation of our study. Instead, we used a pulmonary artery catheter. Another limitation may be seen in the lack of direct measurements of liver blood flow. We considered liver blood flow throughout our experiment to be stable due to the hepatic arterial buffer response (HABR), an intrinsic regulatory mechanism of the hepatic artery that compensates for reductions in portal venous blood flow [39]. The administration of isoflurane as an anesthetic preserves HABR [40]. HABR is impaired during endotoxemia [41] and if blood loss exceeds 30% of blood volume during hemorrhage [42]. However, none of these conditions applied to our experimental setting. Third, we did not randomize pigs to the respective treatments in our cross-over design. We separated the treatment with 100% oxygen from the administration of dobutamine by another 30-min baseline treatment phase. As the only short-time storage of oxygen in the body by myoglobin is in cardiac [43] and red skeletal muscle [44], the additional oxygen could not have had any effect when the dobutamine was started. The half-time of dobutamine is between 2 and 3 min, even in the failing heart [45]. Our final measurements were done 30 min after dobutamine had been stopped. Thus, we can rule out carryover effects both by oxygen, and dobutamine. Finally, the experiments were done in healthy pigs. As our focus of interest is liver transplantation, we will proceed to study ischemia-reperfusion models to learn how results in a transplantation setting compare to findings in this study. To what extent findings are applicable to other pathologic conditions like trauma or sepsis remains to be elucidated in further projects.

In summary, we tested the effect of hyperoxia (F_iO_2 of 1.0) and administration of dobutamine on local hepatic tissue pO_2 in an experimental setting with goal-directed fluid management by dPP to ensure normovolemia. In this setting, we have shown that supplemental oxygen administration significantly increased local hepatic tissue pO_2. In contrast, dobutamine did not increase local hepatic tissue pO_2. Additionally, we have shown that measurements of local hepatic tissue pO_2 at the liver surface compared to intraparenchymal measurements lead to widely scattered results. This may be due to the connective tissue of the liver capsule that impairs proper pO_2 detection by the polarographic probes. Therefore, we do not advise the use of tissue pO_2 measurements at the liver surface.

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