Maintaining oxygen delivery is crucial to prevent intestinal ischemia in critical ill patients

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Abstract

Background
Intestinal ischemia is a common complication with obscure pathophysiology in critically ill patients. Since insufficient delivery of oxygen is discussed, we investigated the influence of oxygen delivery, hemoglobin, arterial oxygen saturation, cardiac index and the systemic vascular resistance index on the development of intestinal ischemia. Furthermore, we evaluated the predictive power of elevated lactate levels for the diagnosis of intestinal ischemia.

Methods
In a retrospective case-control study data (mean oxygen delivery, minimum oxygen delivery, systemic vascular resistance index) of critical ill patients from 02/2009–07/2017 were analyzed using a proportional hazard model. General model fit and linearity were tested by likelihood ratio tests. The components of oxygen delivery (hemoglobin, arterial oxygen saturation and cardiac index) were individually tested in models.

Results
59 out of 874 patients developed intestinal ischemia. A mean oxygen delivery less than 250ml/min/m² (LRT vs. null model: p = 0.018; LRT for non-linearity: p = 0.012) as well as a minimum oxygen delivery less than 400ml/min/m² (LRT vs null model: p = 0.016; LRT for linearity: p = 0.019) were associated with increased risk of the development of intestinal ischemia. We found no significant influence of hemoglobin, arterial oxygen saturation, cardiac index or systemic vascular resistance index. Receiver operating characteristics analysis for
Introduction

Intestinal ischemia (II) in critically ill patients is a life-threatening complication, leading to sepsis [1–3] caused by bacterial translocation [4–6] or direct fecal contamination of the peritoneal cavity. Congestive heart failure, diabetes mellitus, peripheral artery occlusive disease and age older than 60 years are recognized risk factors [7–9].

The mortality in these patients is increased [10–12] and it is one of the major missed diagnoses in deceased patients treated in intensive care units (ICU), implying an even higher incidence [13–15]. Overall mortality is estimated between 50% to 80% [1–3].

Surgical treatment within 24 hours (h) of diagnosis of II was identified as an independent predictor of survival, emphasizing the need for reliable risk stratification, specific markers, early detection and multidisciplinary management [16].

Acute obstruction with or without previously stenotic arterial vessels, mesenteric venous thrombosis and non-occlusive mesenteric ischemia because of impaired regional oxygen delivery are described as distinct pathophysiological entities leading to II. Although the splanchnic circulation receives approximately 20% of the cardiac output, several mechanisms like increased oxygen extraction and vascular autoregulation protect the intestines from ischemia. Nevertheless, a substantial reduction in oxygen delivery (DO₂I in l/min/m²) can lead to an imbalance between oxygen supply and demand and thereby cause II [7, 17–19]. The latter is of special interest for the intensivist as it might be preventable as insufficient DO₂I due to low cardiac output (cardiac index, CI in l/min/m²) combined with mesenteric and systemic vasoconstriction (systemic vascular resistance index, SVRI) caused by endo- or exogenous catecholamines leading to insufficient locoregional oxygen supply [1, 2, 9, 12, 20, 21].

Lactic acid, as well as pH, CO₂ and central venous saturation (ScvO₂), as routine parameters measured in the management of critically ill patients, are commonly used in a clinical setting to detect parenchymatous hypoxia, but the specificity for II is unknown. Furthermore, II per se induces lactic acid accumulation through parenchyma breakdown, as well as further pathological changes in the routine parameters.

Thus, the primary aim of this study is:

I. to define specific critical cut-off values for short term (the minimal DO₂I during the 72 hours period before the diagnosis of II, minDO₂I) or prolonged oxygen delivery (the mean DO₂I during the 72 hours period before the diagnosis of II, meanDO₂I) in the development of II

Secondary objectives of this study are:
I. to identify the role of the independent parameters (hemoglobin, Hb; arterial oxygen saturation, SaO$_2$ and CI) of DO$_2$I in the development of II;

II. to identify the independent parameter (either Hb, SaO$_2$ or CI) whose manipulation is most beneficial in order to increase DO$_2$I to a noncritical value to reduce the risk of II;

III. to evaluate the predictive power of elevated lactate levels, pH, CO$_2$ and central venous saturation (ScvO$_2$) for the diagnosis of II;

IV. to identify the influence of high SVRI on the development of II

**Material and methods**

**Study design**

This study was approved by the local ethics committee (Medizinische Ethikkommission II, University Medical Centre Mannheim, Medical Faculty Mannheim of the University of Heidelberg, Mannheim) (registration number 2016-800R-MA). The study was also registered at the Deutsche Register für klinische Studien (ID: DRKS00016030).

For this retrospective observational, non-interventional, monocenter case-control study the need for informed consent was waived by the local ethics committee.

The study was conducted in the 25-bed ICU of the Department of Anaesthesiology and Critical Care Medicine, University Medical Centre Mannheim, Medical Faculty Mannheim of the University of Heidelberg.

Data were retrospectively analyzed. The inclusion period lasted from 02/2009 to 07/2017 with an average of 1869 patients per year.

All patients who stayed longer than 72 hours, were older than 18 years and had a complete electronic medical record for calculating DO$_2$I values were included in the analysis.

Irreversible parenchymal ischemia is induced in a time frame between 6 and 12h of hypoxia in the intestinal vascular zone [12, 19, 22]. As the goal of this study was to evaluate the impact of hypoxemia on the development of II and to discriminate the diagnosis of II attributable to critical care management from the sequelae of underlying diseases associated with II and originated before ICU admission, we excluded patients with a length of stay (LOS) shorter than 72h to exclude patients with undiagnosed II at admission on the ICU.

Furthermore, patients were excluded if they were <18 years old and if the electronic medical records were incomplete for calculating DO$_2$I values.

As the overall incidence of II is low [3, 23, 24] we opted to include commonly recognized factors and pre-existing conditions [1, 3, 9] for the stratification of the Cox proportional hazards model, that might predestine the patient for intestinal hypoxia in case of acute severe illness necessitating treatment on ICU. So, identified patients with an elevated baseline risk for II by the following criteria: 1) congestive heart failure, 2) diabetes mellitus, 3) peripheral artery occlusive disease, 4) age older than 60 years [7–9].

Patients who developed II after admission with an ICU stay of at least 72h were grouped in the cases group to ensure a suitable amount of collected data for analysis.

The diagnosis of II was confirmed by clinician validation of medical records when at least one of the following criteria was fulfilled:

I. suggestive radiological signs for ischemia

II. endoscopic proof of ischemia

III. II specified in the pathology report
IV. obvious ischemia detected intraoperatively without resection because of futility and an ICU stay of at least 72 hours before the surgical intervention

All other patients without the diagnosis of II during their treatment on ICU were included in the control group, were managed according to the standard operation procedures of our unit, and received radiological or endoscopic interventions respectively surgical interventions as indicated.

Collection of data

All data were collected through Philips IntelliVue Clinical Information Portfolio (ICIP) and Philips Intelli Space Critical Care and Anesthesia (ICCA) System. SaO₂, Hb and lactic acid were measured routinely using a blood gas analyzer (Radiometer ABL 800 Flex, Radiometer, Willich, Germany).

According to the standard operation procedures all patients with impaired cardiopulmonary function were managed with a triple-lumen central venous catheter. Additionally, a transpulmonary thermodilution catheter (Pulsiocath ™, Pulsion Medical Systems, Munich, Germany) was utilized in patients, when indicated by the attending physician.

The Pulse Contour Cardiac Output monitor (PiCCOplus ™, Pulsion Medical Systems, Munich, Germany) was used for measuring CI and SVRI with routine calibrations around every 8h, averaging three daily DO₂I-measurements.

DO₂I was calculated using a simplified version of the standard formula:

\[
DO₂I \text{ (ml/min/m²)} = CI \text{ (ml/min/m²)} \times \text{SaO₂} \times \text{Hb (g/dl)} \times 1.34 \times 10^3 \quad \text{(Eq 1)}
\]

And for calculating the SVRI we used the following formula:

\[
SVRI \text{ (dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^2) = \left(\frac{\text{(mean arterial pressure} - \text{central venous pressure})}{\text{CI}}\right) \times 80 \quad \text{(Eq 2)}
\]

In order to quantify an insufficient oxygen delivery index within 72h before the diagnosis, we calculated meanDO₂I during the stay in ICU as a surrogate for a longer lasting hypoxic status and the minDO₂I during the stay in ICU to capture shorter periods of hypoxia. Furthermore, we calculated the mean CI, mean SaO₂, mean Hb and mean SVRI during the stay in ICU.

Lactate levels were collected in the case group 72h before the diagnosis of II and in the control group we collected all lactate values over the ICU-stay. A plasma lactate concentration of 2mmol/l or less was defined as normal finding as this represents the clearing capacity for lactic acid in normal adults [25].

Statistical analysis

Metric data is presented as mean ± standard deviation, categorical data as absolute frequency (percentage). P-values were calculated using the t-test and Fisher’s exact test.

Because some variables for the DO₂I measurements were not synchronously recorded we allowed an 8h synchronization window for all variables for DO₂I.

Patients in the II group were matched according to the timepoint of the diagnosis of II (in hours) with patients in the control group and an equal LOS (in hours) without II. CI, SaO₂, Hb, meanDO₂I, minDO₂I and meanSVRI from the last 72h was recorded in the individual patient with II and in all patients in the case group with a corresponding LOS.

A stratified (by baseline risk) Cox proportional hazard model with time dependent covariates [26] was then applied to assess the relationship between these parameters and the development of II [7, 8].
We allowed a nonlinear relationship between the regressor and the hazard to develop an II by the application of smoothed regression splines [27]. For each model we assessed the general model fit, the linearity and the non-linearity of the regressor function by appropriate likelihood ratio tests (LRT).

In order to assess the effect of the individual components of DO$_2$I (see Eq 1) we augmented the former meanDO$_2$I model by the individual components (mean Hb, mean SaO$_2$ or mean CI) to derive adjusted coefficients and compared them to the unadjusted coefficients derived from a model that contains only the component of DO$_2$I (Hb, SaO$_2$ and CI). Again, data from the last 72h of patients in the II group were matched with all control patients who had an equal LOS as the case.

Furthermore, we compared the model fit of the augment model with the mean DO$_2$I model and the model that contains only the component of DO$_2$I as regressor by appropriate LRT to determine the relative importance of each independent component.

We further conducted a Receiver Operating Characteristic Curve (ROC) analysis—sensitivity, specificity and Area under the ROC (AUROC) for lactate, pH, CO$_2$, ScvO$_2$ and their predictive value for II.

Statistical analysis was performed with R 3.3.2 (The R foundation for Statistical Computing, Vienna, Austria) [28] and the survival package and SAS 9.4 (Statistical Analysis System) [29, 30]. A p-value $\leq 0.05$ was regarded as statistically significant. No adjustment for multiplicity was applied.

All dedicated statistician (MH) was responsible for the calculations.

Results

From 02/2009 to 07/2017 we analyzed 15032 patients of whom 215 patients developed II during their ICU stay. 119 patients fulfilled the minimum required ICU stay of $>72$h. 60 patients had to be excluded because no advanced hemodynamical monitoring was established. Thus, a total of 59 patients fulfilled all inclusion criteria (Fig 1). Baseline characteristics are presented in Table 1. We identified 33 female and 26 male II patients with an average age of 62.4 $\pm$ 14.6 years. Patients with II had a significantly higher Simplified Acute Physiology Score (SAPS II) score on admission than controls ($47.3 \pm 13.7$ vs. $43.1 \pm 13.1$, p = 0.025). II was associated with a prolongation of the ICU stay ($25.0 \pm 22.2$ vs. $18.5 \pm 16.1$, p = 0.032). ICU-mortality was higher in the II group (66.1%) compared to the control group (32.1%) ($p < 0.0001$). None of the evaluated comorbidities were significantly more prevalent in patients with II.

We found a significant non-linear influence of meanDO$_2$I on ischemia hazard (LRT vs null model: $\chi^2$ (df = 3.23) = 10.536, p = 0.018; LRT for non-linearity: $\chi^2$ (df = 2.23) = 9.281, p = 0.012) (Fig 2A). The application of this model showed, that the relative ischemia hazard (reference: meanDO$_2$I = 500ml/min/m$^2$) is significantly elevated when meanDO$_2$I falls below approximately 250ml/min/m$^2$ and increases disproportionately with smaller values (Fig 2B).

We observed a qualitatively similar relationship between minDO$_2$I and relative ischemia hazard (Fig 3). First, the influence of minDO$_2$I was shown to be linear (LRT vs null model: $\chi^2$ (df = 1.39) = 6.8, p = 0.016; LRT for linearity: $\chi^2$ (df = 1.00) = 5.48, p = 0.019); LRT for non-linearity: $\chi^2$ (df = 0.39) = 1.103, p = 0.191), thus the increase for smaller values is less steep. Secondly, it was observed that the relative ischemia hazard is already significantly elevated at a minDO$_2$I value of approximately 400ml/min/m$^2$ compared to the reference value.

Our assessment of the individual components of DO$_2$I showed that no single component had a significant influence on the ischemia hazard no matter if we adjust for meanDO$_2$I or not (Table 2). Consequently, we could not improve the model fit to our data of the meanDO$_2$I model by adding individual components (all LRT p-values were at least 0.104), but we
observed a significantly poorer model fit when we dropped meanDO$_2$I from the model for each component (all LRT p-values were below 0.024).

Our analysis of lactate levels showed that 51 Patients with II had lactate levels $\geq$ 2mmol/l (86%), eight patients showed lactate levels $<$ 2mmol/l (14%) resulting in a sensitivity of 86.44%. In the control group there were 683 patients with lactate levels $\geq$ 2mmol/l (84%) and 132 (16%) patients with lactate levels $<$ 2mmol/l, leading to a specificity of 16.2%. Receiver

Fig 1. Patient selection flow diagram. II = intestinal ischemia, LOS = length of stay, h = hour.
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| Table 1. Patients baseline characteristics. |
|-------------------------------------------|
|                                           |
| **Intestinal ischemia** | **Nonischemia controls** | **p-value** |
| n                          | 59                        | 815         |
| Sex (m/f)                  | 26/33                     | 494/321     | **0.0136** |
| Age (y)                    | 62.4 ± 14.6               | 60.7 ± 15.9 | 0.3766     |
| SAPS II (points)           | 47.3 ± 13.7               | 43.1 ± 13.1 | **0.0247** |
| Length of stay (d)         | 25.0 ± 22.2               | 18.5 ± 16.1 | **0.0316** |
| ICU-mortality              | 39 (66.1%)                | 262 (32.1%) | $<$0.0001  |
| Congestive heart failure   | 20 (33.9%)                | 205 (25.2%) | 0.1642     |
| Diabetes mellitus          | 25 (42.4%)                | 378 (46.4%) | 0.5903     |
| Peripheral vascular occlusive disease | 8 (13.6%) | 56 (6.9%) | 0.0679     |
| Coronary heart disease     | 8 (13.6%)                 | 155 (19.0%) | 0.3867     |
| COPD                       | 4 (6.8%)                  | 83 (10.2%)  | 0.5041     |
| Artrial fibrillation       | 29 (49.15%)               | 297 (36.44%)| 0.069      |
| Chronic renal disease      | 8 (13.56%)                | 81 (9.94%)  | 0.3714     |
| Nicotine abuse             | 5 (8.47%)                 | 77 (9.45%)  | 1.0        |

Patients baseline characteristics; n = number of patients, m = male, f = female, y = year, SAPS II = simplified acute physiology score II, d = day, ICU = intensive care unit, COPD = chronic obstructive pulmonary disease
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operating characteristics analysis was poor with an Area under the ROC of 0.5324. The analysis of pH also showed a very high sensitivity with 90%, but a very low specificity with 21%. Resulting in a poor receiver operating characteristics analysis with an area under the ROC of 0.52. Furthermore, the variables pCO\textsubscript{2} and ScvO\textsubscript{2} also did not perform well with a sensitivity of 83% and a specificity of 38%, with a resulting ROC analysis of 0.6017 for CO\textsubscript{2} and 77% sensitivity, specificity of 52%, and AUROC of 0.6786 for ScvO\textsubscript{2}, respectively (Fig 4).

Fig 2. A. Regressor plot of meanDO\textsubscript{I} within 72h. DO\textsubscript{I} = oxygen delivery index, h = hour, the solid line shows the regressor plot for meanDO\textsubscript{I}, dashed lines show the standard deviation, above the x-axis the 14.320 DO\textsubscript{I} calculations are plotted as single small lines. B. Relative ischemia risk compared to mean DO\textsubscript{I} within 72h before the onset of intestinal ischemia. Y-axis shows increasing relative ischemia risk with decreasing meanDO\textsubscript{I} values (x-axis, solid line) by DO\textsubscript{I} values below approximately 250ml/min/m\textsuperscript{2} (highlighted by the red marked area), dashed lines show the standard deviation, above the x-axis the 14.320 DO\textsubscript{I} calculations are plotted as single small lines (critical DO\textsubscript{I} values are highlighted as a red line), DO\textsubscript{I} = oxygen delivery index, h = hours. 

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Fig 3. Relative ischemia risk compared to min DO\textsubscript{I} within 72h before the onset of intestinal ischemia. Y-axis shows increasing relative ischemia risk with lower minDO\textsubscript{I} values (x-axis, solid line) by DO\textsubscript{I} values below approximately 400ml/min/m\textsuperscript{2} (highlighted by the red marked area), dashed lines show the standard deviation, above the x-axis the 14.320 DO\textsubscript{I} calculations are plotted as single small lines (critical DO\textsubscript{I} values are highlighted as a red line), DO\textsubscript{I} = oxygen delivery index, h = hours. 

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SVRI had no significant association with ischemia hazard (LRT vs null model: $\chi^2$ (df = 1.41) = 2.522, $p = 0.178$) (Table 3).

**Discussion**

The findings in this study were:

I. There is a critical cut-off value for meanDO$_2$I of approximately 250ml/min/m$^2$ representing a longer state of insufficient oxygen delivery in a 72h timeframe before the clinical diagnosis of II which is affecting the risk for the development of II. Lower meanDO$_2$I values strongly increase risk of II.

Table 2. Individual component of DO$_2$I.

| Component | Unadjusted | Adjusted |
|-----------|------------|----------|
|           | HR         | Coef     | SD | p-value | HR | Coef     | SD | p-value |
| CI        | 0.838      | -0.177   | 0.154 | 0.25    | 0.997  | -0.003   | 0.277 | 0.992 |
| SaO$_2$   | 0.90       | -0.108   | 0.065 | 0.1     | 0.885  | -0.122   | 0.066 | 0.063 |
| Hb        | 1.001      | 0.001    | 0.101 | 0.994   | 1.030  | 0.03    | 0.111  | 0.787 |

Individual component of DO$_2$I; HR = hazard ratio, coef = coefficient, SD = standard deviation, p = p-value, CI = cardiac output index, SaO$_2$ = arterial oxygen saturation, Hb = hemoglobin

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Fig 4. Receiver operating characteristics analysis for lactate, pH, CO$_2$, ScvO$_2$ and the development of intestinal ischemia. Panel A lactate: Area under the ROC curve: 0.5324; sensitivity 86.44% and specificity 16.2% for a cut-off value of lactate $\geq$ 2mmol/l; Panel B pH: Area under the ROC curve: 0.52; sensitivity 90% and specificity 21%; Panel C CO$_2$: Area under the ROC curve: 0.6017; sensitivity 83% and specificity 38%; Panel D ScvO$_2$: Area under the ROC curve: 0.6786; sensitivity 77% and specificity 52%; ROC = Receiver operating characteristic.

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II. Even a single minDOI value smaller than 400ml/min/m² increases the risk for II.

III. Neither Hb, SaO₂ nor CI as individual components of DO₂I showed significant diagnostic superiority compared to DO₂I in predicting II.

IV. Therapeutic decisions based on lactate, pH, CO₂ or ScvO₂ are not useful for the prevention or early detection of II especially because of their low specificity.

V. In our analysis SVRI had no effect on the incidence of II.

**Delivery of oxygen and survival**

To our knowledge no prior study investigated whether there is a crucial DO₂I cut off value for organ dysfunction like II. A meanDO₂I of 250ml/min/m² over 72h on ICU and a minDO₂I value smaller than 400ml/min/m² substantially increases the risk for developing II and could alert the attending clinician accordingly. The fact that minDO₂I has an earlier effect on the development of II may be due to cellular compensatory mechanisms that have not yet been activated, in the sense of ischemic preconditioning.

Ischemic preconditioning reduces ischemia-reperfusion injury by inhibiting and reducing the inflammatory response in the reperfusion phase [31]. Single low DO₂I events without ischemic preconditioning result in reduced mitochondrial ATP generation, as well as other pathological mechanisms. In the subsequent reperfusion, a pronounced inflammatory response occurs, which further exacerbates ischemia [31–33]. Guan et al. [34] showed using vivo microscopy that adverse effects due to short-term ischemia are partly completely reversible in the reperfusion phase. However, they showed that after prolonged periods of ischemia, normal cell structures and functions could not be fully restored in a large proportion of cells and during reperfusion further deterioration occurred.

In the present study, this microscopically proven pathology by Guan et al. [34] is also supported, as short-term low DO₂I values have a markedly lower risk of ischemia than longer-lasting low DO₂I (meanDO₂I) phases.

There are no established guide values for DO₂I and oxygen consumption for critically ill patients. In a normal resting adult the normal DO₂I is approximately 500ml/kg/m² assuming a CI of 2500 ml/min/m², a Hb of 15 g/dl and a SaO₂ of 100%, from which 125ml/min/m² are consumed through the normal metabolism [35]. As a DO₂I of 500ml/min/m² is commonly reported as reference value in healthy subjects and typically not associated with II and post procedural complications it was chosen as a reference value [36, 37]. On top of that a DO₂I of 500ml/min/m² was tested as a safe endpoint for shock resuscitation [38].

Shoemaker et al. studied hemodynamic parameters, DO₂I and oxygen consumption in critically ill patients, showing a correlation between less organ failure as well as survival and supranormal values of DO₂I, oxygen consumption and cardiac index [39–43]. The authors theorized that morbidity and mortality could be reduced in critically ill patients if these parameters were used as therapeutic goals.

| test            | chisq | df   | p-value |
|-----------------|-------|------|---------|
| null model      | 2.522 | 1.414| 0.178   |
| linear          | 1.400 | 1.000| 0.237   |
| non-linear      | 0.641 | 0.414| 0.219   |

Influence of systemic vascular resistance; Chisq = Chi-squared test, df = degrees of freedom

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Subsequently, controlled randomized trials investigated the effect of hemodynamic optimization in critically ill patients, manipulating DO$_2$I to supranormal values [43–50]. Several of these studies [43, 47–51] showed a decrease in mortality and morbidity when DO$_2$I was manipulated to a supranormal value before surgery and during the peri- and postoperative period.

A meta-analysis by Kern et al. [52] summarized relevant prospective randomized trials analyzing hemodynamic optimization in high-risk patients. In trials with hemodynamic optimization before the onset of organ dysfunction a significant reduction in mortality [47–51] could be demonstrated. Hemodynamic optimization after the onset of organ dysfunction however caused no related mortality reduction [44–46, 53]. Our data supports the idea that hemodynamic optimization before II became clinical apparent might prevent these complications in our cases. On the other hand, it remains speculative whether there is a significant risk reduction for II due to supranormal DO$_2$I values.

Effects of Hb, SaO$_2$ and CO on II

Relevant studies in the field utilized standardized protocols to keep DO$_2$I values in normal or supranormal levels by manipulating all DO$_2$I components depending on arbitrarily elected cut-off values for CI, Hb and SaO$_2$ [39–51, 53, 54]. None of them distinguished which component of DO$_2$I is most effective to optimize. In this study we showed, that DO$_2$I as a goal parameter for optimization might be relevant to prevent II, but the individual components seem equally important to prevent II.

The role of lactate, pH, CO$_2$ and ScvO$_2$ in the diagnosis of II

Lactate is a well-known marker of parenchymatous hypoxia regularly reported in studies revising II [55–57] and its measurement is recommended in recent guidelines [3, 9]. On the other hand, many studies and meta-analyses confirm that the classical routine parameters are of no value in distinguishing patients with II from those without [9, 58, 59]. In a retrospective multicenter study by Leone et al. [60] investigating risk factors associated with ICU-mortality in patients with II, lactate levels higher than 2.7mmol/l were found to be an independent predictor for ICU-mortality. Yet the author pointed out that lactate is not a useful tool for diagnosis or exclusion of II, because of its low sensitivity and specificity. Bourcier et al. [61] investigated patients with suspected II and also collected lactate levels, showing no statistically significant difference between lactate levels of II patients and patients without II. In a prospective trial Murray et al. [62] found a significant elevation in D-lactate levels in patients with II compared to controls. Sensitivity and specificity were 90% and 87%. In summary, lactate not differentiated in its D- and L- enantiomers appears to be a good parameter for mortality estimation [60, 63] but not a reliable parameter for the diagnosis of II.

The goal of the study was to evaluate the correlation of DO$_2$I and the development of II in patients treated on the ICU. So, we hypothesize a time dependent clinical inapparent sequence of clinical inapparent inadequate (locoregional) delivery of oxygen, inducing irreversible II and corresponding lactate accumulation leading to clinical detectable sequelae like vasomotor dysfunction and endothelial leak which then enable the clinician at the bedside to diagnose and manage II. We therefore wanted to connote our findings of a “cut-off” DO$_2$I with the corresponding lactate levels. Our findings of relative high mean and minDO$_2$I associated with II might help to explain the relative low sensitivity and specificity of lactate in the diagnosis of II.

Cruz et al. [64] reported an increase in the intestinal-arterial pCO$_2$ gradient in a model of small bowel ischemia-reperfusion that corresponded with the grade of the mucosal damage. In line with that finding, Siniscalchi et al. [65] found a significant lower pH and higher PaCO$_2$ in patients who underwent small bowel transplantation comparing their baseline measurement.
and 120 minutes after reperfusion of the graft. The authors hypothesized that the fall of pH after the revascularization and the concomitant rise in PaCO$_2$ was noted due the increased metabolic activity in the new organ. We hypothesized that an increase in PaCO$_2$ or a reduction of pH, either due to lactic acidosis or due to transient reperfusion of underperfused intestinal organs might be a valuable parameter for II. As shown by our ROC analysis unfortunately neither pH nor PaCO$_2$ showed a clinically useful specificity for the prediction of II. This might be caused by the relative insensitivity of global changes in both parameters compared to direct measurements in the intestinal mucosa. On the other hand, in a substantial part of critical ill patients hypercapnia and the corresponding acidosis are caused by guideline-compliant management [66, 67] and not associated with intestinal ischemia at all. The measurement of the central venous oxygen saturation is discussed in the recent guidelines for the management of septic shock and represents global oxygen extraction and utilization in critically ill patients [68]. As shown by Heino et al. [69] the oxygen extraction in II is increased. Unfortunately, as shown in our ROC analysis corresponding changes in ScvO$_2$ lack the necessary specificity to represent a useful prognostic marker of II in a clinical setting. This finding might be caused by the dichotomy of the parameter regarding oxygen delivery. A low ScvO$_2$ is usually a sign of hypoxia or insufficient cardiac output, an increased ScvO$_2$ usually denotes an impaired oxygen extraction [70, 71].

The role of SVRI in the development of intestinal ischemia

The hypothesis that endo- or exogenous catecholamines may induce II because of reduced oxygen delivery to intraabdominal organs due to mesenteric vasoconstriction is proposed in many guidelines and trials [1, 3, 9, 72]. In this study we utilized systemic vascular resistance index as surrogate for vasoconstriction irrespectively of exogenous catecholamines. We found no significant correlation between SVRI and the incidence of II. It should be noted, as SVRI is the result of the physiological effects of endo- or exogenous catecholamines, our analysis is independent of the catechoalmine therapy and other therapeutical decisions of the attending physicians.

Limitations

Results of this study were potential biased due to a different pre-existing disease profile, the heterogeneity of medical history and the clinical course, for example, new or different comorbidities in the investigated cohort. As it was the goal of this study to evaluate the effects of the delivery of oxygen and its independent parameters (Hb, arterial SaO$_2$ and CI) on the development of II we tried to attenuate these factors by identifying and adjusting for anamnetic proxies and conditions for a higher risk of II like diabetes mellitus, peripheral vascular disease, chronic heart failure, coronary heart and pulmonary diseases and used them for the stratification of the Cox model. Therefore we opted not to include factors like prognostic scores evaluating physiological criteria like APACHE II or SOFA score in the Cox model as they reflect acute severity of illness of the patient and not necessarily predestine the patient for II per se.

As we had no opportunity to acquire advanced hemodynamic data like cardiac output from the patients included in this retrospective study prior to admission to the ICU we explicitly excluded patients with a length of stay shorter than 72h from the study. Naturally we suspect that patients suffering II prior to admission on the ICU might present a significant lower meanDO$_2$I and minDO$_2$I then the II group in this study. Therefore, we acknowledge that we probably evaluated a distinct subgroup of patients suffering II and our findings cannot be extrapolated to all patients with II.
Furthermore we did not account for therapeutic interventions to manage II once the clinical diagnosis was made.

Lastly, in the analysed cohort, surgical patients with abdominal pre-existing conditions might have biased the results.

**Conclusion**

To our knowledge, this is the first study to show a direct correlation between the incidence of II and a critical DO\textsubscript{2}I value. Our findings emphasize the need to keep DO\textsubscript{2}I at an adequate level to prevent deterioration of the patients condition as well as their outcome due to the development of II. This crucial cut-off value for DO\textsubscript{2}I may enable intensive care physicians to identify patients at risk and also allow for optimization of therapy by manipulation of the DO\textsubscript{2}I parameters to prevent II.

**Supporting information**

S1 Dataset. Anonymized data set.
(XLSX)

S2 Dataset. Annotation for the anonymized data set.
(XLSX)

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