Predictors of Response To Intra-Arterial Vasodilatory Therapy of Non-Occlusive Mesenteric Ischemia In Patients With Severe Shock - Results From A Prospective Observational Study

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Abstract

Background: Non-occlusive mesenteric ischemia (NOMI) is a life-threatening condition occurring in patients with shock and is characterized by vasoconstriction of the mesenteric arteries leading to intestinal ischemia and multi-organ failure. Although minimal invasive local intra-arterial infusion of vasodilators into the mesenteric circulation has been suggested as a therapeutic option in NOMI, current knowledge is based on retrospective case series and it remains unclear which patients might benefit. Here, we prospectively analyzed predictors of response to intra-arterial therapy in patients with NOMI.

Methods: Prospective single-center observational study to analyze 28-day mortality (primary outcome) and reduction of blood lactate > 2mmol/l from baseline after 24 hours (key secondary endpoint) in patients with NOMI undergoing intra-arterial vasodilatory therapy. Predictors of response to therapy concerning primary and key secondary endpoint were identified using a) clinical parameters as well as b) data from 2D-perfusion angiography and c) experimental biomarkers of intestinal injury.

Results: A total of 42 patients were included into this study. At inclusion patients had severe shock, indicated by high doses of norepinephrine (NE) (median (Interquartile Range (IQR)) 0.37 (0.21-0.60) µg/kg/min), elevated lactate concentrations (9.2 (5.2-13) mmol/l), and multi-organ failure. Median intestinal fatty-acid binding protein (i-FABP) ($p<0.001$) and smooth muscle protein 22 (SM-22) ($p<0.0001$) plasma concentrations were increased compared to healthy controls indicating significant mucosal and transmural intestinal ischemia at inclusion. 28-day mortality was 71% and higher NE dose and lactate as well as lower thrombocytes, bicarbonate and pH 24 hours following intervention were associated with higher mortality. Patients showed a continuous reduction of lactate following intra-arterial prostaglandin infusion (baseline: (9.2 (5.2-13) mmol/l vs. 24 hours: 4.4 (2.5-9.1) mmol/l, $p<0.001$). 28-day mortality was 59% in patients with a reduction of lactate > 2 mmol/l 24 hours after inclusion ($n=22$), while it was 85% in all other patients ($n=20$) (Hazard Ratio 0.409; 95% CI, 0.14-0.631, $p=0.005$).

Conclusions: A reduction of lactate concentrations was observed following implementation of intra-arterial therapy and lactate reduction was associated with better survival. Our findings concerning outcome predictors in NOMI patients undergoing intra-arterial prostaglandin therapy might help designing a randomized controlled trial to further investigate this therapeutic approach.

Trial registration: Retrospectively registered January 22th 2020 at clinicaltrials.gov (REPERFUSE, NCT04235634), <https://clinicaltrials.gov/ct2/show/NCT04235634?cond=NOMI&draw=2&rank=1>

Background

Non-occlusive mesenteric ischemia (NOMI) is a life-threatening condition that was first described more than 60 years ago in patients with heart failure (1). In the meantime, NOMI has been described in all forms of shock, especially in sepsis (2). The mortality associated with NOMI remains unchanged exceedingly high up to above 90% (3, 4). NOMI accounts for up to 15% of acute mesenteric ischemia cases (5) and is characterized by functional vasoconstriction of the superior mesenteric artery (SMA)

and its smaller branches in the absence of an intraluminal obstruction (2, 4, 5). Spasm of these mesenteric vessels leads to significantly reduced perfusion of the intestine and consequently, mesenteric ischemia, which may result in transmural necrosis. As a consequence of ischemia, the intestinal barrier function can be severely altered resulting in bacterial translocation (6). This process triggers a secondary systemic inflammatory response that may result in remote organ failure (7). NOMI occurs typically in the context of shock, especially following cardiac surgery (1-4), in low output heart failure (1, 2, 4), and a variety of heterogeneous acute critical illnesses all requiring high dose vasopressor therapy such as septic shock (2-4, 8). Various preexisting comorbidities, i.e. heart diseases, chronic or acute kidney disease but also older age and diabetes mellitus increase the risk of developing NOMI (2, 4, 8, 9). Since emergency surgical intestinal resection has repeatedly shown poor survival and even tends to worsen the underlying pathological processes of NOMI (4, 9), current treatment recommendations aim at rapid re-establishment of intestinal perfusion including fluid resuscitation and reduction of vasoconstrictors (10). However, reduction of vasopressor dose is often not feasible in situations of profound shock, and fluid resuscitation does not directly affect underlying mesenteric vasoconstriction. In contrast, minimally invasive local intra-arterial infusion of potent vasodilators into the mesenteric circulation via angiographic cannulation was repeatedly shown to be feasible and effective in counteracting mesenteric vasoconstriction (4, 8, 9), without causing unwanted systemic vascular effects. Although intra-arterial therapy has been established as an interventional therapeutic option in NOMI (10), recommendations are mainly based on small retrospective case series. Importantly, no prospective data exist evaluating criteria that might predict response to local intra-arterial therapy of NOMI.

In this prospective observational study (REPERFUSE) we report clinical outcomes of 42 patients with NOMI undergoing local intra-arterial vasodilatory therapy. The present investigation aimed at identifying predictors of response to therapy concerning survival as well as reversal of intestinal ischemia. For this purpose a) clinical factors as well as b) data from 2D-perfusion angiography and c) experimental biomarkers of intestinal injury are analyzed.

Materials And Methods

Screening and inclusion into the study

This was a prospective, observational, monocentric study investigating outcomes following local intra-arterial prostaglandin therapy in critically ill patients diagnosed with NOMI. The study was conducted in a tertiary care hospital from October 2018 to October 2021. Patients were screened by the medical staff of eight different in house intensive care units (ICUs) for potential existence of NOMI if they fulfilled the following pre-determined inclusion criteria: 1) persistent shock: norepinephrine dose $> 0.2 \mu\text{g/kg/min}$ over > 48 hours AND 2) intestinal failure: paralytic ileus > 24 hours despite prokinetic therapy AND 3) new onset of progressive organ failure (≥ 2 out of six following criteria): increase in vasopressor dose, rise in serum lactate, decrease in Horowitz index, new need for renal replacement therapy, rise in bilirubin, rise in international normalized ratio (INR), or all of the following: rise in alanine-amino-transferase (ALT), aspartate-amino-transferase (AST), creatine-kinase (CK) and lactate dehydrogenase (LDH). Exclusion

criteria were age <18 years and pregnancy. If patients met inclusion criteria, a standardized diagnostic workup following an in house protocol (**Figure 1**) was initiated employing initial biphasic contrast enhanced computed tomography angiography (CT-A) followed by digital subtraction angiography (DSA). Images were acquired using a 64-row scanner (GE LightspeedVCT, GE-Healthcare, Chalfont St.Giles, United Kingdom) or a dual-source CT (Somatom Force, Siemens, Forchheim, Germany) with a reconstructed slice thickness of 1mm. The imaging protocol consisted of an arterial and venous phase of the entire abdomen with threshold based bolus triggering in the aorta. The original radiographic report on CT imaging was independently reviewed by an experienced radiologist. If NOMI was diagnosed and no signs of advanced intestinal necrosis (e.g. free abdominal fluid, pneumatosis intestinalis, portal venous gas) were present, patients were included into the study and intra-arterial vasodilatory therapy was initiated immediately. Prior to final study inclusion, informed consent was obtained from each participant or her/his legal representative. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and approved by the local ethical committee (No. 8092_BO_S_2018). The study was registered at clinicaltrials.gov (REPERFUSE, NCT04235634).

Angiography and local intra-arterial vasodilatory therapy

Vascular access was achieved through the common femoral artery and a 4 French hemostasis sheath (Avanti+, Cordis, Miami Lakes, Florida, USA) was placed. A diagnostic catheter (Radifocus®, Glidecath Cobra2, Terumo Europe, Leuven, Belgium) was advanced in the SMA. Angiography was obtained to verify the correct catheter position. A bolus of 20µg of prostaglandin E1 (Alprostadil, UCB Pharma GmbH, Monheim, Germany) was slowly infused in the SMA over 10 minutes. Subsequently, another angiography documented the early treatment response. The sheath and the catheters were fixed, labeled and attached to a continuous infusion drip of prostaglandin at a dose of 60-80 µg/24 hours depending on patient weight and following previous reported dosing instructions (11-13). The duration of prostaglandin infusion was based on the individual course and continued for at least 24 hours and as long as feasible if clinical improvement was achieved. Clinical improvement was defined as a combination of clinical observations determined by the primarily treating intensivist. Among these criteria of clinical improvement were hemodynamic improvement (indicated by significant reduction of norepinephrine dose compared to baseline), improvement of organ dysfunction (indicated by any reduction of SOFA score), improvement of bowel ischemia (indicated by a significant reduction of lactate concentrations) and resolution of paralytic ileus (indicated by regular bowel movements). Treatment was stopped on individualized decision of the intensive care team if no treatment response was achieved or patient deceased.

End points

The aim of the study was to identify predictors of response to intra-arterial therapy concerning survival as well as reversal of intestinal ischemia. The primary endpoint was 28-day mortality. The key secondary endpoint was a relevant reduction of blood lactate, defined as > 2mmol/l from baseline, 24 hours

following study inclusion. Further secondary endpoints were dose of vasopressor support and degree of organ dysfunction, as indicated by the SOFA score, both at 24 hours following study inclusion. As potential predictors of treatment response were analyzed: a) routine clinical parameters at inclusion and 24 hours after inclusion (available from all patients), b) data from 2D-perfusion angiography at angiographic intervention (from n=30 patients) and c) biomarkers of intestinal ischemia at inclusion (from n=22 patients). These parameters were then stratified for survivors and non-survivors as well as patients with and without a significant reduction of lactate 24 hours following start of intervention, respectively.

Data collection

Routine clinical data were collected at study inclusion and 24 hours following study inclusion using electronic medical records including the patient data monitoring system (PDMS) m-life. SOFA scores were calculated according to the description by Vincent et al. (14). Organ failure was defined as an organ specific SOFA score of equal or greater than two.

2D perfusion angiography

Post-processing of DSA runs was performed on a dedicated workstation (syngo X Workplace® VD20D, Siemens Healthcare) and two radiologists (J.B.H., L.S.B.) agreed upon ROI placement. A reference ROI was fitted to at least two-thirds of the vessel diameter and placed in the SMA next to the tip of the inserted diagnostic catheter and therewith at the location of CM influx. One target ROI was placed in the main stem of the portal vein (ROI-PV), proximal to the bifurcation. A second target ROI was placed in the aorta (ROI-Aorta) close to the origin of the SMA to detect contrast reflux at its origin. Numeric density values for time to peak (TTP), peak density (PD), and the area under the time–density curve (AUC) were recorded. The ratios of the reference to the target ROI, i.e., $TTP\text{-}PV/TTP\text{-}Ref$, $PD\text{-}PV/PD\text{-}Ref$, $AUC\text{-}PV/AUC\text{-}Ref$, $TTP\text{-}Aorta/TTP\text{-}Ref$, $PD\text{-}Aorta/PD\text{-}Ref$, and $AUC\text{-}Aorta/AUC\text{-}Ref$ before and after vasodilatory therapy were calculated. PD is defined as the maximum density in the chosen ROI after CM administration, TTP is characterized as the time from the beginning of the angiographic run to the maximum density within the ROI, and AUC visualizes the density values within the ROI during the span of an angiographic run (15). In addition, we assessed a previously published NOMI score (16, 17) that is comprised of five subjectively assessed categories: vessel morphology, aortal contrast reflux, contrast enhancement of the intestine, distension of the intestine and time to portal vein filling. The score was calculated before and directly after intervention and ranges from 0-11 points, with higher scores indicating more severe angiographic changes characteristic of NOMI.

ELISA measurements

Plasma was taken at inclusion directly before the intervention (n=22 patients) and 24 hours after intervention (n=9 patients) as well as from healthy individuals as controls (n=20). The EDTA plasma samples were centrifuged at 4 °C and 3800 rpm for 10 minutes and stored at –20 °C. Due to various different ICU teams and organizational heterogeneities the blood was taken only in a subset of patients

(n=22). Intestinal fatty-acid binding protein (i-FABP), liver fatty-acid binding protein (L-FABP) are found increased in mucosal intestinal injury (18). Smooth muscle protein 22 (SM22) is a potential plasma marker to detect severe transmural intestinal (7, 19). Enzyme-linked immunosorbent assays (ELISA) were performed for L-FABP and i-FABP from human plasma using the commercially available L-FABP (HK404-01, HycultBiotech, Uden, The Netherlands) and i-FABP kit (HK406-01, HycultBiotech, Uden, The Netherlands) assays, respectively. For L-FABP plasma was diluted 1:20, for i-FABP plasma was diluted 1:2. SM22 was measured in human plasma by commercial human TAGLN/Transgelin/SM22 ELISA kit (LS-F7946, LifeSpan BioSciences, Inc., Seattle, WA, USA). For SM22 ELISA, human plasma was used undiluted. All ELISAs were performed according to manufacturer's instructions.

Statistical analysis

We used GraphPad Prism 7 (La Jolla, CA), IBM SPSS Statistics (version 27 IBM Corp., Armonk, NY) and STATA (version 13.0, StataCorp, College Station, TX) for data analysis and graph generation. Categorical variables are shown as numbers (n) and percentages (%). Continuous variables are shown as median and 25%-75% quartiles, unless indicated otherwise. Variables were checked for normal distribution using the D'Agostino-Pearson omnibus normality test and the Shapiro-Wilk normality test. For comparisons, Fisher's exact test, Chi-squared test, Mann-Whitney U test, Wilcoxon matched – pairs signed rank test, two-sided paired t-test, one-way ANOVA as well as Kruskal-Wallis test were used accordingly. Univariate and multivariate logistic regressions were conducted. Survival data were analyzed by log-rank test as well as by Cox-regression analysis and were visualized by Kaplan-Meier curves. All reported p-values are two-sided unless indicated otherwise; p-values <0.05 were considered statistically significant.

Results

Cohort characterization

From October 2018 to October 2021, a total of 42 patients were diagnosed with NOMI and included into the study. Demographic and clinical parameters at study inclusion are demonstrated in **Table 1**. Most common comorbidities were hypertension, obesity, coronary artery disease (CAD) and chronic kidney disease (CKD). All patients were diagnosed with sepsis. Ninety-five percent of patients had refractory septic shock indicated by high doses of norepinephrine (NE) (Median (Interquartile Range (IQR)) 0.368 (0.212-0.598) µg/kg/min) and severely elevated lactate concentrations (9.2 (5.2-13) mmol/l). All patients suffered from multi-organ failure with 83% presenting with five or six organ failure at inclusion. Seventy-six percent of patients were invasively ventilated, 83% received renal replacement therapy (RRT) and the median SOFA score was 17 (15-19). Routine laboratory parameters that have been associated with NOMI previously (e.g. lactate, CK, LDH, AST, bilirubin) (2, 8, 10, 20) were all significantly elevated before initiation of intra-arterial therapy. Included patients received angiography with initial classification of NOMI morphological severity. The median NOMI score at inclusion was 5 (4-7) points. All patients received a PGE₁ bolus, followed by continuous infusion of PGE₁ for a total of 57 (28-99) hours. The

angiographic cannulation as well as the prostaglandin infusions were found to be safe with no apparent procedure-related or drug-related adverse events.

Biomarkers of intestinal ischemia

In 22 patients, a panel of three biomarkers as surrogates of intestinal ischemia was analyzed at inclusion and compared to 20 healthy controls. Markers of mucosal injury were increased in NOMI patients. Median L-FABP concentrations were more than 10 times higher in NOMI patients compared to healthy controls (197 (179-206) ng/ml vs. 16 (10-18) ng/ml, $p < 0.0001$, **Figure 2A**), and i-FABP was more than 4-fold increased (1990 (671-5186) pg/ml vs. 479 (327-670) pg/ml, $p < 0.001$, **Figure 2C**). SM22, a marker of transmural intestinal ischemia, was also significantly increased in NOMI patients (2116 (1971-2439) pg/ml vs. 1402 (1182-1546) pg/ml, $p < 0.0001$, **Figure 2E**). Additionally, biomaterial at 24 hours after start intervention could be obtained from 9 patients. While L-FABP concentrations did not change significantly (**Figure 2B**), both i-FABP ($p = 0.027$, **Figure 2D**) and SM22 concentrations ($p = 0.004$, **Figure 2F**) decreased significantly within 24 hours of local prostaglandin infusion.

Clinical endpoints

The overall 28-day in-hospital mortality (primary outcome) was 71% (**Figure 3A**). 28-day mortality was 59% in patients, who experienced a reduction of lactate > 2 mmol/l within 24 hours, while it was 85% in all other patients (HR 0.409 (0.14-0.631), $p = 0.005$, **Figure 3B**).

Lactate concentrations continuously increased within the first 48 hours before begin of intra-arterial prostaglandin infusion (lactate at 48 hours before inclusion: (3.3 (1.8-8.6) mmol/l vs. at inclusion: (9.2 (5.2-13) mmol/l ($p = 0.001$), overall from 48 hours before to study inclusion: $p < 0.001$, **Figure 3C**). With intra-arterial prostaglandin therapy, lactate levels (key secondary outcome) declined (lactate at inclusion vs. 6 hours following intervention: 7.3 (4.2-11.3) mmol/l ($p = 0.01$), vs. 12 hours: 6.3 (3.1-9.3) mmol/l ($p < 0.001$), vs. 24 hours: 4.4 (2.5-9.1) mmol/l ($p < 0.001$), overall from inclusion to 24 hours after inclusion: $p = 0.005$, **Figure 3C**). This corresponded to a relative reduction of lactate concentrations of -12% (-36 to +10) at 6 hours, -29% (-50 to +3) at 12 hours and -33% (-69 to -2) at 24 hours (overall $p < 0.001$) compared to baseline lactate (**Figure 3D**). Thirty-two (76%) of patients showed no further increase of lactate and 22 (52%) patients a relevant reduction of lactate > 2 mmol/l within 24 hours.

SOFA scores ($p = 0.569$) and norepinephrine doses ($p = 0.667$) were unchanged at 24 hours after inclusion compared to baseline (results not shown).

Predictors of primary and key secondary endpoint

As potential predictors of primary (28-day mortality) and key secondary outcome (relevant lactate reduction (> 2 mmol/l at 24 hours)) we analyzed: a) routine clinical parameters at inclusion and 24 hours after inclusion, b) data from 2D-perfusion angiography at angiographic intervention and c) experimental biomarkers of intestinal ischemia at inclusion (**Table 2**, **Table 3** and **Suppl. Table 1**, **Suppl. Table 2**).

Survivors (n=12) and non-survivors (n=30) were comparable in most demographic parameters (**Table 2**). Thrombocytes were lower in non-survivors both at inclusion and at 24 hours after inclusion (p=0.024). Non-survivors showed higher INR at inclusion (p=0.017). This corresponded to higher coagulation specific SOFA sub-scores at both inclusion (p=0.003) and 24 hours (p=0.032) after inclusion in non-survivors. NE dose was numerically higher in non-survivors at inclusion (p=0.067). While NE dose decreased in survivors it further increased in non-survivors at 24 hours (p<0.001). Lactate and bicarbonate were not different at inclusion. However, 24 hours following start of intra-arterial therapy, lactate (p=0.002) was significantly higher, whereas bicarbonate (p=0.001) and pH (p=0.034) were significantly lower in later non-surviving patients. L-FABP and SM22 were not different at inclusion in survivors and non-survivors. However, i-FABP was significantly higher in survivors at inclusion (p=0.04). Neither NOMI scores nor various parameters from 2D perfusion angiography at inclusion were different between survivors and non-survivors. On univariate regression analysis no parameters at study inclusion reached statistical significance (**Table 3**). However, higher NE dose and lactate as well as lower thrombocytes, bicarbonate and pH at 24 hours following intra-arterial prostaglandin infusion were all associated with inferior survival. Both higher bicarbonate (p=0.007) and thrombocytes (p=0.016) at 24 hours following therapy were independently associated with better survival in a multivariate regression analysis (**Table 3**).

Patients with (n=22) and without (n=20) a reduction of lactate > 2mmol/l from baseline within 24 hours after initiation of prostaglandin infusion were comparable in most demographic and clinical characteristics at baseline (**Suppl. Table 1**). However, patients with a significant lactate reduction had more frequently gram+ infection (p=0.008) and lower NE doses at inclusion (p=0.021) and 24 hours after inclusion (p=0.009). Lactate concentrations were almost twice as high in patients that significantly reduced lactate 24 hours following start of prostaglandin infusion (p=0.01). Parameters of 2D perfusion angiography were mostly comparable between both groups. However longer time to contrast peak could be found in patients with a significant lactate reduction both in the SMA before vasodilator (p=0.012) and in the aorta after vasodilator administration (p=0.043). Patients with a significant lactate reduction received intra-arterial infusion significantly longer (p=0.001). On univariate regression analysis gram+ infection, higher lactate concentrations at inclusion, higher SMA time to peak values before prostaglandin infusion, lower NE doses at inclusion and 24 hours after inclusion as well as longer infusion time of prostaglandin were associated with significant lactate reduction (**Suppl. Table 2**). On multivariate regression analysis only gram+ infection, lactate concentration at baseline and duration of prostaglandin infusion were independently associated with significant lactate reduction following 24 hours of prostaglandin therapy (**Suppl. Table 2**).

Discussion

In this prospective observational study of 42 critical ill patients with NOMI we investigated outcomes and predictors of response to intra-arterial vasodilatory therapy. In summary, a rapid reduction of lactate concentrations as a surrogate of intestinal ischemia was observed following implementation of intra-arterial therapy and lactate reduction was associated with better survival. Further predictors for response

to intra-arterial vasodilatory therapy were investigated including a variety of clinical routine parameters, data from 2D-perfusion angiography and experimental biomarkers of ischemic intestinal injury.

The inclusion criteria of persistent vasopressor dependent shock, paralytic ileus and new onset organ failure and/or biochemical signs of ischemia were selected for a severely ill patient cohort with profound refractory shock and progressive multi-organ failure. Almost all patients were diagnosed with septic shock, an important risk factor for NOMI (2). A median NOMI score at inclusion of 5 indicated angiographic features of critical NOMI as a score ≥ 3.5 was found to present a threshold for poor outcomes in such patients (17). Both cannulation and prostaglandin infusion were tolerated without any apparent procedure related side effects, which reassures previously made findings (2, 4).

All three investigated biomarkers of intestinal injury were elevated in NOMI patients compared to controls. L-FABP, a nonspecific biomarker of intestinal injury, which is also increased in acute pancreatitis (21) and severe traumatic abdominal injury (22), was more than tenfold increased compared to healthy control. As vasoconstriction of mesenteric arteries in NOMI also may extend to the hepatic artery (23) and L-FABP is released in response to liver ischemia (24), it is conceivable that this may indicate additional hepatic ischemia in patients with NOMI. This hypothesis is further supported by increased values for AST, ALT and bilirubin in all our patients. i-FABP has been explored as a more specific indicator of mucosal intestinal injury (25) in acute mesenteric ischemia in general (26, 27) as well as in NOMI (28) and was found to have a high positive predictive value for diagnosis of NOMI when compared to routine clinical biomarkers (28). Values measured in this cohort were much higher than measured in a patient cohort with acute mesenteric ischemia (19) but lower than measured in a previous cohort of NOMI patients (28). Importantly, no significant difference in i-FABP concentrations could be found between mucosal and transmural ischemia (19). Therefore, we additionally tested SM22, a biomarker that has been suggested to discriminate between mucosal injury and more severe transmural ischemia (19). Patients in the present cohort had significantly higher median SM22 plasma concentrations compared to healthy controls and these levels were within the range that has been previously reported to be associated with histological transmural ischemia (19). This suggests that at least some of our patients already had transmural injury at inclusion despite the absence of radiologic signs of intestinal necrosis (e.g. free abdominal fluid, pneumatosis intestinalis, portal venous gas). In a small subgroup of nine patients additional blood sampling 24 hours following vasodilatory therapy was available. In these patients, i-FABP and SM22 could be significantly decreased.

In our cohort, the 28-day mortality was still high despite all patients receiving prostaglandin infusion. The mortality rate of 71% was however comparable to a recent analysis reporting a 30-day mortality of 66% in NOMI patients of comparable disease severity before commencement of intra-arterial infusion using the vasodilator papaverine (29). Of note, in the same retrospective study, matched control patients, receiving standard medical therapy only, had a miserable survival of only 3% (29). Indeed, a median SOFA score of 17 in this present cohort at inclusion would predict an expected mortality rate of above 90% (30, 31). Severe coagulopathy, indicated by thrombocytopenia and increased INR, was associated with mortality, an observation that confirmed the results of previous retrospective analyses in NOMI patients (2). In

contrast to previous observations (2, 29), NE dose and lactate concentration were not different at inclusion in survivors and non-survivors. However, 24 hours after the start of the intervention, NE dose and lactate concentration were significantly higher while pH and base excess were significantly lower in later non-surviving patients. This observation demonstrates the importance of serial evaluation in adequately predicting the risk of inferior outcomes in NOMI patients undergoing vasodilatory therapy.

28-day mortality was 59% in patients who experienced a reduction of lactate $> 2\text{mmol/l}$ within 24 hours of intra-arterial therapy, while it was 85% in all other patients, suggesting that a relevant reduction of lactate concentration within the first 24 hours following intra-arterial therapy may indicate a better prognosis. At the same time, a continuous increase of lactate concentrations could be observed in this study that was reversed following implementation of intra-arterial vasodilatory therapy. Although uncontrolled, this observation argues for a causal effect of intra-arterial prostaglandin infusion on this surrogate marker of intestinal ischemia. On the one hand initial higher lactate and i-FABP concentrations and on the other hand lower NE doses and an underlying gram+ infection were predictors of such a relevant lactate reduction after 24 hours of prostaglandin infusion. This may suggest that a combination of both a more profound intestinal perfusion deficit (indicated by higher lactate and i-FABP) and a less severe systemic host response dysregulation (lower NE dose, gram+ instead of gram- infection) might dictate the likelihood of a beneficial response to vasodilatory therapy. Correspondingly, a reduction of aortic reflux (indicated by both lower AUC and longer TTP values for the aorta) detected immediately after initial prostaglandin bolus administration was also associated with significant lactate reduction 24 hours later. Disappointingly, neither angiographic NOMI scores and various parameters from 2D perfusion angiography nor markers of intestinal ischemia at inclusion were different between later survivors and non-survivors. The fact that multiple parameters at inclusion that aim at assessing severity of NOMI associated intestinal ischemia fail to predict later outcome certainly underlies the fact that overall prognosis in such critical ill patients with manifest multi-organ failure is only partly dependent on intestinal ischemia itself (32).

This investigation represents the first and largest prospective observational study on NOMI patients to the present date. The strict inclusion and exclusion criteria as well as a rigorous standardized in house diagnostic algorithm allowed for identification of a relatively homogenous cohort of critical ill NOMI patients without apparent evidence of advanced bowel injury requiring emergency surgery. The hypothesis to combine routine clinical parameters of disease severity with innovative 2D perfusion angiography imaging and non-routine biomarkers to predict success of a specific intervention targeting NOMI pathophysiology is novel. However, this study has important limitations, mainly its small sample size, the single center setting, and the lack of a control group. The study was observational, there was no control group and no blinding. Hence, it is unknown if intra-arterial prostaglandin therapy is associated with better outcomes in patients with NOMI. Additionally, 2D-perfusion angiography and bio-sampling were only performed in a subset of patients further limiting the conclusions of this data.

Conclusion

A randomized controlled study, enrolling NOMI patients at the earliest time point possible, is needed to test the value of this therapeutic approach in severe NOMI. This present prospective data demonstrating possible predictors of both mortality as well as initial lactate reduction following commencement of this therapy might assist in future planning of such an investigation.

List Of Abbreviations

ALT = Alanine aminotransferase

ATIII = Antithrombin III

AUC = Area under the curve

AST = Aspartate aminotransferase

BMI = Body mass index

CAD = Coronary artery disease

CK = Creatine kinase

CKD = Chronic kidney disease

CHF = Congestive heart failure

COPD = Chronic obstructive pulmonary disease

CRP = C-reactive protein

ECMO = Extracorporeal membrane oxygenation (vv = venovenous, va = venoarterial)

ELWI = Extravascular lung water index

FFP = Fresh frozen plasma

GCS = Glasgow Coma scale

GEDI = Global enddiastolic index

Hb = Hemoglobin

Hct = Hematocrit

HR = Hazard Ratio

ICU = Intensive care unit

i-FABP = intestinal Fatty-acid binding protein

INR = international normalized ratio

L-FABP = Liver Fatty-acid binding protein

LDH = Lactate dehydrogenase

MAP = Mean arterial pressure

NE = Norepinephrine

NOMI = Non-occlusive mesenteric ischemia

OR = Odds ratio

PCT = Procalcitonine

PD = Peak density

PGE₁ = Prostaglandin E₁

PTCA = Percutaneous transluminal coronary angioplasty

PTT = Partial thromboplastin time

PV = Portal vein

RCT = Randomized controlled trial

RRT = Renal replacement therapy

SMA = Superior mesenteric artery

SM22 = Smooth muscle protein 22

SOFA = Sequential Organ Failure Assessment

TTP = Time to peak

WBC = White blood cell count

Declarations

Ethics approval and consent to participate

The ethical committee of Hannover Medical School approved the protocol (No. 8092_BO_S_2018) and written informed consent was obtained from participants or authorized representatives. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was registered at clinicaltrials.gov (REPERFUSE, NCT04235634).

Consent of publication

Not applicable

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

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Authors contributions

KS, NR, TP, AMH collected clinical data from the PDMS. KS, NR, TP, AMH, JF and SD calculated statistics and generated the figures for publication. NR, TP, AMH, KS and SD performed ELISA experiments. JBH, LSB, BCM performed angiographic interventions and 2D perfusion angiography. BS, JJS, AS, MB, OW, MMH, CF, WK and HJG recruited patients. MMH, TW, HH, HW, BS, JJS, TP, AMH, NR, KS and SD interpreted data and wrote the manuscript. KS and SD had the original idea for this trial and wrote the proposals. All authors read and approved the final manuscript.

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Not applicable.

References

1. Ende N. Infarction of the bowel in cardiac failure. *N Engl J Med*. 1958;258(18):879-81.
2. Stahl K, Busch M, Maschke SK, Schneider A, Manns MP, Fuge J, et al. A Retrospective Analysis of Nonocclusive Mesenteric Ischemia in Medical and Surgical ICU Patients: Clinical Data on Demography, Clinical Signs, and Survival. *J Intensive Care Med*. 2020;35(11):1162-72.

3. Soussi S, Taccori M, De Tymowski C, Depret F, Chaussard M, Fratani A, et al. Risk Factors for Acute Mesenteric Ischemia in Critically Ill Burns Patients-A Matched Case-Control Study. *Shock*. 2019;51(2):153-60.
4. Stahl K, Rittgerodt N, Busch M, Maschke SK, Schneider A, Manns MP, et al. Nonocclusive Mesenteric Ischemia and Interventional Local Vasodilatory Therapy: A Meta-Analysis and Systematic Review of the Literature. *J Intensive Care Med*. 2020;35(2):128-39.
5. Clair DG, Beach JM. Mesenteric Ischemia. *N Engl J Med*. 2016;374(10):959-68.
6. Samel S, Keese M, Kleczka M, Lanig S, Gretz N, Hafner M, et al. Microscopy of bacterial translocation during small bowel obstruction and ischemia in vivo—a new animal model. *BMC Surg*. 2002;2:6.
7. Piton G, Capellier G. Biomarkers of gut barrier failure in the ICU. *Curr Opin Crit Care*. 2016;22(2):152-60.
8. Kramer SC, Gorich J, Oertel F, Scheld H, Heindel W. [Non-occlusive mesenteric ischemia]. *Rofo*. 2003;175(9):1177-83.
9. Trompeter M, Brazda T, Remy CT, Vestring T, Reimer P. Non-occlusive mesenteric ischemia: etiology, diagnosis, and interventional therapy. *Eur Radiol*. 2002;12(5):1179-87.
10. Tilsed JV, Casamassima A, Kurihara H, Mariani D, Martinez I, Pereira J, et al. ESTES guidelines: acute mesenteric ischaemia. *Eur J Trauma Emerg Surg*. 2016;42(2):253-70.
11. Stockmann H, Roblick UJ, Kluge N, Kunze U, Schimmelpenning H, Kujath P, et al. [Diagnosis and therapy of non-occlusive mesenteric ischemia (NOMI)]. *Zentralblatt fur Chirurgie*. 2000;125(2):144-51.
12. Ernst S, Luther B, Zimmermann N, Bohner H, Wilke R, Feindt P, et al. [Current diagnosis and therapy of non-occlusive mesenteric ischemia]. *Rofo*. 2003;175(4):515-23.
13. Schindler G, Bruch HP. [The current status of the diagnosis and therapy of nonocclusive intestinal ischemia (NII)]. *RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin*. 1991;155(2):123-7.
14. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-10.
15. Murray T, Rodt T, Lee MJ. Two-Dimensional Perfusion Angiography of the Foot: Technical Considerations and Initial Analysis. *J Endovasc Ther*. 2016;23(1):58-64.
16. Minko P, Groesdonk H, Stroeder J, Miodek J, Graeber S, Bucker A, et al. A scoring system for the assessment of angiographic findings in non-occlusive mesenteric ischemia (NOMI). *Rofo*.

2012;184(9):805-9.

17. Minko P, Stroeder J, Groesdonk HV, Graeber S, Klingele M, Buecker A, et al. A scoring-system for angiographic findings in nonocclusive mesenteric ischemia (NOMI): correlation with clinical risk factors and its predictive value. *Cardiovasc Intervent Radiol*. 2014;37(3):657-63.
18. Thuijls G, van Wijck K, Grootjans J, Derikx JP, van Bijnen AA, Heineman E, et al. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. *Ann Surg*. 2011;253(2):303-8.
19. Schellekens D, Reisinger KW, Lenaerts K, Hadfoune M, Olde Damink SW, Buurman WA, et al. SM22 a Plasma Biomarker for Human Transmural Intestinal Ischemia. *Ann Surg*. 2018;268(1):120-6.
20. Fujiwara S, Sekine Y, Nishimura R, Tadasa K, Miyazaki S. Treatment of nonocclusive mesenteric ischemia with type B aortic dissection using intra-arterial catheterization after trauma surgery: case report. *Surg Case Rep*. 2018;4(1):5.
21. Kocak E, Akbal E, Koklu S, Adam G. Evaluation of serum L-FABP levels in patients with acute pancreatitis. *Ulus Travma Acil Cerrahi Derg*. 2015;21(1):39-43.
22. Voth M, Holzberger S, Auner B, Henrich D, Marzi I, Relja B. I-FABP and L-FABP are early markers for abdominal injury with limited prognostic value for secondary organ failures in the post-traumatic course. *Clin Chem Lab Med*. 2015;53(5):771-80.
23. Yoshimaru K, Matsuura T, Yanagi Y, Takahashi Y, Kohashi K, Kaku N, et al. Successful Urgent Living Donor Liver Transplantation for Massive Liver Necrosis Accompanied by Nonocclusive Mesenteric Ischemia in a Biliary Atresia Infant: A Case Report. *Transplant Proc*. 2020;52(9):2802-8.
24. Monbaliu D, de Vries B, Crabbe T, van Heurn E, Verwaest C, Roskams T, et al. Liver fatty acid-binding protein: an early and sensitive plasma marker of hepatocellular damage and a reliable predictor of graft viability after liver transplantation from non-heart-beating donors. *Transplant Proc*. 2005;37(1):413-6.
25. Schellekens DH, Grootjans J, Dello SA, van Bijnen AA, van Dam RM, Dejong CH, et al. Plasma intestinal fatty acid-binding protein levels correlate with morphologic epithelial intestinal damage in a human translational ischemia-reperfusion model. *J Clin Gastroenterol*. 2014;48(3):253-60.
26. Memet O, Zhang L, Shen J. Serological biomarkers for acute mesenteric ischemia. *Ann Transl Med*. 2019;7(16):394.
27. Sun DL, Cen YY, Li SM, Li WM, Lu QP, Xu PY. Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-analysis. *Sci Rep*. 2016;6:34371.
28. Matsumoto S, Shiraishi A, Kojima M, Funaoka H, Funabiki T, Saida F, et al. Comparison of diagnostic accuracy for nonocclusive mesenteric ischemia in models with biomarkers including intestinal fatty acid-binding protein in addition to clinical findings. *J Trauma Acute Care Surg*. 2019;86(2):220-5.

29. Winzer R, Fedders D, Backes M, Ittermann T, Grundling M, Mensel B, et al. Local Intra-arterial Vasodilator Infusion in Non-Occlusive Mesenteric Ischemia Significantly Increases Survival Rate. *Cardiovasc Intervent Radiol*. 2020;43(8):1148-55.

30. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26(11):1793-800.

31. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286(14):1754-8.

32. Calame P, Nuzzo A, Ronot M. Local Intra-Arterial Vasodilator Infusion in Non-Occlusive Mesenteric Ischemia: Dealing with One Consequence Hoping to Affect the Cause? *Cardiovasc Intervent Radiol*. 2021;44(3):507-8.

Tables

Table 1: Baseline demographic and clinical characteristics. Demographic and clinical characteristics of the whole patient cohort (n=42) at inclusion. Values are presented as median (25% to 75% interquartile range) or if categorical as numbers and percentages.

Category	Median (IQR)/No (%)
	(n=42)
Age - yr	61 (48-70)
Sex - no (%)	
male	22 (52.4)
female	20 (47.6)
BMI - kg/m ²	27.7 (23.3-29.8)
Comorbidities - no (%)	
Adipositas	15 (35.7)
Hypertension	24 (57.1)
Diabetes	8 (19)
COPD	4 (9.5)
Heart insufficiency	11 (26.2)
CAD	16 (38.1)
CABG	4 (9.5)
PTCA	10 (23.8)
CKD	15 (35.7)
chronic renal replacement therapy	10 (23.8)
immunosuppression	3 (7.1)
Sepsis - no (%)	42 (100)
Side of infection - no (%)	
pulmo	23 (54.8)
abdomen	33 (78.6)
urogenital	8 (19)
soft tissue	11 (26.2)
endocarditis	3 (7.1)
more than one	27 (64.3)
identified pathogen - no (%)	
gram+	15 (35.7)

gram-	20 (47.6)
viral	3 (7.1)
fungi	11 (26.2)
more than one	13 (31)
non identified	11 (26.2)
Renal replacement therapy - no (%)	32 (76.2)
Invasive ventilation – no (%)	35 (83.3)
Oxygenationindex (PaO ₂ /FiO ₂)	200 (134-286)
SOFA-Score– points	17 (15-19)
Norepinephrine - no (%)	40 (95.2)
Norepinephrine dose - µg/kg/min	0.368 (0.212-0.598)
Argipressin– no (%)	9 (21.4)
Dobutamine– no (%)	4 (9.5)
Organ failure - no (%)	
respiratory (PaO ₂ /FiO ₂ <300mmHg)	39 (92.9)
coagulation (Thrombocytes<100 ³ /µl)	32 (76.2)
liver (Bilirubin>33µmol/l)	32 (76.2)
cardiovascular (vasopressor or inotrope)	40 (95.2)
neurological (GCS<13)	35 (83.3)
renal (Creatinine>170µmol/l)	37 (88.1)
Multi organ failure - no (%)	
2	0 (0)
3	4 (9.5)
4	2 (4.8)
5	16 (38.1)
6	19 (45.2)
pH	7.27 (7.18-7.36)
Bicarbonate - mmol/l	20 (16-22)
Lactate - mmol/l	9.2 (5.2-13)

CK - IU/l	1748 (332-5400)
LDH - U/l	1174 (526-3877)
AST - U/l	267 (143-1422)
ALT - U/l	127 (57-390)
Bilirubin - $\mu\text{mol/l}$	78 (30.5-158)
Leucocytes - 1000/ μl	10.7 (7.9-21.2)
CRP - mg/l	108 (44-182)
PCT - $\mu\text{g/l}$	5.7 (1.8-23.6)
Thrombocytes - 100 ³ / μl	69 (34.5-141)
Simplified NOMI score - points	5 (4-7)

ABBREVIATIONS:

ALT – Alanine aminotransferase, ATIII – Antithrombin III, AUC – Area under the curve, AST – Aspartate aminotransferase, BMI – Body mass index, CAD – Coronary artery disease, CK – creatine kinase, CKD – Chronic kidney disease, COPD – Chronic obstructive pulmonary disease, CRP – C-reactive protein, GCS – Glasgow Coma scale, LDH – Lactate dehydrogenase, NE – Norepinephrine, PCT – Procalcitonine, PTCA – Percutaneous transluminal coronary angioplasty, SOFA – Sequential Organ Failure Assessment

Table 2: Demographic, clinical, angiographic and biochemical characteristics for non-surviving (n=30) and surviving (n=12) patients. Values are presented as median (25% to 75% interquartile range) or if categorical as numbers and percentages. Peak density (PD), Time to peak (TTP) and Area under the curve (AUC) are in relation to the superior mesenteric artery (SMA) as reference.

Category	deceased	alive	p
	(n=30)	(n=12)	
Age - yr	58 (48-70)	67 (45-73)	0.534
Sex - no (%)			0.379
male	17 (56.7)	5 (41.7)	
female	13 (43.3)	7 (58.3)	
BMI - kg/m ²	26.2 (21.9-28.9)	29.2 (26.7-30.4)	0.043
Comorbidities - no (%)			
Adipositas	9 (30)	6 (50)	0.222
Hypertension	15 (50)	9 (75)	0.139
Diabetes	6 (20)	2 (16.7)	0.804
COPD	4 (13.3)	0 (0)	0.184
Heart insufficiency	7 (23.3)	4 (33.3)	0.505
CAD	13 (43.3)	3 (25)	0.269
CABG	4 (13.3)	0 (0)	0.184
PTCA	8 (26.7)	2 (16.7)	0.492
CKD	13 (43.3)	2 (16.7)	0.103
chronic renal replacement therapy	8 (26.7)	2 (16.7)	0.492
immunosuppression	2 (6.7)	1 (8.3)	0.850
Sepsis - no (%)	30 (100)	12 (100)	1
Side of infection - no (%)			
pulmo	19 (63.3)	4 (33.3)	0.078
abdomen	25 (83.3)	8 (66.7)	0.234
urogenital	5 (16.7)	3 (25)	0.534
soft tissue	9 (30)	2 (16.7)	0.375
endocarditis	1 (3.3)	2 (16.7)	0.130
more than one	19 (63.3)	8 (66.7)	0.839
identified pathogen - no (%)			
gram+	8 (26.7)	7 (58.3)	0.053

gram-	14 (46.7)	6 (50)	0.845
viral	2 (6.7)	1 (8.3)	0.850
fungi	8 (26.7)	3 (25)	0.912
more than one	8 (26.7)	5 (41.7)	0.342
non identified	9 (30)	2 (16.7)	0.375
At inclusion			
SOFA-Score - points	17.5 (15.8-19)	16 (12.5-18.8)	0.221
Coagulation SOFA - points	2 (2-3)	0.5 (0-2)	0.003
Norepinephrine - no (%)	28 (93.3)	12 (100)	0.359
Norepinephrine dose - µg/kg/min	0.411 (0.253-0.631)	0.241 (0.182-0.442)	0.067
Argipressin– no (%)	7 (23.3)	2 (16.7)	0.634
Dobutamine– no (%)	4 (13.3)	0 (0)	0.184
Invasive ventilation – no (%)	25 (83.3)	10 (83.3)	1.000
Oxygenationindex (PaO ₂ /FiO ₂)	202 (125-301)	195 (158-237)	0.765
Renal replacement therapy - no (%)	23 (76.7)	9 (75)	0.909
Organ failure - no (%)			
respiratory (PaO ₂ /FiO ₂ <300mmHg)	29 (96.7)	10 (83.3)	0.130
coagulation (Thrombocytes<100 ³ /µl)	26 (86.7)	6 (50)	0.012
liver (Bilirubin>33µmol/l)	23 (76.7)	9 (75)	0.909
cardiovascular (vasopressor or inotrope)	28 (93.3)	12 (100)	0.359
neurological (GCS<13)	26 (86.7)	9 (75)	0.359
renal (Creatinine>170µmol/l)	27 (90)	10 (83.3)	0.547
Multi organ failure - no (%)			
2	0 (0)	0 (0)	
3	3 (10)	1 (8.3)	0.868
4	1 (3.3)	1 (8.8)	0.492
5	10 (33.3)	6 (50)	0.315
6	16 (53.3)	3 (25)	0.096

pH	7.26 (7.16-7.34)	7.34 (7.21-7.39)	0.180
Bicarbonate - mmol/l	19 (16-22)	20.5 (18.25-24)	0.179
Lactate - mmol/l	9.9 (5.4-13.5)	8.6 (4.8-12.6)	0.409
CK - U/l	1729 (280-3106)	3270 (507-9938)	0.291
LDH - U/l	1305 (546-4658)	859 (419.5-2883.3)	0.525
AST - U/l	635 (176-2911)	204 (117-724)	0.877
ALT - U/l	173 (58-407)	78 (38-234)	0.573
Bilirubin - µmol/l	85 (28-172)	71 (47-120)	0.633
Creatinine - µmol/l	85 (59.3-132.3)	100 (74-236.3)	0.152
Urea - mmol/l	4.6 (3.6-9)	5.8 (4.5-14.5)	0.204
Hb - g/dl	8.8 (7.7-9.9)	10.4 (8.9-11)	0.097
Hkt - %	25.3 (23.4-29.9)	30.6 (26.5-34.1)	0.083
Leucocytes - 1000/µl	10.1 (6.3-19.8)	14.4 (9.1-26.3)	0.441
CRP - mg/l	108 (43-246)	108 (48-150)	0.139
PCT - µg/l	5.9 (1.6-27.9)	5.5 (3.8-14.9)	0.929
Thrombocytes - 100 ³ /µl	54 (31-94)	146 (59.8-189)	0.054
INR	1.77 (1.25-2.13)	1.40 (1.29-1.72)	0.017
PTT - sec	54 (45-65.5)	53 (42-69)	0.931
ATIII - mg/dl	42.5 (34.5-55.8)	57 (46.5-62.5)	0.254
i-FABP - pg/ml	1377 (422-4795)	5676 (1588-7978)	0.04
SM22 - pg/ml	2132 (2031-2435)	1968 (1760-2449)	0.23
L-FABP - ng/ml	194 (178-207)	201 (177-207)	0.508
After 24 hours			
SOFA-Score - points	17.5 (15-20)	17 (13-18)	0.152
Coagulation SOFA - points	2 (1.5-3.5)	2 (1-2)	0.032
Norepinephrine - no (%)	28 (93.3)	10 (83.3)	0.319
Norepinephrine dose - µg/kg/min	0.461 (0.248-0.733)	0.155 (0.053-0.205)	< 0.001
Argipressin - no (%)	6 (20)	2 (16.7)	0.804

Dobutamine - no (%)	4 (13.3)	1 (8.3)	0.651
Invasive ventilation – no (%)	25 (83.3)	10 (83.3)	1
Oxygenationindex (PaO ₂ /FiO ₂)	207 (138-314)	251 (223-280)	0.519
Organ failure - no (%)			
respiratory (PaO ₂ /FiO ₂ <300mmHg)	26 (86.7)	10 (83.3)	0.780
coagulation (Thrombocytes<10 ³ /μl)	27 (93.1)	10 (83.3)	0.337
liver (Bilirubin>33μmol/l)	24 (80)	9 (81.8)	0.896
cardiovascular (vasopressor or inotrope)	28 (93.3)	11 (91.7)	0.850
neurological (GCS<13)	25 (83.3)	9 (75)	0.534
renal (Creatinine>170μmol/l)	28 (93.3)	9 (75)	0.097
Multi organ failure - no (%)			
2	1 (3.3)	1 (8.3)	0.492
3	1 (3.3)	0 (0)	0.522
4	4 (13.3)	0 (0)	0.184
5	7 (23.3)	4 (33.3)	0.505
6	17 (56.7)	6 (50)	0.695
pH	7.32 (7.26-7.36)	7.4 (7.34-7.44)	0.034
Bicarbonate - mmol/l	22 (18.5-24)	26 (22.5-27)	0.001
Lactate - mmol/l	6.6 (3.5-12.8)	2.4 (1.4-4.1)	0.002
CK - IU/l	1487 (504-5875)	1851 (722-33115)	0.504
LDH - U/l	1397 (443-5818)	885 (336-1345)	0.438
AST - U/l	1065 (618-4168)	420 (133-1218)	0.382
ALT - U/l	320 (173-1418)	130 (46.8-410.3)	0.606
Bilirubin - μmol/l	85 (41-169)	67 (35-111)	0.369
Creatinine - μmol/l	50 (34-102)	74.5 (48.3-144.3)	0.235
Urea - mmol/l	3.3 (1.7-7.1)	5.9 (2.3-13.1)	0.123
Hb - g/dl	8.6 (7.9-9.9)	9.1 (8.5-10.5)	0.470
Hct - %	24.9 (22.1-29.2)	27.2 (25.1-30.1)	0.367
Leucocytes - 1000/μl	12.9 (6.8-19.1)	12.8 (9-22)	0.943

CRP - mg/l	96.5 (41.8-226)	121 (72.5-187)	0.764
PCT - µg/l	4.9 (1.1-22.7)	5.8 (3.65-17.45)	0.818
Thrombocytes - 1000/µl	59 (20.5-102)	97 (68.3-138.8)	0.024
INR	1.85 (1.36-2.24)	1.46 (1.28-2.11)	0.239
PTT - sec	53 (44.3-65.3)	55 (40-61.3)	0.280
ATIII - mg/dl	51 (39.5-58)	53.5 (47-66.5)	0.123
2D-perfusion angiography (directly pre-vasodilator)			
Simplified NOMI score	5 (4-7)	5 (3-7)	0.876
PD-PV	0.67 (0.47-0.1.31)	0.62 (0.57-1.88)	0.402
TTP-PV - sec	11.57 (9.92-13.21)	10.88 (9.91-14.18)	0.608
AUC-PV	0.56 (0.29-0.97)	0.75 (0.38-1.58)	0.423
PD-Aorta	0.71 (0.28-1.55)	1.68 (0.28-6.33)	0.326
TTP-Aorta - sec	6.76 (6.03-9.73)	7 (5.62-9.53)	0.741
AUC-Aorta	0.64 (0.43-1.56)	1.36 (0.23-5.36)	0.380
2D perfusion angiography (directly post-vasodilator)			
Simplified NOMI score	2.5 (1-3)	2 (1-3.3)	0.633
PD-PV	0.88 (0.39-1.83)	1.37 (0.34-1.65)	0.565
TTP-PV - sec	10.28 (7.88-12.07)	10.24 (9.69-11.52)	0.777
AUC-PV	0.66 (0.5-0.94)	0.69 (0.15-0.81)	0.316
PD-Aorta	0.48 (0.31-1.29)	0.39 (0.24-1.26)	0.430
TTP-SMA - sec	7.79 (6.28-9.99)	7.37 (6.64-8.27)	0.493
AUC-Aorta	0.47 (0.3-1.37)	0.34 (0.20-1.13)	0.473
Association with other outcomes			
Lactate (at 24 hrs after inclusion)			
Reduction of lactate - no (%)	21 (70)	11 (91.7)	0.136
Δlactate - mmol/l	-1 ((-6)-(+1.2))	-5 ((-8.6)-(-1.7))	0.082
Δlactate - %	-18.5 ((-57.4)-(+17.9))	-64.6 ((-75.9)-(-35.6))	0.019
Organ dysfunction (at 24 hrs after inclusion)			

Reduction of SOFA - no (%)	8 (26.7)	6 (50)	0.147
ΔSOFA - points	0 ((-1)-(+2))	-0.5 ((-1)-(+0.75))	0.421
SOFA change - %	0 ((-5.7)-(+12.4))	-2.4 ((-9.3)-(+4.7))	0.276
Vasopressor support (at 24 hrs after inclusion)			
Reduction of norepinephrine - no (%)	12 (40)	9 (75)	0.040
ΔNE - µg/kg/min	0.0 ((-0.11)-(+0.15))	-0.09 ((-0.28)-(-0.00))	0.164
ΔNE - %	0.0 ((-20.4)-(+43.1))	-38.0 ((-84.6)-(-8.9))	0.058

ABBREVIATIONS:

ALT – Alanine aminotransferase, ATIII – Antithrombin III, AUC – Area under the curve, AST – Aspartate aminotransferase, BMI – Body mass index, CAD – Coronary artery disease, CK – creatine kinase, CKD – Chronic kidney disease, COPD – Chronic obstructive pulmonary disease, CRP – C-reactive protein, GCS – Glasgow Coma scale, Hb – Hemoglobin, Hct – Hematocrit, i-FABP – intestinal Fatty-acid binding protein, INR – international normalized ratio, LDH – Lactate dehydrogenase, L-FABP – Liver Fatty-acid binding protein, NE – Norepinephrine, PCT – Procalcitonine, PD – Peak density, PTCA – Percutaneous transluminal coronary angioplasty, PTT – Partial thromboplastin time, PV – Portal vein, SM22 – Smooth muscle protein 22, SOFA – Sequential Organ Failure Assessment, TTP – Time to peak

Table 3: Predictors of primary outcome. Primary outcome was 28-day mortality. Shown are results of both univariate and multivariate logistic regression analyses.

characteristic	univariate			multivariate		
	OR	95% CI	p	OR	95% CI	p
<i>At inclusion</i>						
BMI - kg/m ²	0.852	0.723 - 1.005	0.057			
INR	3.245	0.726 - 14.50	0.123			
Thrombocytes - 1000/ μ l	0.993	0.985 - 1.001	0.071			
iFABP – pg/ml	1.000	0.999 - 1.000	0.058			
<i>After 24h</i>						
Norepinephrine dose - μ g/kg/min	139.023	2.84 - 6801.66	0.013			
pH	0.000	0.000 - 0.592	0.038			
Bicarbonate - mmol/l	0.659	0.488 - 0.892	0.007	0.586	0.397 - 0.863	0.007
Lactate - mmol/l	1.364	1.044 - 1.782	0.023			
Thrombocytes - 1000/ μ l	0.985	0.971 - 0.999	0.037	0.976	0.957 - 0.996	0.016

ABBREVIATIONS:

BMI – Body mass index, i-FABP – intestinal Fatty-acid binding protein, INR – international normalized ratio, PTT – Partial thromboplastin time

Figures

Figure 1

Standardized diagnostic workup for patients with suspected NOMI. If patients met inclusion criteria, a standardized diagnostic workup following an in house protocol was initiated employing initial biphasic contrast enhanced computed tomography angiography (CT) and digital subtraction angiography (DSA). If both examinations suggested presence of NOMI and excluded complications that required emergency surgical exploration a joint decision (Surgery, Critical Care, Interventional Radiology Team) was made to commence on intra-arterial prostaglandin therapy. If patients or their legal representative gave informed consent, patients were included into the study.

Figure 2

Biomarkers of intestinal ischemia. Violin plots showing analysis of L-FABP (A), i-FABP (C) and SM22 (E) in NOMI patients (n=22) at inclusion compared to healthy controls (Ctrl) (n=20). Change of L-FABP (B), i-FABP (D) and SM22 (F) after 24 hours of prostaglandin therapy compared to baseline in a subset of NOMI patients (n=9).

Figure 3

Primary and key secondary outcomes. Kaplan Meier graphs showing the 28-day survival course in the overall cohort (primary outcome **(A)**) and in patients stratified for lactate reduction > 2mmol/l **(B)**. Violine plots showing time course of lactate concentration 48, 24, 12 and 6 hours before inclusion, at inclusion as well as after 6, 12 and 24 hours (key secondary outcome) following inclusion **(C)**. Violine plots demonstrating reduction of lactate concentration in relation to baseline at 6, 12 and 24 hours following inclusion **(D)**.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Suppl.Table1.doc](#)
- [Suppl.Table2.doc](#)