Diagnosis of infection in patients undergoing extracorporeal membrane oxygenation: A case-control study

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Objective: Diagnosis of infection in patients receiving extracorporeal membrane oxygenation is challenging in clinical practice but represents a crucial aspect of the upgrading of therapeutic options. The aim of this study was to analyze the role of C-reactive protein and procalcitonin in the diagnosis of infection in patients requiring extracorporeal membrane oxygenation and to assess the difference between venovenous and venoarterial extracorporeal membrane oxygenation settings.

Methods: A case-control study was performed on 27 patients. Serum values of procalcitonin and C-reactive protein were analyzed according to the presence of infection.

Results: Forty-eight percent of patients had infection. Gram-negative bacteria were the predominant pathogens, and *Candida albicans* was the most frequent isolated microorganism. Procalcitonin had an area under the curve of 0.681 ($P = .0062$) for the diagnosis of infection in the venoarterial extracorporeal membrane oxygenation group but failed to discriminate infection in the venovenous extracorporeal membrane oxygenation group ($P = .14$). The area under the curve of C-reactive protein was 0.707 ($P < .001$) in all patients receiving extracorporeal membrane oxygenation. In patients receiving venoarterial extracorporeal membrane oxygenation, procalcitonin had good accuracy with 1.89 ng/mL as the cutoff (sensitivity = 87.8%, specificity = 50%) and C-reactive protein with 97.70 mg/L as the cutoff (sensitivity = 85.3%, specificity = 41.6%). The procalcitonin and C-reactive protein combined assay had a sensitivity of 87.2% and specificity of 25.9%. Four variables were identified as statistically significant predictors of infection: procalcitonin and C-reactive protein combined assay (odds ratio, 1.184; $P < .001$), age (odds ratio, 0.980; $P < .001$), presence of infection before extracorporeal membrane oxygenation implantation (odds ratio, 1.782; $P < .001$), and duration of extracorporeal membrane oxygenation support (odds ratio, 1.056; $P < .001$).

Conclusions: Traditional and emerging inflammatory biomarkers, especially if compounded in the procalcitonin and C-reactive protein combined assay, can aid in the diagnosis of infection in patients undergoing venoarterial extracorporeal membrane oxygenation. (J Thorac Cardiovasc Surg 2012;143:1411-6)

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Extracorporeal membrane oxygenation (ECMO) represents an effective tool for the treatment of heart and lung failure. Nevertheless, clinicians may encounter many hardships in the management of this innovative therapeutic

option. One of the most problematic challenges is to define the presence and onset of infection and sepsis, because these critically ill patients invariably present clinical signs of systemic inflammatory response.¹ In such patients, the systemic inflammatory response syndrome (SIRS) is due to both the underlying acute disease and the host response to the presence of the extracorporeal circuit itself. The issue is critical because mortality in sepsis is high and early therapeutic intervention can improve prognosis.² On the other hand, broad use of antibiotics in all patients with SIRS may lead to a prevalence of resistant strains with increasing toxicity and costs. Moreover, when ECMO is used as a bridge to other potential therapeutic options, including organ transplant and long-term assist device implantation, the presence of infection is to be rigorously established to evaluate whether patients' eligibility criteria are met.

This study analyzes the role of C-reactive protein (CRP) and procalcitonin (PCT) in the diagnosis of bacterial and fungal infection in critically ill patients requiring ECMO, and a new diagnostic test for clinical practice is presented.

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Abbreviations and Acronyms

ARDS	= acute respiratory distress syndrome
CI	= confidence interval
CRP	= C-reactive protein
ECMO	= extracorporeal membrane oxygenation
ICU	= intensive care unit
NPV	= negative predictive value
OR	= odds ratio
PCT	= procalcitonin
PPV	= positive predictive value
ROC	= receiver operating characteristic
SE	= sensitivity
SIRS	= systemic inflammatory response syndrome
SP	= specificity
VA	= venoarterial
VV	= venovenous

MATERIALS AND METHODS**Setting and Study Population**

After ethical committee approval, we carried out an observational study on 27 adult patients who were treated with venovenous (VV) ECMO or venoarterial (VA) ECMO between November 2009 and January 2011, and admitted to the cardiovascular intensive care unit (ICU) of Istituto Scientifico San Raffaele.

Eleven patients with severe acute respiratory distress syndrome (ARDS) were treated with VV ECMO, and 16 patients with refractory cardiogenic shock were treated with VA ECMO. Among patients receiving VV ECMO, 7 had confirmed or strongly suspected ARDS due to H1N1 influenza A infection. The other 4 patients treated with VV ECMO had ARDS after polytrauma, cardiogenic shock, pneumonia with negative microbiological tests, and pancreatic surgery. None of the patients receiving VA ECMO had evidence of infection at the time of cannulation, except 1 patient with H1N1 myocarditis with positive pharyngeal swab. Thirteen of 27 patients had infection, and 14 patients were part of the control group.

Clinical Management

The ECMO circuit setup consisted of a centrifugal pump and a heparin-coated polymethylpentene oxygenator. Two patients received a circuit without an oxygenator for isolated refractory acute heart failure with preserved pulmonary function. Because all the other components of the circuit and clinical management were identical to those of the patients receiving VA ECMO, these 2 patients were included in the VA ECMO group.

All patients were intubated during ECMO support, except 1 patient with non-H1N1-related pneumonia who received VV ECMO after failure of noninvasive ventilation. Baseline monitoring consisted of invasive pressure monitoring, pulse oximetry, continuous electrocardiography, urine output, and central venous pressure. Chest radiogram and transesophageal echocardiographic evaluations were performed and repeated as needed. Thermodilution cardiac output measurements were done. Arterial blood gas analysis was performed every hour. Evaluation of hematocrit, white blood cell count, coagulative profile (activated clotting time, prothrombin time, partial thromboplastin time, antithrombin, free hemoglobin, fibrinogen, D-dimer, and C protein), and electrolytes were performed every 6 hours or when deemed necessary. Continuous clinical monitoring for bleeding was performed, and laboratory measurement was requested more frequently if necessary. Daily evaluation of cardiac enzymes, hepatic enzymes, and creatinine was performed. Blood gas analysis from radial

artery, pre-oxygenator blood, and post-oxygenator blood was performed daily. Continuous evaluation of the ECMO circuit, clotting formation, and pressure difference was performed.

Hemolysis was monitored by daily measurement of serum concentrations of lactate dehydrogenase and free hemoglobin. Hemolysis was diagnosed in the presence of lactate dehydrogenase serum levels greater than 1000 U/L and a serum free hemoglobin level greater than 40 mg/L in 2 consecutive samples within 24 hours. In addition to these elements, a reduction of hemoglobin serum values and eventually hematuria strongly supported the diagnosis.

Anticoagulation was achieved by intravenous continuous infusion of unfractionated heparin titrated to maintain an activated partial thromboplastin time between 45 and 50 seconds. In case of heparin-induced thrombocytopenia, unfractionated heparin was discontinued and intravenous bivalirudin infusion was started.

In addition to anticoagulation therapy, standard intravenous therapy included gastric prophylaxis with histamine H₂-receptor antagonists, antibiotic prophylaxis with cefazolin for the first 48 hours after cannulation procedure, hydration, and diuretics. Patients with defined or suspected H1N1 influenza A infection received antiviral therapy with oseltamivir 150 mg twice per day and broad-spectrum antibiotics.

Infection Monitoring and Diagnosis

For infection surveillance and management, we followed international guideline recommendations.³ Infection diagnosis followed Centers for Disease Control and Prevention criteria for specific types of infections in the acute care setting. The Centers for Disease Control and Prevention developed criteria for the diagnosis of 48 specific sites or types of infection and grouped them into 13 major site categories. The diagnosis is based on the presence of a combination of criteria (including clinical signs and symptoms, vital signs, microbiological investigations, and clinical evidence) that are different and clearly stated according to the different types of infection.⁴

Three sets of blood cultures, deep tracheal aspirate or bronchoalveolar lavage, and urine samples were sent periodically to the laboratory for microbiological examination. Whenever an intravascular device was changed or removed, the tip was sent for microbiological investigation. Three sets of blood cultures were obtained in case of fever (38°C) or increase in white blood cell count. A deep tracheal aspirate and eventually a bronchoalveolar lavage were obtained whenever respiratory infection was suspected, such as in changes on chest radiography or evidence of worsening in respiratory performance.

A urinary sample was sent for cultural examination whenever standard monitoring cultural examinations were performed and whenever deemed appropriate. Because the ECMO circuit included the heat exchanger, the changing of temperature alone was not regarded as a sign of infection. When infection was clinically suspected, an empiric wide-spectrum antibiotic therapy was administered immediately after collecting samples for microbiology. Once the causative pathogen was known and the antibiogram was available, the antibiotic therapy was pathogen-tailored. The oxygenator and cannulae were not changed after infection identification.

Parameters of Interest

Two separate blood samples were collected each morning to determine CRP and PCT values, and only 1 value of CRP and of PCT was analyzed per day. PCT values were detected with the Elecsys BRAHMS PCT assay (Brahms, Berlin, Germany), and CRP was determined by a turbidimetric immunoassay (Siemens Healthcare Diagnostics Inc, Deerfield, Ill).

Statistical Analysis

Analysis of the parameters of interest (CRP and PCT) was performed on the values measured once daily during the ECMO run and not on baseline values. Categorical variables are expressed as numbers and percentages,

TABLE 1. Study population baseline characteristics

Parameter	Total (n = 27)	VV ECMO (n = 11)	VA ECMO (n = 16)	P value
Age, y	54.9 ± 11.3	49.6 ± 13.1	58.6 ± 8.6	.01
Gender (male), n	20 (74.1%)	6 (54.6%)	14 (87.5%)	.07
Weight, kg	73.2 ± 13.6	73.1 ± 17.2	73.3 ± 11.1	.7
Height, cm	170.2 ± 6.8	168.5 ± 9.3	171.2 ± 43.5	.5
BMI	25.5 ± 3.4	26.3 ± 3.5	25.0 ± 3.4	.3
BSA	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	.9
Medical hospitalization, n	13 (48.2%)	7 (63.6%)	6 (37.5%)	.8
Elective surgery hospitalization, n	12 (44.4%)	3 (27.3%)	9 (56.3%)	.08
Nonelective surgery hospitalization, n	2 (7.4%)	1 (9.1%)	1 (6.3%)	.9
APACHE II score	14.9 ± 7.1	12.1 ± 4.6	16.8 ± 8.0	.1
SOFA score	8.0 ± 3.3	7.8 ± 4.0	8.2 ± 2.8	.3

ECMO, Extracorporeal membrane oxygenation; BMI, body mass index; BSA, body surface area; APACHE II, Acute Physiology And Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

whereas continuous variables are shown as mean ± standard deviation or as median and interquartile range if the standard deviation is larger than the mean in magnitude.

For group comparisons, binomial test was used for dichotomous variables, whereas Mann–Whitney *U* test or Mood's median test was performed for assay mean or median difference, respectively. Moreover, the Spearman rank-order correlation coefficient was used to compare PCT and CRP variation.

The relation among PCT, CRP, infection, and other parameters under study was analyzed with a generalized estimating equations model, taking into account correlations within patients' measurements, assuming the same correlation between any 2 elements of a cluster (exchangeable correlation matrix).^{5,6}

Receiver operating characteristic (ROC) analysis⁷ was used to identify the most appropriate cutoff values for the diagnosis of infection. The performance of the diagnostic tests was evaluated with the nonparametric method of DeLong and colleagues,⁸ assessing the difference from the non-discriminating ROC curve (area under the curve = 0.5). Sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and misclassification rate were assessed with reference to PCT and

CRP cutoff values, and their 95% CI was calculated with binomial approximation. Calculation of SE, SP, PPV, and NPV is referred to in the text as "accuracy evaluation." To set the false-negative count to zero and to confirm a negative test result, both tests were assessed in parallel with "the OR rule" (positive diagnosis if either test is positive and negative diagnosis if both tests are negative).⁹ This resulted in the creation of a new variable that we called the "PCT and CRP combined assay."

Because of the presence of a conditional dependence between the 2 diagnostic tests, we calculated the covariance of SE and SP and corrected the estimate of the diagnostic performance accordingly.¹⁰ Data were analyzed with SAS 2002–2008 software (release 9.2 by SAS Institute Inc, Cary, NC).

RESULTS

The study population baseline characteristics are shown in Table 1, and the study population data are shown in Table 2. The mean number of days on ECMO support was 6.6 ± 3.8, specifically 7.0 ± 2.7 days in VV cases and 6.4 ± 4.5 days in VA cases.

Eight patients (29.6%) died on ECMO, and no significant difference in mortality between the VV ECMO and VA ECMO groups was observed. The median ICU stay was 15 (7–32) days, and the median hospital stay was 16 (10–51) days, with no statistically significant difference between the groups.

No patient had hemolysis. Thirteen patients (48%) had bacterial or fungal infection: In 7 patients (26%), infection was acquired while on extracorporeal support, and the other 6 patients (22%) had preexisting infection. An overview of infections is shown in Table 3.

We observed 3 episodes of bloodstream infection and 10 infections with negative blood cultures. Among patients without bloodstream infection, we reported 8 pneumonias (7 episodes with positive tracheal specimen and 1 case with positive bronchoalveolar lavage) and 2 episodes of infection with negative microbiological investigations.

Twelve different pathogens were isolated in a total of 13 isolates: gram-negative bacteria were the most common (54%), followed by fungi (23%) and gram-positive

TABLE 2. Study population data

Parameter	Total (n = 27)	VV ECMO (n = 11)	VA ECMO (n = 16)	P value
CRP, mg/L	200.7 (78.4–240.9)	216.9 (142.3–264.0)	111.3 (76.0–206.4)	.03
CRP maximum value registered, d	2 (1–4)	2 (1–3)	3 (1–4)	.6
PCT, ng/mL	3.5 (0.6–15.1)	4.2 (0.3–13.4)	3.1 (0.9–21.0)	.9
PCT maximum value registered, d	2 (1–4)	2 (0–5)	1.5 (1–3.5)	.2
WBC, 10 ⁹ /L	14.2 (9.9–17.9)	11.5 (5.3–17.4)	14.6 (11.4–17.9)	.2
WBC maximum value registered, d	3 (1–6)	4 (3–7)	2 (0.5–3.5)	.1
PC, %	48.6 (42.1–72.3)	47.9 (47.0–64.7)	48.6 (42.1–72.3)	.9
PC maximum value registered, d	2 (1–6)	5 (2–7)	2 (0.5–5)	.6
Lactates, mmol/L	4.22 (2.36–6.73)	2.66 (1.9–7.8)	4.5 (2.9–6.1)	.5
ECMO, d	6.6 ± 3.8	7.0 ± 2.7	6.4 ± 4.5	.4
Hospital stay, d	16 (10–51)	17 (11–41)	15.5 (7–52)	.06
ICU stay, d	15 (7–32)	15 (10–32)	15.5 (6–29.5)	.07
Death on ECMO, n	8 (29.6%)	4 (36.4%)	4 (25.0%)	.9
Infection, n	13 (48.1%)	5 (45.5%)	8 (50%)	.8

ECMO, Extracorporeal membrane oxygenation; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; PC, protein C; ICU, intensive care unit.

TABLE 3. Infection overview

Patient	Extracorporeal support	Type of infection*	Pathogen
1	VV ECMO	Pneumonia	<i>Acinetobacter baumannii</i>
2	VV ECMO	Bloodstream	<i>Candida albicans</i>
		Bloodstream	<i>Corynebacterium minutissimum</i>
3	VV ECMO	Pneumonia	<i>Stenotrophomonas maltophilia</i>
4	VV ECMO	Pneumonia	<i>Enterobacter aerogenes</i>
5	VV ECMO	Pneumonia	No pathogen isolated
6	VA ECMO	Pneumonia	<i>Serratia marcescens</i>
7	VA ECMO	Pneumonia	<i>Aspergillus fumigatus</i>
8	VA ECMO	Pneumonia + bloodstream	<i>Escherichia coli</i>
		Pneumonia	<i>Klebsiella pneumoniae</i>
9	VA ECMO	Bloodstream	<i>Candida albicans</i>
10	VA ECMO	Pneumonia	MRSA
11	VA ECMO	Pneumonia	<i>Haemophilus influenzae</i>
12	VA ECMO	Cholecystitis	No pathogen isolated
13	VA ECMO	Pneumonia	<i>Staphylococcus aureus</i>

MRSA, Methicillin-resistant *Staphylococcus aureus*. *According to Centers for Disease Control and Prevention criteria for specific types of health care-associated infection.

microorganisms (23%). The most frequently isolated pathogen was a fungus: *Candida albicans* was isolated in 2 episodes. Moreover, *Staphylococcus aureus* was the most frequent isolated gram-positive bacterium (67%).

PCT mean values were associated with the ECMO configuration (regression coefficient = -9.327, $P = .047$), adjusted for CRP value (regression coefficient = 0.042, $P = .03$). Therefore, a stratified analysis according to the ECMO configuration was mandatory to detect the optimal cutoff for the diagnosis of infection. On the contrary, we found that CRP mean values were significantly associated with age (regression coefficient = -5.075, $P = .002$) and gender (regression coefficient = -90.752, $P = .01$) but not with the ECMO configuration. Thus, a single cutoff value for CRP was appropriate for both the VV ECMO and VA ECMO groups. In addition, we found a significant positive correlation between PCT and CRP (Spearman's rank correlation coefficient = 0.38, $P < .001$).

The ROC curve of PCT was not significantly different from the nondiscriminating ROC curve ($P = .07$). However, if we distinguish between the 2 types of ECMO configuration, we found that PCT is a reliable biomarker for the diagnosis of infection in patients undergoing VA ECMO (area under the curve, 0.681; 95% CI, 0.551–0.811; $P = .0062$) (Figure E1) but not in patients receiving VV ECMO ($P = .14$). On the other hand, the ROC analysis confirmed a good accuracy of CRP in the discrimination of patients with and without infection in all ECMO cases (area under the curve, 0.707; 95% CI, 0.623–0.791; $P < .001$) (Figure E2).

In the light of these data, we focused only on patients receiving VA ECMO. We performed an accuracy evaluation of PCT as a possible diagnostic test for infection and compared it with CRP. We confirmed a good accuracy of the PCT diagnostic test with 1.89 ng/mL as the optimal cutoff point (SE = 87.8% [95% CI, 78.6–96.9], SP = 50% [95% CI, 33.7–66.3], PPV = 70.5% [95% CI, 59–81.9], NPV = 75% [95% CI, 57.7–92.3], misclassification rate = 28.2% [95% CI, 18.7–37.8]) and the CRP diagnostic test with 97.70 mg/L as the cutoff (SE = 85.3% [95% CI, 76.9–93.7], SP = 41.6% [95% CI, 30.6–52.6], PPV = 56.3% [95% CI, 46.7–65.9], NPV = 76.2% [95% CI, 63.3–89.1], misclassification rate = 37.9% [95% CI, 30–45.8]).

The probability of a negative test result in infection detection, when performing both diagnostic tests in parallel, decreased to 0.018 (SE = 98.2%, SP = 20.8%). Because of the presence of a conditional dependence between PCT and CRP, however, the estimate of the diagnostic performance of the 2 tests in parallel was adjusted according to the SE and SP covariance of 0.110 and 0.051, respectively (SE = 87.2%, SP = 25.9%).

Four variables were identified as statistically significant predictors of infection: parallel test result, that is, the “PCT and CRP combined assay” (odds ratio [OR] = 1.184; 95% confidence interval [CI], 1.073–1.307, $P < .001$), age (OR = 0.980; 95% CI, 0.972–0.988, $P < .001$), presence of infection before ECMO implantation (OR = 1.782; 95% CI, 1.462–2.171, $P < .001$), and duration of ECMO support (OR = 1.056; 95% CI, 1.029–1.084, $P < .001$).

DISCUSSION

This is the first study to address the role of traditional and emerging biomarkers in the diagnosis of infection in patients undergoing ECMO. The most interesting result is the creation of a new test, the “PCT and CRP combined assay,” which was proved to be a statistically significant predictor of infection in patients receiving VA ECMO, along with younger age, presence of infection before the ECMO support, and longer duration of the ECMO support. It is a promising finding, especially because infection in patients undergoing extracorporeal support is a major complication.

Infection rates and causal organisms of 20,741 patients receiving ECMO were recently reported in a query conducted on the Extracorporeal Life Support Organization registry on behalf of the Extracorporeal Life Support Organization Task Force on Infections and ECMO.¹¹ Our study confirmed similar results, because we observed that bacterial or fungal infection developed in approximately half of the patients receiving ECMO. Of note, such infections were not always correlated to the cannulation site; rather, we observed mainly bloodstream infections and pneumonia.

A recent study by Sun and colleagues¹² reported an ECMO-related infection rate of 13.5% in a series of 334 patients. Because the aim of our study was to establish the role of serum biomarkers in the diagnosis of infection in patients on ECMO, we studied the day-by-day changes in biomarker values in patients with or without infection during ECMO support regardless of whether the infection was preexisting. Among the 13 patients with infection of our study, only 7 (26%) had ECMO-related infection. Furthermore, Bizzarro and colleagues¹¹ reported an infection rate of 20.9% in 2298 adult patients, which is similar to the infection rate we observed in our sample.

However, few patients on ECMO are 100% infection free. Even at the time of cannulation, it is difficult to define whether a patient is truly infection free, because ECMO is often used in patients with ARDS or who have undergone elective or nonelective surgery.

Moreover, ECMO is frequently used as a bridge to other therapies, such as heart or lung transplantation and long-term ventricular assist device implantation. However, the presence of infection jeopardizes patients' candidacy to receive these therapeutic options. For this reason, reliable tools for the diagnosis of infection are strongly needed, irrespective of the speculations concerning whether the infection can be defined as related to ECMO or not.

Traditional inflammatory marker assays (eg, CRP and white blood cell count) are often distorted in such patients by the presence of non-septic SIRS. Because the extracorporeal circuit is a foreign body in constant contact with the patient's blood, it triggers the activation of defense mechanisms, resulting in a marked inflammatory response.

In regard to PCT, patients with established sepsis diagnosis generally have higher serum levels than those with SIRS only, and patients with severe sepsis and septic shock are reported to have the highest levels.^{13,14} However, no study previously analyzed PCT as an infection marker in patients undergoing extracorporeal support. Few pioneering studies described PCT kinetics in cardiopulmonary bypass, which is routinely used in cardiac surgery.

Significantly increased PCT values are not observed in the absence of postoperative complications,¹⁵ and PCT levels in patients with infection are generally higher than in patients with noninfectious complications.¹⁶ Nevertheless, it is difficult to recommend cutoff points.

The presence of H1N1 influenza A pneumonia in 7 of the 27 patients is not a limitation of the study, because PCT is supposed to have low or undetectable levels in the case of viral infection.¹⁷⁻¹⁹ Furthermore, some studies also successfully demonstrated that PCT can assist in bacterial infection diagnosis and tailored antibiotic use in patients with H1N1 pneumonia.^{20,21}

In regard to the other acute-phase reactants, a record of increased PCT values must be interpreted cautiously. There

is an overlap between SIRS and sepsis, and many situations other than infection may trigger PCT synthesis and release, including inhalational injury, burn injury, pancreatitis, mechanical trauma, extensive surgery (eg, aortic, cardiac, colonic),^{16,22,23} and cardiogenic shock.²⁴ We acknowledge that many of these conditions were present in our study population and may have partly influenced the PCT values and our results. Of note, several studies available in the literature concluded that a combination of PCT and CRP would provide the most useful information in the diagnosis of infection.^{21,22}

Our study demonstrated that a concomitant PCT and CRP assay is useful in the critical care setting of patients undergoing VA ECMO, because PCT and CRP reach a strong SE (87.2%) when performed together, even with a low SP (25.9%). Furthermore, because the PCT and CRP combined assay was proven to be a statistically significant predictor of infection, its use would be of benefit to clinical routine practice. The other 3 predictors of infection that we found (age, presence of infection before ECMO implantation, and duration of ECMO support) cannot assist the medical attending team in day-to-day clinical decision-making. We showed that the PCT and CRP combined assay can aid in the diagnosis of infection in patients with VA ECMO, and further study will help us to analyze its role in the management of antibiotic therapy.

The low SP of the PCT and CRP combined assay is to be interpreted in light of the fact that we chose to privilege sensitivity to have a high NPV and to exclude the presence of infection as certain as possible if the test was negative. This observation may justify sparing antibiotic therapy for patients with a negative PCT and CRP combined assay test result, with a low error rate.

Our study also shows that PCT is not a reliable marker of infection in patients undergoing VV ECMO. Although the number of patients studied is small, we can argue that because the circuit is the same for VV ECMO and VA ECMO, such difference should be attributed to the patients. In particular, almost every patient with ARDS requiring VV ECMO had primary lung infection in contrast with the primary cardiac failure, which was typical of patients supported with VA ECMO. This observation paves the way for new studies to characterize the different categories of patients requiring ECMO treatment according to disease and comorbidity.

Study Limitations

The study has 4 important limitations. First, the small number of patients does not allow strong and general conclusions, even if the results are impressive. Second, distinguishing between SIRS and sepsis in patients on ECMO is an important problem. Nevertheless, these data would suggest no change in the clinical management of these patients, because the overlap among cardiogenic shock,

SIRS, ECMO itself, and sepsis will always be part of the clinical scenario. Third, in a study conducted on 194 patients with community-acquired infection, Gaini and colleagues²⁵ found that interleukin 6, lipopolysaccharide binding protein, and CRP performed best in distinguishing between SIRS and sepsis, whereas PCT performed best in distinguishing between sepsis and severe sepsis.²⁵ Because the patients included in the study had community-acquired infection instead of nosocomial infections and were not admitted to an ICU, it would be of interest to perform a similar study in the setting of critical care medicine. However, the transferability of this knowledge in the clinical application of ECMO is hard. Fourth, we were unable to identify a new test for the diagnosis of infection in patients undergoing VV ECMO, and further studies on this topic are strongly warranted.

CONCLUSIONS

We suggest a concomitant PCT and CRP assay with definite cutoff values as a new test to identify infection in patients undergoing VA ECMO. PCT routine dosing may be useful for infection diagnosis in patients requiring ECMO and would lead to a more rational and appropriate clinical management of these high-risk patients.

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FIGURE E1. ROC curve of PCT in patients treated with VA ECMO. *ROC*, Receiver operating characteristic.

FIGURE E2. ROC curve of CRP in all patients treated with ECMO. *ROC*, Receiver operating characteristic.