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Fever following extracorporeal membrane oxygenation decannulation: Infection, thrombosis or just physiology?

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ABSTRACT

Purpose: Fever is frequent after extracorporeal membrane oxygenation (ECMO) decannulation. We aimed to evaluate the incidence of post-decannulation fever and describe its causes.

Methods: Adult ECMO patients who were successfully weaned from ECMO were retrospectively included. Minimal and maximal core temperatures were collected daily for each patient from 48 h before decannulation up to 5 days after. Patients were grouped according to the cause of fever (infection, thrombosis, or no evident cause) and compared. Plasma cytokine profile was obtained, each day from decannulation to 5 days after for 20 patients.

Results: Between January 2021 and December 2022, 123 patients successfully weaned from ECMO were included. Post-decannulation fever occurred in 54 patients (44 %). It was associated with an infection in 39 patients (72 %) and with a thrombosis in 6 patients (11 %), and no cause was identified in the remaining 9 (17 %). Prolonged ECMO duration, extended ICU length-of-stay, diabetes and vascular comorbidities were significantly associated with a higher risk of infection. Finally, the pro-inflammatory cytokine profiles did not differ between febrile and afebrile patients.

Conclusion: Post-decannulation fever was common, and was mainly due to infections or thrombosis. Fever should therefore not be considered as a benign inflammatory reaction until proven otherwise.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) has become a widespread therapy for refractory cardiogenic shock and respiratory acute failure but remains associated with various complications [1]. While most of the researches tend to focus on patient selection and management during ECMO support, the post-weaning phase remains underexplored. Importantly, even after ECMO decannulation, patients

remain vulnerable to specific complications. Fever is a common clinical finding after ECMO decannulation [2,3]. However, the causes, the physiopathology and the incidence remained poorly investigated. This knowledge gap may therefore expose patients to suboptimal management. While infections is a frequent cause of fever in ICU [4,5], a proportion of patients may present isolated fever without any apparent underlying causes [6]. Isolated fever, especially after a surgical procedure, is frequent and often attributed to a benign inflammatory

Abbreviations: ARDS, Acute respiratory distress syndrome; CKD, Chronic kidney disease; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; CT, computed tomography; ECMO, Extracorporeal membrane oxygenation; ECLS, Extracorporeal life support; ICU, Intensive care unit; IL, Interleukin; IFN, Interferon; LVAD, Left ventricular assist device; SAPS II, Simplified acute physiology score II; SIRS, Systemic inflammation release syndrome; SOFA, Sepsis organ failure assessment; TNF, Tumor necrosis factor; VA-ECMO, Venoarterial extracorporeal membrane oxygenation; VV-ECMO, Venovenous extracorporeal membrane oxygenation.

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reaction [4]. Extensive work-up is usually not advised in this context, due to a limited diagnostic yield [7]. Given the vulnerability of ECMO patients and the critical nature of post-decannulation phase, failing to promptly identify and treat severe complications, such as infection or thrombosis, could lead to serious consequences. Therefore, we conducted this retrospective cohort study in patients who had been successfully weaned from ECMO to evaluate the incidence of fever after decannulation and describe its possible associated causes.

2. Materials and methods

2.1. Study design

This retrospective, single-center cohort study includes patients hospitalized in the intensive care unit (ICU) of Pitié-Salpêtrière Hospital between January 2021 and December 2022, supported by and successfully weaned from venoarterial (VA)- or venovenous (VV)-ECMO. Patients were included if they had refractory cardiogenic shock (SCAI D-E) or acute respiratory distress syndrome requiring VA- or VV-ECMO support, were weaned from their ECMO, and survived at least seven days after ECMO removal. Patients implanted with a left ventricular assist device (LVAD) were excluded, as the inflammatory response might have been affected by the presence of the device itself and the surgical procedure.

Following the ethical standards of our hospital's Institutional Review Board and French law, informed consent was not necessary, due to the retrospective and observational design of our study. The database is registered at the Commission Nationale de l'Informatique et des Libertés (CNIL, registration no. 1950673).

2.2. Definitions

Fever was defined as a core body temperature $\geq 38^\circ\text{C}$, referring to the temperature criterion used by Bone et al. [8]. Hypothermia was defined as a core body temperature $< 35^\circ\text{C}$ [9]. Post-ECMO decannulation fever was defined as a fever (see above) occurring within the 48 h following ECMO weaning. Core body temperature was measured either directly on the ECMO machine (when the patient had a blood temperature measurement on it), or with urinary catheter. To be noted, ear thermometers are not used in our unit for ECMO patients.

ECMO-related thrombosis was diagnosed either with ultrasound (for femoral and jugular veins, inferior vena cava or cardiac cavities thrombosis) or with a computed tomography (CT) scan, performed within 24 h after ECMO removal.

Ventilator-associated pneumonia (VAP) is defined, in our unit, as a clinical suspicion (at least one of the following: fever $\geq 38^\circ\text{C}$; WBC count $\geq 11,000/\text{mm}^3$; purulent sputum; decrease in $\text{PaO}_2/\text{FiO}_2$ ratio or hemodynamic impairment) plus significant quantitative growth of a bacteria ($\geq 10^4$ colony-forming units/mL) of distal BAL fluid samples, in patients having received mechanical ventilation (MV) for at least 48 h [10,11]. VAP episodes were retrospectively collected from the patients' chart. Bloodstream infection (BSI) was defined as a bacterial infection identified on blood cultures. If a coagulase-negative *Staphylococcus* strain was identified, it was considered as a BSI only if 2 sets of blood cultures grew with the same pathogen exhibiting the same antibiotic resistance profile. Soft tissues infection was defined as the presence of a cellulitis, typically in the site of ECMO cannulas, together with a pathogenic germ identified by specific culture of a sample collected in the former site of cannulas.

As part of the management temperature in ECMO patients, ECMO heaters are not routinely used. Paracetamol is used in case of severe hyperthermia (core temperature $\geq 39^\circ\text{C}$) or chills, and ECMO heaters only in patients with core temperature $< 36^\circ\text{C}$.

2.3. Study groups

We divided the population into 2 groups: febrile patients, defined as at least one core temperature report $\geq 38^\circ\text{C}$ in the 48 h following ECMO decannulation, and afebrile patients. Patients who developed fever after ECMO decannulation were divided into 3 subgroups, according to the cause of fever: infection, either ongoing at the time of ECMO decannulation or developing within the 2 days after; thrombosis, either due to ECMO cannulas (femoral vein or artery, jugular vein, inferior vena cava) or due to underlying disease (intracardiac thrombosis); and fever without obvious causes (hereafter called isolated fever).

Patients having both an infection and a thrombosis were included in the infection subgroup. Infections diagnosed during the weaning period were classified as of new-onset (occurring after decannulation), or ongoing (diagnosed within 72 h before decannulation). Daily minimal and maximal core temperatures as well as white blood cell (WBC) count were collected for each patient from 48 h before to 5 days after decannulation.

In our ICU, and according to the suspected source of infection, multi-site cultures were systematically obtained in case of post-decannulation fever, and included blood cultures, cannula-site sampling, and lung sampling. To be noted, as all patients had urinary catheters, we did not conduct urine culture. As part of our standard of care and regardless the presence or absence of fever, ultrasound (femoral vessels, inferior vena cava and cardiac chambers) and computed tomography (CT) scan were systematically obtained within 48 h following decannulation to detect thrombosis (venous or arterial). Noteworthy, pre-existing thrombosis were assessed with ultrasound or CT scan only if patients presented clinical signs of thrombo-embolic disease. Finally, As D-dimers have a poor specificity to diagnose a thrombo-embolic disease in ICU and ECMO patients, we did not measure their levels routinely.

Patients were compared based on the presence or absence of fever. Secondly, an analysis was conducted on the three pre-defined subgroups of febrile patients (infection, thrombosis, and isolated fever) to identify potential discriminative factors between different fever causes.

2.4. Data collection

The following data were collected from the medical records via a secure data collection file: age, sex, weight, body mass index (BMI), presence of cardiovascular diseases, diabetes mellitus, hypertension and chronic renal insufficiency, simplified acute physiology score (SAPS) II, sepsis-related organ-failure assessment (SOFA) score at ICU admission, date of ECMO implantation, type of ECMO (VV or VA), indication and duration of ECMO support. Significant events after decannulation, such as episodes of ICU-acquired infections, presence and site of vascular thrombosis, duration of ICU stay and survival to ICU discharge were also recorded.

2.5. Cytokine analysis

To explore the hypothesis of fever induced by cytokine release or persistent production after ECMO weaning, 12 cytokines (interleukin (IL)-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17 A, IL-22, Tumor necrosis factor-alpha (TNF- α), interferon-gamma (IFN- γ), and IFN- α [12] were measured the day of ECMO decannulation, and daily in the three following days in 20 patients. The cytokine profile was obtained only for the last 20 patients included in the analysis, because cytokine measurements, which is now performed systematically after ECMO removal as part in routine care in our patients, was implemented in our unit in May 2022. Data were provided for an exploratory analysis. This population included 6 afebrile patients (without infection and thrombosis), 5 febrile patients presenting an infection, 3 febrile patients presenting venous thrombosis, and 6 patients with isolated fever. Plasma cytokine levels were measured by digital ELISA and multiplex assay [12] and compared between groups.

2.6. Statistical analysis

We followed the STROBE (strengthening the reporting of observational studies in epidemiology) recommendations for reporting cohort studies [13]. Continuous variables were expressed as median (interquartile range, IQR) and categorical variables were expressed as number (%). Categorical variables were analyzed by Chi-squared tests. Continuous variables were compared using *t*-test in case of normal distribution, and using Mann-Whitney or Kruskal-Wallis test if the variable had a non-normal distribution. Variable normality was assessed visually by looking the variable’s distribution graph and confirmed by a Kolmogorov-Smirnov test. A *p* value ≤ 0.05 was considered statistically significant. We performed Principal Component Analyses (PCA) individually for interleukin measurements on days 0 through 3 and projected the subjects on a scatter plot. Subjects were color-coded: red for infections, blue for thrombosis, and green for those with neither infection nor

thrombosis. Due to the limited number of subjects with interleukin measurements (*n* = 20), we did not conduct formal statistical tests. All statistical analyses were performed using Statview software and R version 4.2.1.

3. Results

3.1. Patient characteristics

During the study period, 448 patients received a VA- or a VV-ECMO for refractory cardiogenic shock (CS) or ARDS, respectively (Fig. 1). Among them, 182 (41 %) patients died during ECMO support. 143 patients (31.9 %) were excluded from the analysis for the following reasons: missing data, early transfer to their referring hospital after removal (< 72 h), bridge to a LVAD therapy and transfer to a lung transplant center. One-hundred and twenty-three (27 %) patients had a complete

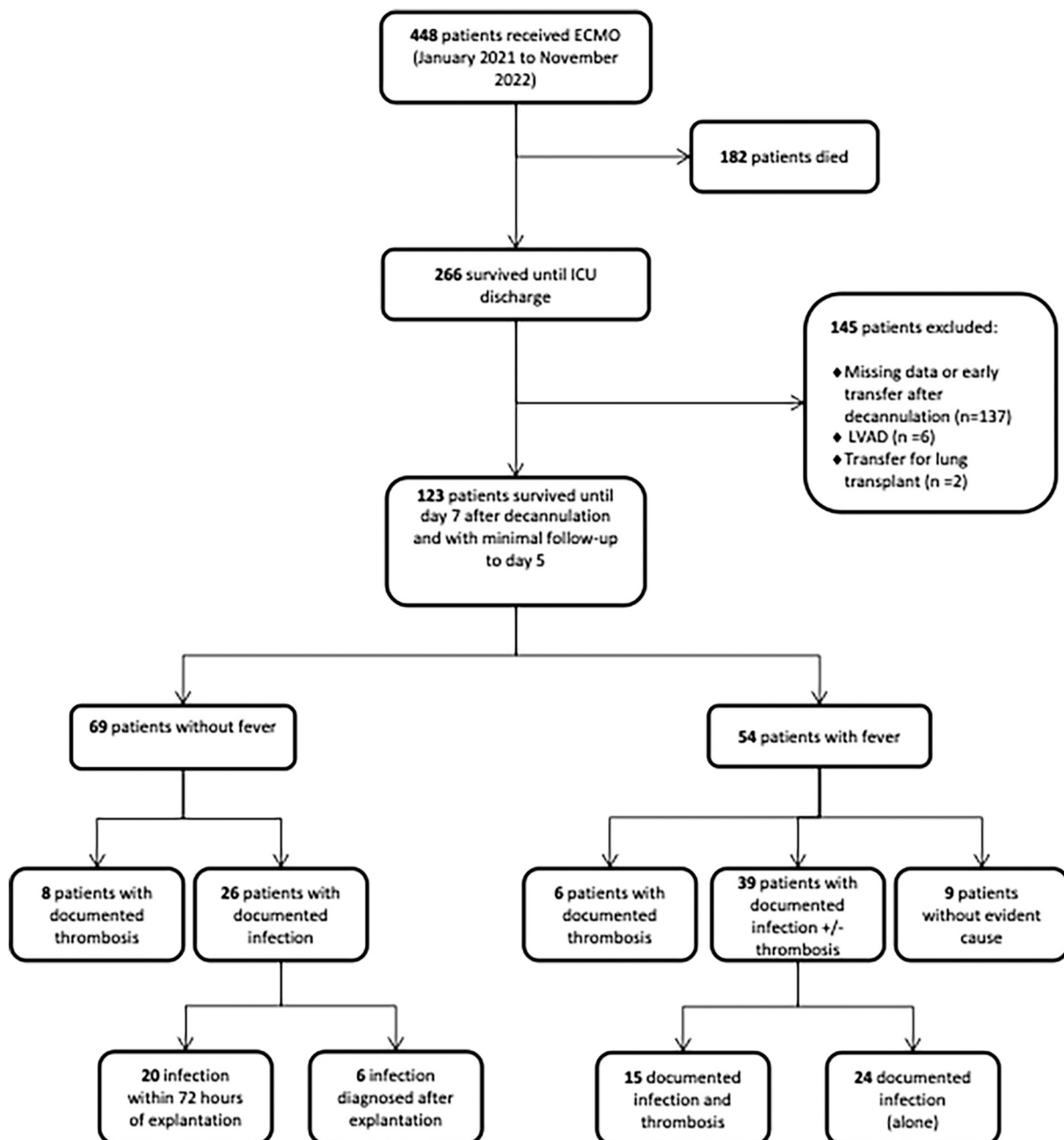


Fig. 1. Flow chart of the study.

follow-up until day 5 after ECMO removal and were included in the final analysis (Fig. 1). The main characteristics of this population are provided in Table 1. Briefly, their median (IQR) age was 47 (38–57) years, 63 % of the patients were male, 61 % received VA-ECMO for CS and 39 % VV-ECMO for ARDS. The median (IQR) duration of ECMO support was 12 (6–30) days, and the ICU length of stay was 29 (17–49) days. Among patients successfully weaned from ECMO, the ICU-mortality rate was 8 %.

The ECMO decannulation phase was associated with significant complications. Noteworthy, ICU-acquired infections occurred in 61 % of patients, while 41 % experienced thrombotic events. Venous thrombosis were more frequent than arterial and cardiac thrombosis (92 %, 10 % and 3 % of thrombotic events, respectively). Characteristics of patients according to the supposed cause of fever (infection, thrombosis or isolated fever) are shown in Table 2.

3.2. Comparisons of febrile and afebrile patients following ECMO decannulation

Fever after decannulation occurred in 54 patients (44 %). Among them, 39 patients (72 %) presented an infection and 21 a thrombosis (39 %); including 15 thrombosis associated with infection and 6 isolated thrombosis, see Fig. 1), suggesting a possible association. There were no identified potential causes of fever in the remaining nine patients (17 %). Table 1 displays the characteristics of patients according to the presence or absence of post-decannulation fever. Febrile patients were comparable to afebrile patients, with notable differences in the distribution of VV- and VA-ECMO modalities between groups. Indeed, febrile patients had a higher incidence of VV-ECMO utilization. Fig. 2 illustrates the temperature kinetic in febrile and afebrile patients, spanning from 2 days before ECMO removal to the subsequent 5 days. Although temperature was within the normal range in the 2 days before ECMO decannulation (i.e. <38 °C) in both groups, patients who developed subsequent post-ECMO decannulation fever had significantly higher body temperature in the 2 days preceding ECMO weaning than others (Table 1 and Fig. 2).

Only 4 patients had hypothermia after ECMO decannulation; in 2 patients, it occurred 24 h after decannulation and in the 2 others 48 h after decannulation. Three out of them had concomitant sepsis, whereas one patient had hypothermia without sepsis. Interestingly, one patient had hypothermia 24 h after ECMO decannulation and fever the day after; he was diagnosed with VAP at that time. Three out of those 4 with hypothermia (75 %) died in the ICU.

Paracetamol was used in 10 to 15 % of patients in the observation period (eFigure 1 in the online supplement), mostly as an analgesic, since numerically, more patients without fever received paracetamol than febrile patients.

3.3. Comparison of patients who developed post-decannulation fever

The analysis of temperature trends among patients who developed fever after ECMO decannulation, categorized by etiology (infection, thrombosis, or isolated fever), revealed no statistically significant differences in terms of fever onset, peak temperature, and duration (Fig. 3 and Table 2). Indeed, fever occurred mostly within the 24 h following decannulation and persisted indistinctly among subgroups up to 5 days after. Fever duration and the temperature kinetics did not yield any additional discriminative information. When comparing patients with infection-related fever to those with thrombosis-related fever or isolated fever, we observed a higher prevalence of VV-ECMO, prolonged mechanical ventilation, and extended ICU stays among the former group. Nevertheless, the ICU mortality rate remained consistent across all three groups.

Table 1

Characteristics of patients according to the presence or absence of fever after extracorporeal membrane oxygenation removal.

Parameters	Overall population N = 123	Patients with post decanulation fever N = 54	Patients without post decanulation fever N = 69
Age, years	47 (38–57)	47 (37–57)	47 (38–56)
Body mass index, kg/m ²	29 (24–33)	30 (28–35)	27 (22–32)
Male sex	78 (63)	34 (63)	44 (64)
Admission SAPS II	58 (40–68)	60 (43–68)	50 (40–58)
Admission SOFA score	10 (6–13)	11 (7–14)	10 (6–13)
Comorbidities			
Diabetes mellitus	25 (20)	7 (13)	18 (26)
Cardiovascular disease*	42 (34)	12 (22)	30 (43)
Hypertension*	25 (20)	10 (19)	15 (22)
Chronic renal insufficiency	11 (9)	1 (2)	10 (14)
ECMO type*			
Veno-arterial	75 (61)	26 (48)	49 (71)
Veno-venous	48 (39)	28 (52)	20 (29)
Reason for ECMO			
Acute respiratory distress syndrome	49 (40)	28 (52)	21 (30)
Acute myocardial infarction CS	57 (46)	22 (41)	35 (51)
Pulmonary embolism	2 (2)	1 (2)	1 (1)
Post-cardiac surgery CS	7 (6)	3 (6)	4 (6)
Post-heart transplantation CS	8 (7)	0	8 (12)
Duration of ECMO support, days	12 (6–30)	12 (6–36)	12 (6–19)
Temperature before ECMO removal, °C			
Day –1*	37.1 (36.8–37.4)	37.2 (37–37.7)	37 (36.7–37.2)
Day –2*	37 (36.7–37.3)	37.2 (36.7–37.6)	37 (36.7–37.2)
Characteristics at ECMO weaning			
Temperature, °C*	37.3 (36.9–37.7)	37.7 (37.2–38)	37.1 (36.8–37.4)
White blood cells count, Giga/L	13.2 (9.8–18.6)	13.9 (11.1–19)	12.9 (9.0–16.8)
Ongoing infection	69 (56)	34 (63)	35 (51)
Infection at the time or in the 5 days following ECMO decannulation*	76 (61)	39 (72)	37 (54)
Ventilator-associated pneumonia	54 (72)	30 (77)	24 (65)
Bloodstream infection	11 (15)	5 (13)	6 (16)
Skin and soft tissue	8 (11)	4 (10)	4 (11)
Mediastinitis/ lung abscess/empyema	1 (1)	0	1 (2)
Candidemia	1 (1)	0	1 (2)
Thrombosis after ECMO decannulation†	51 (41)	21 (39)	30 (43)
Arterial thrombosis	5 (4)	2 (4)	3 (4)
Venous thrombosis	47 (38)	21 (39)	26 (38)
Intra-cardiac thrombosis‡	4 (3)	0	4 (6)
ICU length of stay, days	29 (17–49)	29 (18–57)	29 (16–41)
ICU mortality rate	10 (8)	4 (7)	6 (9)

Results are expressed as median (IQR) or n (%). p-values are reported only for variables for which a statistical difference is observed. For variables without p-value, the p-value for difference between groups is >0.05.

Abbreviations: SAPS II, severe acute physiology score; SOFA, sequential organ failure assessment; ECMO, extra corporeal membrane oxygenation; CS, cardiogenic shock; ICU, intensive care unit.

* p < 0.05.

† Some patients may have multiple thrombosis location.

‡ Including 2 thrombus in the left ventricle, one in the right atrium and one in the left atrium.

Table 2
Characteristics of patients with post-decannulation fever according to the cause of fever.

Parameter	Infection N = 39	Thrombosis N = 6	Isolated fever N = 9
Age, years	46 (36–57)	58 (49–60)	43 (39–55)
Male sex	25 (64)	4 (67)	5 (56)
Type of ECMO *			
Veno-arterial	14 (36)	6 (100)	6 (66)
Veno-venous	25 (64)	0	3 (33)
Duration of ECMO support*	19 (8–43)	5 (3–9)	7 (6–24)
White blood cell count, Giga/L			
At ECMO withdrawal	14.0 (11.2–18.9)	9.1 (5.9–20.2)	13.8 (11.4–20.5)
Peak in the 5 days following ECMO removal	18.9 (14.5–25.8)	14.3 (11.4–28.7)	21.8 (14.1–31.8)
Timing of fever			
Within the 24 h following ECMO removal	29 (74)	5 (83)	7 (78)
24–48 h after ECMO removal	10 (26)	1 (7)	2 (12)
Maximal temperature in the 5 days following ECMO removal, °C	38.6 (38.4–39)	38.6 (38.1–39)	38.7 (38.4–39)
ICU length of stay, days *	36 (24–68)	16 (14–36)	19 (14–38)
ICU mortality rate	3 (8)	0	1 (11)

Results are expressed as median (IQR) or n (%). p-values are reported only for variables for which a statistical difference is observed. For variables without p-value, the p-value for difference between groups is >0.05.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

* p < 0.05.

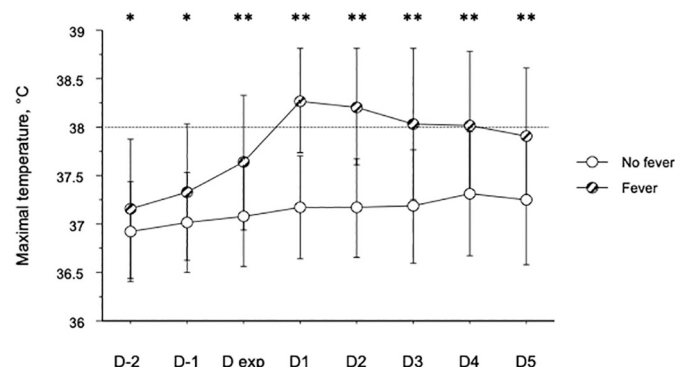


Fig. 2. Temperature kinetics of patients who developed fever (hatched circles, n = 54) and not (white circles, n = 69) from 2 days before ECMO weaning (D-2) to 5 days after ECMO weaning (D5). D: day, D exp.: day of ECMO removal. * p < 0.05 for comparison between groups. ** p < 0.0001 for comparison between groups.

3.4. Cytokines analysis

The analysis of the cytokine profiles after decannulation revealed no significant difference among subgroups (eFigure 2, online supplement). Similarly, the comparison between afebrile and febrile patients (regardless of the etiology of fever) yielded similar results, with no differences observed between the two groups (eFigure 3, online supplement).

We performed PCA individually for interleukin measurements on days 0 (day of ECMO explantation) through day 3 after ECMO explantation. Subsequently, we projected the subjects onto a scatter plot with dimension 1 on the x-axis and dimension 2 on the y-axis. Subjects were color-coded: red for those with infections, blue for those with thrombosis, and green for those with neither condition (eFigure 4). Our detailed analysis primarily focuses on day 1 as the most informative for

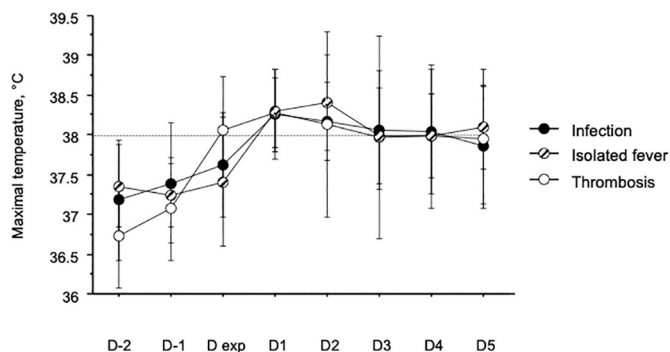


Fig. 3. Temperature kinetic of patients who developed fever according to its cause, from 2 days before ECMO weaning (D-2) to 5 days after ECMO weaning (D5). D: day, D exp.: day of ECMO removal. Black circles: patients with infection, n = 39. White circles: patients with thrombosis, n = 6. Hatched circles: patients with isolated fever, n = 9.

predicting fever causes. Day 0 was considered too early for reliable predictions, and by days 2 or 3, the causes of fever may have already been identified or treated, potentially complicating the interpretation of interleukin data.

The first two dimensions of the PCA explained a substantial 61.4 % of the total day 1 interleukins variability. Dimension 1 differentiated individuals with high values for IFN α , IL4, IFN γ , IL12, IL17, IL1, TNF α , and IL5 (strongest) from those with low values for IL10, TNF α , IL8, IL1, IL22, and IL17 (weakest). Dimension 2 distinguished individuals with elevated IL8, IL10, and IL6 (strongest) from those with low levels of IL10, TNF α , IL8, IL1, IL22, and IL17 (weakest).

The first two dimensions explained 50.8 %, 53.7 %, and 39.6 % of the total dataset's inertia for interleukin measurements at days 0, 2, and 3, respectively.

Similarly, PCA for interleukin measurements, when grouping the patients in 2 groups, according to the presence of fever or not (whatever the cause of fever), yielded similar results: interleukin measurements alone may not reliably predict the presence of fever in this small patient subset (eFigure 5).

4. Discussion

This study reports the incidence of fever following ECMO decannulation in a monocentric cohort. Our findings can be summarized as follow. Firstly, fever is a common clinical finding in the post-decannulation phase. There is a paucity of data in the literature. Post-decannulation fever was observed in 44 % of our cohort, confirming previous finding: in a retrospective study on VV-ECMO patients, the incidence of fever following decannulation was 51 % [2]. A recent large study found that 62 % of patients developed post-ECMO fever, that was not associated with impaired prognosis [9]. Secondly, fever was associated with an infectious process in a significant number of cases (72 %), highlighting the vulnerability of ECMO patients to infection, even after decannulation. The clinical implications are substantial, as early detection of infection directly impact mortality [14]. Furthermore, while current practices tend to follow the so called “less is more strategy” and do not recommend thorough work-up in case of isolated fever [15], our findings suggest the opposite and challenge this concept in this specific setting. Thirdly, although the results were not statistically significant, it is important to note that probable non-infectious causes of fever were prevalent in the present cohort, with an emphasis on thrombotic event. The diagnosis of thrombosis significantly impacts clinical management and should therefore be ranked highly in the differential diagnosis after ECMO decannulation. Several retrospective studies reported a high incidence of thrombosis after decannulation [16,17]. However, latest guidelines do not warrant routine screening

following ECMO weaning. Our results confirmed previous findings regarding the high incidence of thrombosis following ECMO decannulation and emphasizes the importance of research to improve the definition of post-decannulation thrombosis and to refine screening strategies [17]. Last, we could not identify with the use of PCA distinct clusters indicating that interleukin measurements alone may not reliably predict the underlying cause of fever in our patients, but this subgroup analysis must be considered exploratory due to the small number of subjects included.

Fever is neither a sensitive nor a specific clinical sign. Obviously, the absence of fever following decannulation does not exclude infection, especially in frail patients who received immunomodulatory drugs. Indeed, 52 % of our cohort presented an infection without fever during the weaning and decannulation period. In infection, fever results from a complex interplay between pathogens and immune system and its absence may reflect an impaired and depressed immune response. This theory is however considered oversimplified and was challenged by the results of several studies [18,19]. Indeed, in a prospective study on 525 patients with sepsis, authors reported that the pro-inflammatory cytokine profiles did not differ between febrile and afebrile patients. In line with these results, we were unable to show any differences in cytokines production between febrile and afebrile patients. Although these results are limited by the small sample size of the present study, measured plasma levels of cytokines were relatively low across all groups, suggesting that other unmeasured mechanisms are involved in the pathophysiology of fever. Previous study on sepsis reported that endothelial dysfunction, which is affected as well during ECMO support, might play a role in the pathophysiology of fever [20,21].

Finally, in this work, 17 % of the patients presented fever without any evident underlying cause. Fever is likely often multi-factorial and the pathophysiology of post-decannulation fever remains unexplained. Interestingly, about 50 % of patients in each group (fever vs no fever) presented an ongoing infection before ECMO weaning. Infection and cytokine profiles were not different after decannulation. This highlights well that there is a knowledge gap in pathophysiology and that further research on the field is required.

Inflammation causes by the procedure itself might explain this clinical finding. One hypothesis that could account for an isolated fever without any apparent cause following ECMO decannulation is related to a reset of the hypothalamic thermoregulation center. Indeed, during ECMO support blood is cooled in the extracorporeal circuit, potentially prompting an adjustment of the thermoregulation center to normalize core body temperature. Following ECMO weaning, this adjustment might persist for several days, despite the cessation of blood cooling, leading to hyperthermia. While there is not data supporting this hypothesis during ECMO support, Challenger et al. investigated the impact of continuous renal replacement therapy (CRRT), a form of extracorporeal support, on body temperature of critically ill patients [22]. Authors reported significant body temperature changes during CRRT, with cooling at the time of initiation and warming at the time of cessation. The median temperature increased sharply 12 h following CRRT cessation and decreased slightly only after 48 h, a similar pattern observed in the present study. Those results suggests that extracorporeal support may directly impact thermoregulation centers.

Only 4 patients (3 %) had hypothermia after ECMO withdrawal, among whom one had subsequent fever. A recent study found a higher rate (10 %) of post-ECMO hypothermia, that was associated with a bad prognosis [9]. Although 3/4 of our patients with hypothermia died, the small number of cases precludes any conclusion.

This study has several limitations that will need to be addressed in future studies. Firstly, it is a retrospective, single-center study performed in an experienced ECMO center. Several factors may impact body temperature besides the ECMO decannulation procedure. These potential confounders could not be addressed due to the study design. Interestingly, paracetamol was numerically more frequently used in non-febrile patients as an analgesic, before and after decannulation. Therefore, the

incidence of post-decannulation fever might have been underestimated. In addition, due to the study design, we can obviously not establish any causation between fever, infection and thrombosis but only suggest a possible association. Secondly, only 27 % of the patients screened were included for analysis. Our findings therefore only apply to these patients and a selection bias cannot be excluded. Thirdly, we need to acknowledge that febrile patients classified in the isolated fever group (no underlying causes of fever observed) might have had a cause that we could not identify. Nevertheless, we conducted thorough diagnostic testing to eliminate major potential causes of fever in the ICU. Fourthly, the information regarding the use of ECMO heaters (we use it only in patients with core temperature < 36 °C) was not available, therefore the pre-ECMO decannulation temperature may be actually lower than reported in some patients. However, it is unlikely that the use of ECMO heaters before decannulation change the post-decannulation temperature, therefore our observation and results regarding post-decannulation fever should not be impacted. Fourthly, the use of other extracorporeal devices, such as CRRT, could as well affect patients' temperature and was not analyzed in the present study. Finally, the small number of assessments for cytokine profiles prevented us from thoroughly exploring the hypothesis that post-decannulation fever may be induced by cytokine release.

5. Conclusion

Post-decannulation fever was a common clinical finding. Infections and thrombosis were observed in 83 % of the cases and may be associated with fever. It appears reasonable to not consider fever as a benign procedural inflammatory reaction until proven otherwise. A thorough diagnostic work-up should be performed during this critical phase, as it may significantly impact therapeutic management. The pathophysiology remains however unexplained and further research is required.

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Credit authorship contribution statement

Benjamin Assouline: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Gianluca Belli:** Writing – review & editing, Writing – original draft, Data curation. **Karim Dorgham:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis. **Quentin Moyon:** Writing – review & editing, Writing – original draft, Formal analysis. **Alexandre Coppens:** Writing – review & editing, Writing – original draft, Formal analysis. **Marc Pineton de Chambrun:** Writing – review & editing, Writing – original draft, Data curation. **Juliette Chommeloux:** Writing – review & editing, Writing – original draft, Data curation. **David Levy:** Writing – review & editing, Writing – original draft, Data curation. **Ouriel Saura:** Writing – review & editing, Writing – original draft, Data curation. **Guillaume Hekimian:** Writing – review & editing, Writing – original draft, Data curation. **Matthieu Schmidt:** Writing – review & editing, Writing – original draft, Data curation. **Alain Combes:** Writing – review & editing, Writing – original draft, Data curation. **Charles-Edouard Luyt:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcrc.2024.154945>.

Data availability

All relevant data are within the manuscript and its Supporting Information files.

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