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ORIGINAL SCIENTIFIC PAPER

Acute mesenteric ischaemia in refractory shock on veno-arterial extracorporeal membrane oxygenation

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Background Acute mesenteric ischaemia is a severe complication in critically ill patients, but has never been evaluated in patients on veno-arterial extracorporeal membrane oxygenation (V-A ECMO). This study was designed to determine the prevalence of mesenteric ischaemia in patients supported by V-A ECMO and to evaluate its risk factors, as well as to appreciate therapeutic modalities and outcome.

Methods In a retrospective single centre study (January 2013 to January 2017), all consecutive adult patients who underwent V-A ECMO were included, with exclusion of those dying in the first 24 hours. Diagnosis of mesenteric ischaemia was performed using digestive endoscopy, computed tomography scan or first-line laparotomy.

Results One hundred and fifty V-A ECMOs were implanted (65 for post-cardiotomy shock, 85 for acute cardiogenic shock, including 39 patients after refractory cardiac arrest). Overall, median age was 58 (48–69) years and mortality 56%. Acute mesenteric ischaemia was suspected in 38 patients, with a delay of four (2–7) days after ECMO implantation, and confirmed in 14 patients, that is, a prevalence of 9%. Exploratory laparotomy was performed in six out of 14 patients, the others being too unstable to undergo surgery. All patients with mesenteric ischaemia died. Independent risk factors for developing mesenteric ischaemia were renal replacement therapy (odds ratio (OR) 4.5, 95% confidence interval (CI) 1.3–15.7, p=0.02) and onset of a second shock within the first five days (OR 7.8, 95% CI 1.5–41.3, p=0.02). Conversely, early initiation of enteral nutrition was negatively associated with mesenteric ischaemia (OR 0.15, 95% CI 0.03–0.69, p=0.02).

Conclusions Acute mesenteric ischaemia is a relatively frequent but dramatic complication among patients on V-A ECMO.

Keywords Acute cardiovascular care • cardiogenic shock • cardiac arrest • veno-arterial ECMO • mesenteric ischaemia

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Introduction

Acute mesenteric ischaemia is a dreadful condition leading rapidly to shock and ultimately death.[1] While arterial embolism or thrombosis are responsible for most of the cases, non-occlusive acute mesenteric ischaemia more often complicates the evolution of critically ill patients, resulting from severe hypoperfusion states.[2] Indeed, between 6% and 16% of patients with septic shock die of acute mesenteric ischaemia.[3] More specifically, the prevalence of acute mesenteric ischaemia is less than 0.5% after cardiac surgery, but raises to 10% among post-cardiac surgery patients with multi-organ failure.[4,5] In addition, acute mesenteric ischaemia is likely delayed or under-diagnosed, with acute mesenteric ischaemia being the ultimate diagnosis in 20% of septic shock mimickers.[6] The high mortality rate, ranging between 58%[7] and 96%[8] in critically ill patients, advocates for an early and accurate diagnosis of this complication.

Nowadays, the most severe patients with cardiogenic shock or with selected refractory cardiac arrest may receive mechanical support by veno-arterial extracorporeal membrane oxygenation (V-A ECMO).[9–11] Strikingly, acute mesenteric ischaemia has never been evaluated in patients with refractory shock requiring V-A ECMO, whereas this population has risk factors for acute mesenteric ischaemia, including vascular comorbidities, cannula in the aorta, compromise in vascular/myocardial performance, arrhythmias or high dose of vasopressor.[7]

Our hypothesis was that acute mesenteric ischaemia was frequent in patients with refractory shock requiring V-A ECMO and associated with dismal prognosis. Thus, our aims were to determine first the prevalence of acute mesenteric ischaemia in patients treated by V-A ECMO and second to evaluate risk factors, as well as to assess therapeutic modalities and outcomes of these patients.

Materials and methods

Study design and population

We performed a retrospective study in the cardiovascular surgical intensive care unit (ICU) of a tertiary hospital referral centre for medical/surgical cardiac emergencies (Henri Mondor Hospital, Créteil, France).[12]

All consecutive adult patients requiring V-A ECMO from January 2013 to January 2017 for a refractory cardiogenic shock or cardiac arrest were included.[13] We excluded patients who died within 24 h after V-A ECMO implantation. Patients who received two V-A ECMO supports during hospitalization (n=3) were considered as independent cases (none experienced mesenteric ischaemia).

V-A ECMO management

In the case of acute cardiogenic shock or post-cardiotomy cardiogenic shock refractory to conventional management, or refractory cardiac arrest, peripheral V-A ECMO could be decided after multidisciplinary consensus.[14,15] Initial flow was set at 50–65 mL/kg per min and adjusted according to clinical and biological signs of hypoperfusion.[15] An intra-aortic balloon pump (IABP) was added in the case of velocity time integral <5–6 cm and pulse arterial pressure <10 mmHg. V-A ECMO weaning was performed according to recommendations.[16] Norepinephrine was the vasopressor of choice to maintain a mean arterial pressure of 65–70 mmHg. Systemic anticoagulation was started at day 1 post-implantation, except in the case of major bleeding. Unfractionated heparin was adjusted to target an anti-Xa assay of 0.3–0.5 UI/mL. Anti-platelet agent was added in the case of ischaemic heart disease. Renal-replacement therapy (RRT) was initiated in the case of severe metabolic acidosis (pH <7.15 and bicarbonates <15 mmol/L), hyperkalaemia refractory to medical treatment, or symptomatic fluid overload with anuria. Enteral nutrition was begun at day 2 (with the aim of achieving 20–25 kcal/kg per day at day 5); if digestive intolerance occurred despite prokinetics, parenteral nutrition was initiated.

Acute mesenteric ischaemia management

Patients with suspicion of acute mesenteric ischaemia underwent either digestive endoscopy, abdominal computed tomography (CT) scan or emergency gastro-intestinal surgery to confirm or inform the diagnosis. The diagnosis of acute mesenteric ischaemia was based on the analysis of digestive endoscopy or abdominal CT scans or perioperative findings.[7,8] Acute mesenteric ischaemia was suspected in the case of persistent or worsening shock, melena, rectal bleeding or abdominal distension, or unresolving hyperlactataemia. According to our protocol, endoscopy (rectosigmoidoscopy or colonoscopy) was the first-line exam. Ischaemic colitis was classified in three stages:[17] alternating normal mucosae with mild mucosal lesions as stage I, longitudinal ulcers with clear limits with bleeding submucosae as stage II, and grey-black appearance of the mucosa and extensive necrosis of the lamina propria as stage III. A contrast-enhanced abdominal CT scan, with unenhanced early arterial and portal venous phases, could also be performed after digestive endoscopy (or if endoscopy was inconclusive despite persistent suspicion) to look for signs of vascular insufficiency or ischaemic intestinal injury and arguments for an aetiology of acute mesenteric ischaemia (occlusive or non-occlusive).[18] If acute mesenteric ischaemia was highly suspected, while endoscopy was not immediately available and the patient's severity did not allow for CT scan, a surgical exploration was directly performed.

In agreement with surgical recommendations,[19,20] an exploratory laparotomy was performed in the case of a stage II ischaemic colitis associated with persistent or worsening multi-organ failure or a stage III ischaemic colitis, or evidence of peritonitis, perforation, or acute mesenteric ischaemia on CT scan. If the patient's condition was considered too unstable to be transferred to the operating room, laparotomy was refuted.

Data collection

Data were retrospectively extracted from electronic and paper records.

At ECMO implantation, we collected demographics, characteristics and co-morbidities, indication of V-A ECMO, Simplified Acute Physiology Score (SAPS) II, need for IABP and relevant biological parameters. Vasoactive-Inotropic Score (VIS) was calculated as dobutamine dose (μg/kg per min) + 100× epinephrine dose (μg/kg per min) + 100× norepinephrine dose (μg/kg per min).[21]

Within five days after ECMO implantation, we collected: de novo atrial fibrillation, onset of second shock (i.e. septic, haemorrhagic shock or worsening of vasoplegia without evidence of sepsis, defined as a 20% increase of norepinephrine dose lasting for more than 8 h) with the maximum dose of norepinephrine, RRT and route of feeding (enteral or parenteral). On the day of the suspicion, we collected ECMO flow, use of anticoagulant/anti-platelet agents, use of antimicrobial therapy for more than 24 h before acute mesenteric ischaemia suspicion. Digestive symptoms and relevant biological parameters on the day of the suspicion were also noticed.

We extracted surgical management, length of stay and ICU survival of the patients.

Ethics and consent

According to French law, patients or next of kin were informed at admission of the anonymous data extraction and analysis from medical files.[22] The Comité d'Ethique de la Recherche en Anesthésie-Réanimation approved this study (CERAR, IRB 00010254-2019-031). Data are presented according to STROBE guidelines.[23]

Statistical analysis

Continuous variables were summarized using median (interquartile range), or mean (standard deviation), as appropriate. Categorical variables were reported as proportions. Missing data were handled using case-complete analysis.

Patients with and without mesenteric ischaemia were compared regarding relevant explanatory variables (demographic data, comorbidities, admission Sequential Organ Failure Assessment score, SAPS II, biological parameters and the need for organ support in the first five days). We performed χ^2 test for categorical variables, and Student *t*-test, Mann–Whitney or Kruskall–Wallis test, when appropriate, for continuous variables. A multivariable analysis was performed using logistic regression including admission and early in-ICU factors associated with acute mesenteric ischaemia in univariate analysis. Among these factors with p value<0.15, only three clinically relevant factors were studied, due to the low number of events.

All tests were two-sided, with $p<0.05$ considered statistically significant. We performed analysis using STATA/SE 14.0 (College Station, Texas, USA).

Results

During this four-year period, 197 patients required V-A ECMO support. Among them, 47 were excluded because they died within 24 h of V-A ECMO implantation (the vast majority were admitted for refractory cardiac arrest). Finally, this study focused on 150 V-A ECMOs (*Figure 1*).

Characteristics of the patients

Patients were mainly men (71%) with an age of 58 (48–69) years. Cardiovascular co-morbidities are reported in *Table 1*.

V-A ECMO indications were mainly for acute cardiogenic shock (57%, including 39 cases of refractory cardiac arrests). Peripheral femoral V-A ECMO was inserted in all cases. IABP was used in 19% of patients.

Acute mesenteric ischaemia suspicion and application of the diagnosis strategy

Acute mesenteric ischaemia was suspected in 38 patients supported by V-A ECMO (25%). The delay between V-A ECMO initiation and mesenteric ischaemia suspicion was four (2–7) days (*Figure 2*). Symptomatology and patients' characteristics on the day of the suspicion are reported in *Table 2*.

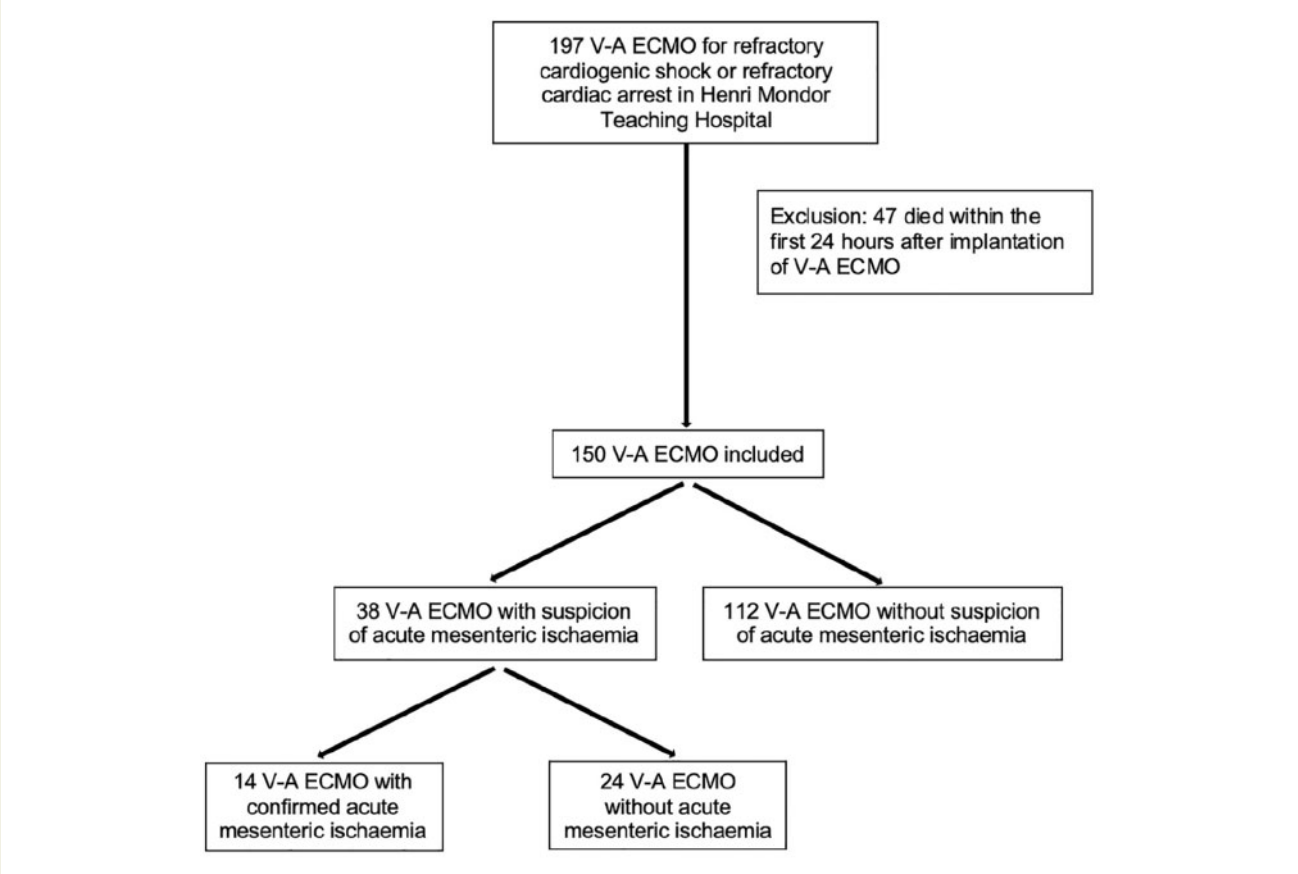
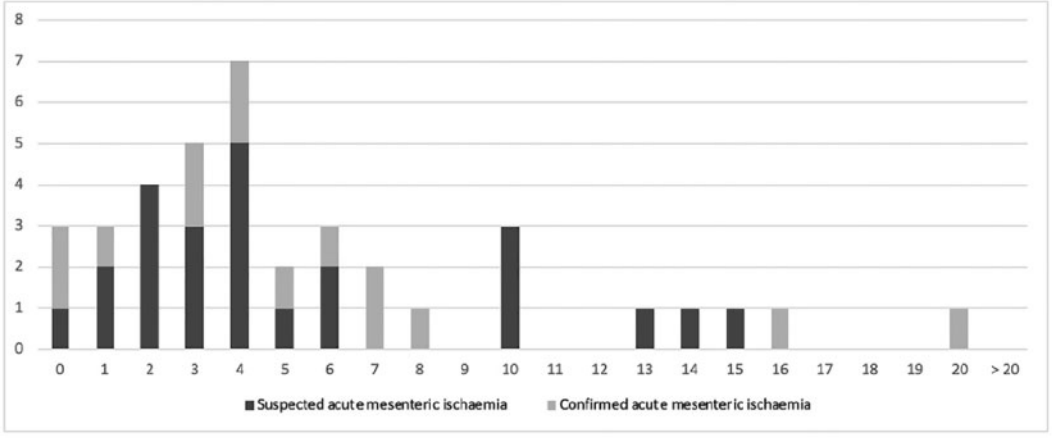


Figure 1 Flow chart. V-A ECMO: veno-arterial extracorporeal membrane oxygenation.

Table 1 Patients' initial characteristics.

Characteristics	All V-A ECMO *N* = 150	Acute mesenteric ischaemia *n*=14	No acute mesenteric ischaemia *n*=136	*p*
Age, years	58 (48–69)	57 (47–70)	58 (48–68)	0.82
Male gender	104 (71)	10 (71)	94 (69)	0.99
BMI, kg/m^2	25 (23–29)	26 (22–27)	25 (23–29)	0.55
Comorbidities				
Hypertension	63 (42)	6 (43)	57 (42)	0.99
Diabetes	36 (24)	3 (21)	33 (24)	0.99
Permanent atrial fibrillation	45 (30)	8 (57)	37 (27)	0.03
Peripheral arterial disease	8 (5)	1 (7)	7 (5)	0.55
Ischaemic heart disease	47 (31)	3 (21)	44 (32)	0.55
COPD	10 (7)	2 (14)	8 (6)	0.24
Tabagism	51 (35)	5 (38)	46 (34)	0.77
V-A ECMO for surgical reason	65 (43)	8 (57)	57 (42)	0.21
V-A ECMO for medical reason	85 (57)	6 (43)	79 (58)	0.21
Refractory cardiac arrest	39 (26)	5 (36)	34 (25)	0.28
Intra-aortic balloon pump	28 (19)	3 (21)	25 (18)	0.73
Delay between admission and V-A ECMO, days	0 (0–1)	0 (0–2)	0 (0–1)	0.27
SAPS II	54 (38–70)	56 (45–73)	53 (38–70)	0.47
Lactate level at day 0, mmol/L	5.2 (3–9.1)	7.8 (2.6–10.2)	5.1 (3–9.1)	0.49
Creatinine level at day 0, µmol/L	137 (100–183)	170 (135–192)	134 (100–175)	0.21
Vasoactive-Inotropic Score	70 (34–139)	136 (51–238)	70 (34–129)	0.05

Data are expressed as median (interquartile 25–75) or number (percentage), as appropriate.
V-A ECMO: veno-arterial extracorporeal membrane oxygenation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; SAPS 2: Simplified Acute Physiology Score 2



Day of V-A ECMO support	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	>20
Number of V-A ECMO	150	150	145	131	121	101	85	71	63	59	52	45	39	36	29	23	19	18	16	14	11	0
Survivors	150	150	146	138	131	127	124	121	117	115	114	111	109	107	101	100	98	98	95	93	90	66

Figure 2 Number of suspected and confirmed acute mesenteric ischaemia according to the duration of V-A ECMO support. V-A ECMO: veno-arterial extracorporeal membrane oxygenation.

Table 2 Characteristics of patients with suspected acute mesenteric ischaemia.

Characteristics	All acute mesenteric ischaemia suspicions *N*=38	Confirmed acute mesenteric ischaemia *n*=14	No acute mesenteric ischaemia *n*=24	*p*
In the five days after V-A ECMO				
Septic shock	18 (47)	7 (50)	11 (46)	0.99
Haemorrhagic shock	15 (39)	9 (64)	6 (25)	0.04
Highest norepinephrine dose, µg/kg per min	1.8 (0.7–2.2)	2.3 (1.4–3.0)	1.2 (0.7–2.1)	0.049
Renal replacement therapy	17 (45)	9 (64)	8 (33)	0.09
On the day of the suspicion				
Renal replacement therapy	16 (42)	10 (71)	6 (25)	0.008
Use of norepinephrine	32 (86)	13 (100)	19 (79)	0.14
Highest norepinephrine dose, µg/kg per min	1.6 (0.5–2.6)	2.6 (1.5–2.9)	1.1 (0.2–1.8)	0.03
V-A ECMO flow, L/min	4 (3.5–4.5)	3.8 (3.5–4.5)	4 (3.5–4.7)	0.73
Anti-platelet agent	24 (63)	7 (50)	17 (71)	0.30
Curative anticoagulation	16 (42)	4 (29)	12 (50)	0.31
SOFA score	17 (15–19)	19 (17–20)	16 (14–19)	0.008
Lactate level, mmol/L	2.8 (1.5–4.7)	3.9 (2.6–6.5)	2.3 (1.3–4.1)	0.047
Clinical and biological features on the day of suspicion				
Worsening shock	32 (84)	14 (100)	18 (75)	0.07
Abdominal distension	6 (16)	4 (29)	2 (8)	0.17
Abdominal pain	3 (8)	0 (0)	3 (13)	0.28
Rectal bleeding	5 (13)	2 (14)	3 (13)	0.99
Melena/bloody stools	4 (11)	3 (21)	1 (4)	0.13
Intra-abdominal pressure >12 mmHg	2 (6)	1 (8)	1 (5)	0.99
Arterial lactataemia > 2 mmol/L	24 (63)	11 (79)	13 (54)	0.18
SGOT > 5N	10 (29)	4 (31)	6 (27%)	0.99
White blood cell count > 15 G/L	17 (50)	6 (50)	11 (50)	0.99
Gram-negative bloodstream infection	2 (5)	1 (7)	1 (4)	0.99

V-A ECMO: veno-arterial extracorporeal membrane oxygenation; SOFA: Sequential Organ Failure Assessment; SGOT: serum glutamic-oxaloacetic transaminase

As detailed in *Figure 3*, first-line exam was endoscopy in 33 patients, CT scan in two patients and first-line laparotomy in three patients; three patients had both endoscopy and CT scan (two after inconclusive colonoscopy and one after abnormal colonoscopy but requiring CT scan to appreciate ischaemia extent).

Findings of the diagnosis strategy

Acute mesenteric ischaemia was confirmed in 14 of the 150 V-A ECMOs, that is, a prevalence of 9% of the patients. Diagnosis was performed by endoscopy in eight patients (stage I *n*=2; stage II *n*=3; stage III *n*=3) and by CT scan in four patients (non-occlusive mesenteric ischaemia *n*=3; arterial occlusive mesenteric ischaemia, *n*=1) (*Figure 3*). Last, acute mesenteric ischaemia was confirmed by direct observation in two of the three patients who had immediate surgery without endoscopy or CT scan, due to severe shock associated with abdominal distension.

Among the 12 patients with acute mesenteric ischaemia without first-line surgery, four had exploratory laparotomy, two had a stage I ischaemic colitis with stable conditions, and six were considered too severe, with futile surgery. Finally surgery was performed in six cases of mesenteric ischaemia (two first-line and four after endoscopy/CT scan demonstration). Bowel resection was performed in four of the patients for extensive (*n*=3) or focal (*n*=1) ischaemia; two patients had a subtotal colectomy, one a right colectomy extended to 2 m of ileum and the last one a left colectomy. No resection was performed in two patients because of diffuse (>90%) necrosis. Antimicrobial therapy was introduced or continued in 93% in the patients with acute mesenteric ischaemia.

Variables associated with acute mesenteric ischaemia

In univariate analysis, patients with and without acute mesenteric ischaemia did not differ at admission (*Table 1*), except for a higher prevalence of permanent atrial fibrillation and higher VIS. Similarly, at suspicion, no clinical or biological feature differed between patients with further confirmed or refuted acute mesenteric ischaemia, except slightly higher lactataemia in acute mesenteric ischaemia (*Table 2*).

However, characteristics of the patients differed during the first five days after V-A ECMO implantation: patients were more severe in the acute mesenteric ischaemia group, with significant higher rate

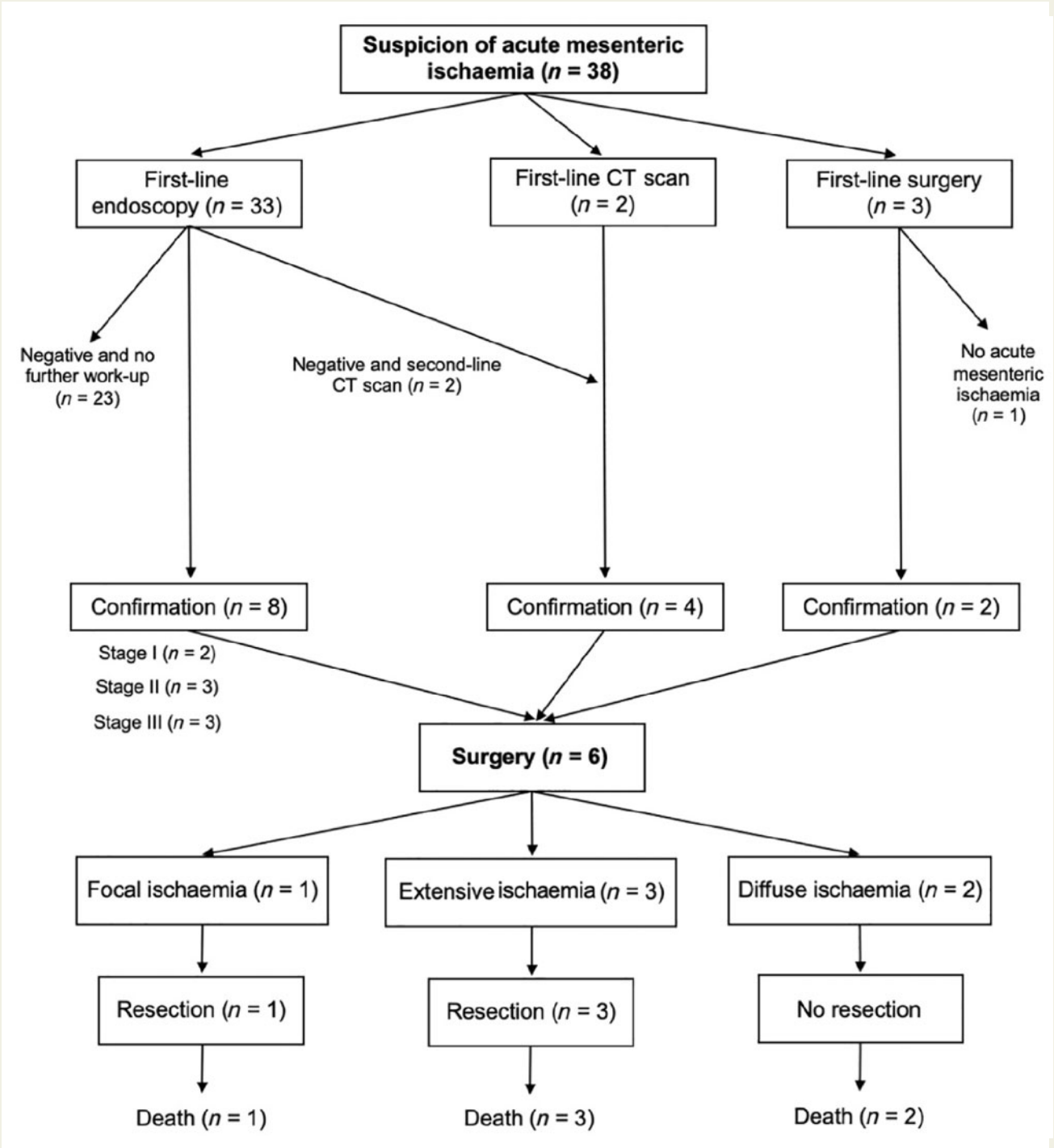


Figure 3 Diagnostic procedures in the case of suspicion of acute mesenteric ischaemia. CT: computed tomography.

of RRT support and higher doses of norepinephrine (*Table 3*). Patients with acute mesenteric ischaemia also experienced more episodes of second shock.

In multivariable analysis, independent factors associated with acute mesenteric ischaemia onset were RRT (odds ratio (OR) 4.5, 95% confidence interval (CI) 1.3–15.7, p=0.02) and a second shock in the first five days after implantation (OR 7.8, 95% CI: 1.5–41.3, p=0.02). Conversely, initiation of enteral nutrition in the first five days was negatively associated with acute mesenteric ischaemia onset (OR 0.15, 95% CI: 0.03–0.69, p=0.02).

Outcome of acute mesenteric ischaemia

While overall ICU mortality was 56%, patients with confirmed acute mesenteric ischaemia had a mortality rate of 100%.

Table 3 Initial management of patients and outcome.

Characteristics	All V-A ECMO N=150	Acute mesenteric ischaemia n=14	No acute mesenteric ischaemia n=136	p
Renal replacement therapy in the first five days	47 (32)	9 (64)	38 (28)	0.01
Use of norepinephrine in the first five days	136 (94)	12 (92)	124 (95)	0.54
Highest norepinephrine dose in the first five days, µg/kg per min	1.0 (0.5–2.0)	2.3 (1.4–3.0)	1.0 (0.5–1.9)	0.01
Second shock in the first five days	76 (51)	12 (86)	64 (47)	0.009
Enteral nutrition in the first five days	128 (88)	10 (71)	118 (90)	0.06
Parenteral nutrition in the first five days	7 (5)	2 (14)	5 (4)	0.14
Curative anticoagulation in the first five days	85 (58)	5 (36)	80 (61)	0.09
ICU length of stay, days	19 (10–32)	11(3–22)	19 (10–33)	0.07
ICU mortality	84 (56)	14 (100)	70 (51)	< 0.001

Data are expressed as median (interquartile 25–75) or number (percentage), as appropriate.
ECMO: veno-arterial extracorporeal membrane oxygenation; ICU: intensive care unit

Discussion

In this large series of 150 V-A ECMO for refractory post-cardiotomy shock, refractory cardiac arrest or refractory acute heart failure, acute mesenteric ischaemia was suspected in one-fourth of patients, and confirmed in one-tenth of patients. Except for higher haemodynamic severity in acute mesenteric ischaemia patients, neither early clinical sign nor biological event predicted fairly the onset of acute mesenteric ischaemia. RRT and early second shock after V-A ECMO implantation were independently associated with acute mesenteric ischaemia, whereas initiation of enteral nutrition was negatively associated with acute mesenteric ischaemia. Finally, surgery was performed in 42% of confirmed cases, but acute mesenteric ischaemia prognosis was dreadful, with a 100% mortality rate.

It is remarkable that our acute mesenteric ischaemia incidence of 9% is very close of the one encountered in septic shock,[3] complicated cardiac surgery[4] or severe burns.[8] As far as we are aware, our study is the first that specifically evaluates acute mesenteric ischaemia in patients supported by V-A ECMO for refractory cardiogenic shock or cardiac arrest. A recent series reported that among 1166 patients on ECMO, 35 underwent urgent gastro-intestinal surgery, including 15 digestive ischaemia, with a mortality rate of 80%, but no detail is available about the pre-surgery events in this mixed population of veno-venous (V-V) ECMO) and V-A ECMO.[24] Similarly, in 355 patients supported by ECMO (329 patients on V-V ECMO, 16 patients on V-A ECMO and 10 patients on V-V-A ECMO), 13 patients underwent emergent laparotomy, finding nine bowel ischaemia.[25] In addition, decompressive laparotomy was performed in 11 patients with abdominal compartment syndrome in a mixed population of 175 patients with V-V and V-A ECMO, without details on peroperative constatations.[26] With inherent limitations of epidemiology based on autopsy findings, postmortem examinations reported undiagnosed mesenteric ischaemia in only 1/78 or 1/19 adult patients on V-A ECMO support.[27,28] Pathophysiology of cardiogenic shock and its consequences on the digestive tract imply decreased cardiac output and major inflammation, prompting selective vasoconstriction of the mesenteric arterioles; gut congestion due to decreased venous return may also impair organ perfusion.[29] In addition, the use of intra-aortic guidewires and cannulas may increase the risk of embolism. Despite the absence of strong experimental or clinical data on the effect of V-A ECMO on the gut, intestinal blood flow and oxygen supply restoration may improve overall gastro-intestinal tract perfusion after the initial phase of ischaemia–reperfusion.[30] However, the respective part of underlying comorbidities, aetiology, shock and mechanical support in the development of acute mesenteric ischaemia cannot be inferred with the current data. As all patients exhibited severe baseline conditions with refractory shock, whereas V-A ECMO support management was standardized and without evident technical issues, we may infer that initial shock drives much more acute mesenteric ischaemia onset that ECMO mechanical support by itself. Because V-A ECMO is increasingly used as a life-saving support but is not devoid of risks, it is mandatory to provide strong descriptive and outcome data regarding complications related to techniques[31] and patients.[32] Our work brings never-reported insights to the ECMO literature.[33]

Here we report that all patients with acute mesenteric ischaemia died. This can be explained by the combination of two severe conditions, that is, refractory shock on V-A ECMO mechanical support, carrying by itself a 50–75% intra-hospital mortality,[15] and acute mesenteric ischaemia by itself, which has an independent mortality rate of 58%[7] to 96%[8] in ICU populations.

In previous studies, risk factors such as age, IABP, vasopressors and major inflammation have been proposed as non-occlusive acute mesenteric ischaemia risk factors,[4,7,8,34,35] but they were not identified in our study. In 9445 post-cardiac surgery patients, in whom 40 non-occlusive mesenteric ischaemia cases occurred, VIS was reported to be the strongest predictor of acute mesenteric ischaemia onset, whereas age and lactate level were less importantly associated.[35] If our patients had higher VIS at ECMO implantation, and higher norepinephrine doses during the early course, we did not identify these parameters as being risk factors for acute mesenteric ischaemia. The independent risk factors identified in our study broaden the data from previous studies and pathophysiology. It is very likely that a second shock, like sepsis or haemorrhage, occurring early after ECMO

implantation acts as a 'second-hit' and further impairs gut vasculature and perfusion. Respective participation of overwhelming cardiogenic shock, haemorrhage or sepsis in this second shock is a major contributor to lethal complications. To note, patients on V-A ECMO sometimes experience unexplained shock after implantation; it is plausible that this secondary circulatory imbalance may be due to underlying gut ischaemia, that is, that the second shock may be more the cause than the consequence of mesenteric ischaemia. The retrospective design of our analysis precludes further causality link. We also noticed that the early use of RRT was associated with the onset of acute mesenteric ischaemia. Likewise, RRT in the first seven days was associated with acute mesenteric ischaemia in critically ill burns.[8] Similarly, we highlighted that enteral nutrition was associated with a lower incidence of acute mesenteric ischaemia in V-A ECMO patients. If enteral nutrition may be as beneficial as parenteral nutrition in non-selected patients with shock and mechanical ventilation,[36] patients with V-A ECMO might specifically benefit from enteral feeding. Similar to several observational series,[37,38] a recent study found that early enteral nutrition was associated with lower mortality in patients requiring at least two days of V-A ECMO.[39]

Our findings generate major key messages. First, acute mesenteric ischaemia remains a major diagnostic and therapeutic challenge. Surprisingly, in our population, the usual underlying cardiovascular comorbidities could not discriminate between patients who will or will not develop acute mesenteric ischaemia in the following days. Similarly, when acute mesenteric ischaemia was suspected, clinical or biological data performed poorly at the bedside to identify patients with acute mesenteric ischaemia. This underlines that the suspicion threshold should be very low, speculating that early diagnosis might improve prognosis by offering non-futile surgery. Indeed, the largest series of non-selected critically ill patients highlighted that surgical treatment of acute mesenteric ischaemia in less than 24 h after diagnosis reduced mortality.[7] This is reinforced by the demonstration that one extra-digestive organ failure predicts irreversible transmural intestinal necrosis with a hazard ratio of 3.1 in acute mesenteric ischaemia.[40] In a V-A ECMO population, conservative treatments have no place for stage II–III ischaemic colitis or evidence of mesenteric ischaemia, considering the severity of these patients. Second, our results question the optimal diagnosis strategy. On-demand first-line endoscopy avoids transfer of the patient outside the ICU. An alternative could be to perform a systematic and early digestive endoscopy in all V-A ECMO, notably in the first days after implantation. But, except for clinical or biological suspicion, no data suggest the optimal timing. Other help could come from biomarkers. Although often perceived as the hallmark of acute mesenteric ischaemia, lactate level was normal in one-fourth of the series of 780 critically ill patients.[7] We confirm this apparent provocative finding in our study, with exactly the same proportion of patients with documented mesenteric ischaemia having lactataemia lower than 2.0 mmol/L. The interest of gut biomarkers such as intestinal fatty acid-binding protein,[41] citrulline[42] or combination of lactate, aspartate aminotransferase, procalcitonin, myoglobin[43] deserves further investigations. Third, higher VIS in acute mesenteric ischaemia patients, CT scan findings and peroperative findings suggest that non-occlusive acute mesenteric ischaemia is the predominant mechanism, rather than occlusive aetiology. The global hypoperfusion states following shock and subsequent multiorgan failure are largely involved in the onset of diffuse mesenteric ischaemia. This reinforces the importance of providing early haemodynamic optimization beyond macrohaemodynamic parameters that can be corrected despite persistent severe microcirculation impairment.[44] The respective part of optimal flow, volume or arterial pressure remains to be determined on V-A ECMO. Fourth, we found that no single isolated factors at admission or at suspicion were able to identify patients who developed acute mesenteric ischaemia. On the contrary, the early evolution of the patient during the first days after V-A ECMO implantation was much more contributive. This suggests that attention should be paid to haemodynamic and severity evolution, and acute mesenteric ischaemia should be suspected in patients experiencing initial unfavourable course (need for RRT, aggravation of vasoplegia).

This study has several strengths. It is the first that specifically describes acute mesenteric ischaemia in patients on V-A ECMO and that identifies risk factors in this population. Moreover, our ECMO supports are homogenous, excluding V-V ECMO, which is a very different population with a lower degree of extra-pulmonary organ failure; on the contrary, patients on V-V and V-A ECMO were gathered in previous studies. Finally, during the four years of the study, all consecutive patients undergoing V-A ECMO in our ICU were included without missing data and without change in medical or of surgical practices.

This study deserves recognition of several limitations, partially related to its single centre observational retrospective design, restraining from generating causative mechanisms. First, as we did not have a systematic diagnosis strategy, the diagnosis tree was not the same for all patients, and some patients may have experienced undiagnosed mesenteric ischaemia, with insufficient degree of clinical suspicion to initiate investigations: either by self-resolution of low severity mesenteric ischaemia, or by very early massive mesenteric ischaemia. Indeed, moribund patients (mainly after cardiac arrest) were excluded from the analysis and some of them may have presented overwhelming shock due to, or aggravated by, acute mesenteric ischaemia. This is plausible, especially as we reported that physicians performed poorly at the bedside in diagnosing acute mesenteric ischaemia. As a result, our 9% prevalence likely reflects the lowest boundary of the real one. Second, our study focused on 14 patients with a confirmed acute mesenteric ischaemia on V-A ECMO. Therefore, no conclusions about the benefits or risks of surgery should be drawn, as we entail the risk of self-fulfilling prophecy. Indeed, some patients were considered too severe to be operated, and surgery futile, which led to death; it is unknown whether survival would have been possible in the case of laparotomy. Similarly, we cannot exclude that an earlier diagnosis would have also led to futile surgery. Third, this study mixes two entities, namely bowel ischaemia and ischaemic colitis. Rectosigmoidoscopy may miss ischaemia restricted to the area supplied by the superior mesenteric artery. But gastro-intestinal endoscopy is easily achievable in the ICU, whereas transport for CT scan carries a high risk on V-A ECMO support. Moreover, contrast-enhanced CT scan is difficult to interpret due to flow changes associated with V-A ECMO.[45] However, a negative endoscopy with persistent suspicion should not preclude obtaining CT scan, especially when identifying a time-sensitive, life-threatening condition. We also gathered patients with refractory cardiogenic shock and cardiac arrest. The latter may have specific clinical features and outcomes, as suggested by the fact that most of the cases of mesenteric ischaemia in patients with medical indication of ECMO occurred after cardiac arrest.[46,47] While

this overall analysis increased the size of the cohort of V-A ECMO, this brings heterogeneity in initial insult. Finally, statistical overadjustment may occur due to the low number of events.

To conclude, acute mesenteric ischaemia is diagnosed in one-tenth of patients with refractory shock on V-A ECMO surviving beyond the first 24 h of implantation. Dramatic outcome justifies a low level of suspicion with endoscopy, especially in the most severe patients in the first days of mechanical support. Despite unknown outcome of earlier diagnosis or more aggressive management, further studies are required to determine the impact of different diagnostic strategies, such as systematic digestive endoscopy or dosage of biomarkers.

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