Usefulness of Lung Ultrasound for early detection of Hospital-Acquired Pneumonia in Patients on Venous-Arterial Extra Corporeal Membrane Oxygenation.

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Research

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Abstract

BACKGROUND: Hospital-Acquired Pneumonia (HAP) is the most common and severe complication in patients treated with veno-arterial extracorporeal membrane oxygenation (ECMO). HAP early detection is challenging but crucial for improving clinical outcomes. We conduct an observational study to assess whether Lung Ultrasound (LUS) improves detection of HAP in in patients treated with veno-arterial ECMO.

METHODS: We conducted a single-center, prospective, observational study including adult patients receiving veno-arterial extracorporeal membrane oxygenation assistance that presented acute respiratory failure. Bedside LUS and chest radiography were performed at the time of inclusion when HAP was suspected. Then the patients were independently assessed for HAP including microbiological evidence. The sonographic features of HAP on veno-arterial ECMO were determined. We then compared the performance of the lung ultrasound simplified clinical pulmonary score (LUS-sCPIS), including bio-clinical data and the Doppler detection of intrapulmonary shunt, to the sCPIS, including bio-clinical and chest radiological data for detection of HAP.

RESULTS: We included 70 patients, of which 44 (63%) were independently diagnosed with hospital-acquired pneumonia. LUS examination revealed that Doppler intrapulmonary shunt ($P=0.0000043$) and dynamic air bronchogram ($P=0.00024$) were the most frequent hospital-acquired pneumonia-related signs. The LUS-sCPIS (Area under the curve = 0.77) yielded significantly better results than the sCPIS (Area under the curve = 0.65; $P = 0.004$), while leukocyte count, temperature and chest radiology were not discriminating for the hospital-acquired pneumonia diagnosis.

CONCLUSION: The diagnosis of hospital-acquired pneumonia is a daily challenge for the clinician managing patients on veno-arterial ECMO . Lung ultrasound is more powerful than chest radiography and can be a valuable aid as initial imaging modality for the diagnosis of pneumonia. Intrapulmonary shunt detected using color Doppler and dynamic air bronchogram appear to be particularly discriminating for the diagnosis of hospital-acquired pneumonia.

CLINICAL TRIAL REGSITRATION: NA

Background

Veno-Arterial Extracorporeal Membrane Oxygenation (VA ECMO) is an effective rescue therapy providing temporary cardiac and respiratory support for patients with refractory cardiogenic shock. VA ECMO allows organ perfusion and oxygenation while awaiting myocardial recovery, cardiac transplantation or long-term mechanical circulatory support. Significant progress in device technology and in the management of critically ill patients has allowed an international expansion of use of VA ECMO.[1] In the United States, there were 11 times more VA ECMO for acute myocardial infarction in 2014 than in 2000, with mortality decreasing over this period from 100–45.1%.[2] However, short-term mortality remains high, with an overall survival rate of 40% [3], mainly due to the very high incidence of complications, among which infectious complications are predominant. According to recent studies, hospital-associated

pneumonia (HAP) is the most frequent nosocomial infection among VA ECMO patients.[4,5] Its occurrence has been consistently associated with a longer duration of ECMO support and mechanical ventilation, and an increased mortality.[6] However, due to the lack of international validated diagnostic gold standard procedure, early diagnosis of HAP in VA ECMO patients remains a daily challenge.[7]

Point-of-care lung ultrasound (LUS) was demonstrated to be a performant tool in case of acute respiratory failure for ICU patients[8,9], community-acquired pneumonia,[10,11] ventilator-associated pneumonia [12,13]. The LUS diagnosis of ventilator-associated pneumonia in intensive care units is more challenging in comparison with the diagnosis of community-acquired pneumonia in emergency departments due to the limited access to the mechanically ventilated patients and the high prevalence of atelectasis. However, several studies have demonstrated that the combination of LUS findings with other clinical markers improved the diagnostic accuracy. This bio-clinical and lung ultrasound approach has been successfully applied to diagnose postoperative pneumonia after cardiac surgery.[14] The substitution of chest radiography by color Doppler LUS in the simplified clinical pulmonary infection score (sCPIS), improved diagnostic accuracy for postoperative pneumonia in patients who underwent cardiac surgery with cardiopulmonary bypass. Although LUS appears superior to chest radiography in the evaluation of a critically ill patient with respiratory failure, no convincing evidence is yet available on whether LUS reliably improves the diagnosis of HAP in VA ECMO patients.

The aim of this study was to assess the feasibility, the sonographic features and performance of color Doppler LUS for the diagnosis of HAP in patients under VA ECMO.

Methods

Patient Selection and Study design

Adult patients admitted to the Cardiac Surgery Intensive Care Unit (ICU) of La Pitié-Salpêtrière University Hospital Assistance Publique Hôpitaux de Paris. Sorbonne Université, Paris, France) from May 2018 to May 2020, assisted with VA ECMO and with acute respiratory failure during ECMO support were consecutively enrolled. Each patient gave written informed consent to participate in the study. In case of patients' inability, the legally authorized delegate provided informed consent. The study protocol complied with the Declaration of Helsinki and was approved by the CERAR (Ethics Committee of the Société Française d'Anesthésie et de Réanimation, IRB 00010254 – 2019–174). Acute respiratory failure was defined by at least one of the following criteria: the necessity to increase the fraction of delivered oxygen in the sweep gas by 20% for more than 6 hours; the need to increase the inspired fraction of oxygen (FiO_2) by 20% for more than 6 hours in patients under mechanical ventilation; clinical signs of acute respiratory distress (cyanosis, pulse oximeter oxygen saturation (SpO_2) less than 90%, tachypnea > 25 breaths/min, upper thoracic or intercostal in drawing), *de novo* dependence on high-flow nasal oxygen therapy or non-invasive ventilation and/or the need for oro-tracheal intubation.

Pneumonia Diagnosis

The criteria for the diagnosis of pneumonia were based on the guidelines for the management of adults with HAP.[15,16] Clinical and radiological criteria were used to identify pneumonia ($\geq$ two criteria among fever $> 38.5^{\circ}\text{C}$, leukocytosis $> 11.10^9/\text{L}$ or leukopenia $< 4.10^9/\text{L}$, purulent tracheobronchial secretions and a new or persistent pulmonary infiltrate on bedside chest radiography). A positive quantitative culture of a lower respiratory tract sample was a main criterion to establish the diagnosis: either a positive bronchoalveolar lavage fluid (significant threshold $\geq 10^4$ colony-forming units (CFU) /ml), or a positive plugged telescopic catheter (significant threshold $\geq 10^3$ CFU/ml). The final diagnosis of pneumonia was retained when it was made by at least two of three independent senior physicians and rejected when ruled out by at least two of the three physicians, unaware of LUS examination, sCPIS or LUS-sCPIS values.

Measurement of Intrapulmonary Shunt Using Doppler with Color-flow Mapping

Within consolidations, blood flow signals were detected using Doppler with color-flow mapping as previously described.[17,18] To detect low velocity flow and avoid interference from respiratory movement and heart beats, the following parameters were selected : velocity of 0.21 m/s, Doppler angle of 0° to 180° , wall filter range 70–120 kHz. The color Doppler gain was increased until the background noise appeared as a colored “snowstorm” across the image, and was then backed off until only a few random specks remained visible. The color Doppler window was then focused on the consolidation; if no signal was detected, the steering angle of the color Doppler window was changed to avoid a lack of detection caused by an ultrasound beam perpendicular to the flow signal. As shown in Fig. 1A and 1B. Additional movie files show in more details the use of color Doppler ultrasound without intrapulmonary shunt (Additional file 1) or with intrapulmonary shunt (Additional file 2), corresponding respectively to Fig. 1A and 1B. An intrapulmonary shunt was defined as a persistent area of color signal with a tubular, curvilinear, or branching distribution persisting during the respiratory cycle.. When blood flow signals were detected on color Doppler ultrasound, pulse-wave Doppler was used to obtain their spectral waveform.

Lung Ultrasound, sCPIS and LUS-sCPIS

Bedside lung ultrasound was performed on the day of inclusion by an experimented physician for pulmonary ultrasound (performance of more than 100 pulmonary ultrasounds examinations). The “ultrasound” physician was not involved in the management of the patient. The images were recorded and analyzed only once, in a blinded fashion. Lung ultrasound examination and the analysis of the images were standardized. The areas to be examined were divided in 12 regions i.e., 6 regions per hemithorax as previously described.[19] Ultrasound signs suggestive of pneumonia were the presence of juxta pleural consolidations associated or not with B lines[13,20], one or more pulmonary consolidations, the presence of an intrapulmonary shunt,¹⁰ and/or the presence of static or dynamic air bronchogram within these consolidations(Fig. 1C and Additional File 3).[21] To assess the loss of aeration in each lung zone, a numeric value was assigned according to the most-severe lung ultrasound finding detected in the corresponding examined region. The lung ultrasound aeration score was calculated as the sum of the

numeric values assigned to each examined region, ranging from 0 to 36.[22] The standardized LUS protocol used in this study is detailed in supplemental data (See Supplemental Table 1).

We used the simplified sCPIS (See Supplemental Table 2) described by Luna et al.[23] and the LUS-sCPIS described by Dureau et al. in cardiac surgery patients (See Supplemental Table 3). [14] In this score, the "chest radiography" criterion is replaced by an ultrasound criterion, the presence or not of an intrapulmonary shunt within a consolidation, visualized using color Doppler. The presence of an intrapulmonary shunt is quoted as 2 points.

Statistical Analysis

By estimating the prevalence of pneumonia at 50% in patients on VA ECMO [4,5], a sample size of 70 patients was calculated to detect a change in sensitivity percentage value for LUS-sCPIS from 50–80%, with an 80% power at 0.05 alpha risk. Quantitative variables are presented by their median and quartiles (25th and 75th percentile). Qualitative variables are represented by their numbers and percentages. The two groups were compared in univariate analysis using the Mann-Whitney Wilcoxon test for quantitative variables and the Chi-2 or Fisher test for qualitative variables. Sensitivity, specificity, positive predictive value, negative predictive value, area under the receiver operating characteristic (ROC) curves were calculated to determine the diagnostic performance of the sCPIS and LUS-sCPIS and pulmonary ultrasound parameters studied independently: dynamic air bronchogram, intrapulmonary shunt or a combination of these two parameters.

The diagnostic performances of the sCPIS and LUS-sCPIS were described using ROC curves. The areas under the curves (AUCs) of the ROC curves were compared using a non-parametric Delong test. Due to the small number of missing data, no imputation was performed. The significance threshold was chosen at 5%. The analyses were performed with R software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Between May 2018 and May 2020, 1296 critically ill patients were hospitalized in the cardiac ICU, 241 were assisted with VA ECMO and 70 included and evaluated (Fig. 2). Diagnosis of HAP was established in 44 patients (63%). The study population consisted of 70% men and 30% women. The median age was 63.1 years [56.0–68.1]. Fifty patients had cardiogenic shock after cardiac surgery (71.4%). Of these patients, 18 had undergone heart transplantation, 15 valvular surgery, 5 coronary bypass surgery, and 6 combined surgery. The median CBP duration was 138 minutes and the median preoperative Euroscore 2 was 20.5 [3.66–32.0].[24] The 20 patients assisted for medical reasons had refractory cardiogenic shock related to ischemic heart disease (N = 17) or myocardial rejection after heart transplantation (N = 3). Fifty-nine patients were on mechanical ventilation on the day of inclusion (84%). Five patients received *de novo* treatment with non-invasive ventilation or high-flow nasal oxygen therapy without the need for intubation afterwards. The median time from ECMO initiation to inclusion was 5 days [2.25–7.00]. The rate of patients on antibiotic therapy at inclusion was higher in the pneumonia group (75% vs. 46%, P =

0.015), as was the median total duration of mechanical ventilation (16.0 days [9.00–30.5] vs. 7.5 days [5.00–16.2], $P = 0.002$). Other descriptive data are presented in Table 1.

Table 1
Patient characteristics.

Patient characteristics	Total (n = 70)	Pneumonia		P
		No (n = 26)	Yes (n = 44)	
Baseline characteristics				
Age (y)	63.1 [56.0–68.1]	63.5 [57.5–67.3]	62.6 [53.8–68.5]	0.45
Male (%)	49 (70)	18 (69)	31 (70)	0.91
Comorbidities				
BMI	26.0 [24.2–30.8]	27.5 [25.0–30.8]	26.0 [23.8–29.5]	0.45
Euroscore 2	20.5 [3.66–32.0]	15.5 [5.99–25.0]	21.1 [2.56–32.5]	0.86
SOFA	12.0 [10.0–14.5]	12.0 [11.0–16.0]	11.5 [10.0–14.0]	0.2
Diabetes mellitus (%)	18 (26)	9 (35)	9 (20)	0.19
COPD (%)	8 (11)	4 (15)	4 (9)	0.46
Reason for admission				
Heart surgery	50 (71)	17 (65)	33 (75)	0.46
Heart transplantation	18 (26)	7 (27)	11 (25)	0.86
CBP length (min)	138 [99–190]	120 [99–142]	152 [100–207]	0.099
At day of inclusion				
ICU stay before inclusion (d)	5.00 [2.25–7.00]	3.50 [2.00–5.75]	5.00 [3.00–7.25]	0.073
Days of ECMO before inclusion	5.00 [2.25–7.00]	3.50 [2.00–6.00]	5.00 [3.00–7.25]	0.073
ECMO output (L/min)	4.0 [3.3–4.5]	4.0 [3.52–4.52]	4.0 [3.0–4.5]	0.4
FmO ₂	0.7 [0.6- 0.8]	0.7 [0.6–0.8]	0.7 [0.5–0.8]	0.45
Mechanical ventilation (%)	59 (84)	22 (85)	37 (84)	1

Values are given as the median [IQR] or number (%). ASA, Physical status score; BMI, body mass index; COPD, chronic obstructive pulmonary disease, CPB, cardiopulmonary bypass; ICU, intensive care unit; ECMO, extra corporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; FemO₂, Fraction of delivered oxygen in the sweep gas on VA ECMO; SOFA, Sequential Organ Failure Assessment

Patient characteristics	Total (n = 70)	Pneumonia		P
		No (n = 26)	Yes (n = 44)	
FiO ₂	0.6 [0.5- 0.7]	0.6 [0.4–0.9]	0.6 [0.5–0.7]	0.69
Vasopressor support (%)	50 (71)	22 (85)	28 (64)	0.06
Inotropic support (%)	39 (56)	15 (58)	24 (55)	0.8
Dobutamine (µg/kg/min)	3.00 [0–5.0]	3.85 [0–5.0]	2.75 [0–5.0]	0.56
Antibiotics at inclusion (%)	45 (60)	12 (46)	33 (75)	0.015
Leucocyte count (10 ⁹ /l)	12.8 [9.27–17.5]	13.3 [8.84–17.6]	12.2 [9.36–17.0]	0.55
<i>Outcome</i>				
Duration of mechanical ventilation (d)	13.0 [6.0–26.8]	7.50 [5.0–16.2]	16.0 [9.00–30.5]	0.02
Days of ECMO (d)	14.0 [8.25–22.0]	13.0 [7.75–20.2]	15.0 [10.0–26.8]	0.19
ICU mortality (%)	33 (49)	14 (58)	19 (43)	0.23
Values are given as the median [IQR] or number (%). ASA, Physical status score; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; ICU, intensive care unit; ECMO, extra corporeal membrane oxygenation; FiO ₂ , fraction of inspired oxygen; FemO ₂ , Fraction of delivered oxygen in the sweep gas on VA ECMO; SOFA, Sequential Organ Failure Assessment				

Considered independently, the discriminating criteria of the sCPIS for the diagnosis of pneumonia were the abundance of tracheal secretions and their purulent aspect. Tracheal secretions were described as abundant in 52% of the patients with pneumonia (N = 23) versus 19% (N = 5) in the group without pneumonia (P = 0.0064). Tracheal secretions were scanty in 23% (N = 10) of patients with pneumonia versus 58% (N = 15) of patients without pneumonia (P = 0.00016). Secretions were purulent in 43% (N = 19) of patients with pneumonia versus 19% (N = 5) of patients without pneumonia (P = 0.041). Temperature, leukocyte count and chest radiography findings were not significantly different between the two groups (See Supplemental Table 4).

Lung consolidations were found in almost all patients (94%). In 25% of patients, pulmonary edema, defined as more than 2 examined regions characterized by 2, was observed on top of consolidation. Pulmonary edema was more frequent in patients with pneumonia (30%) than in patients without pneumonia (20%), but the difference did not reach statistical significance (P = 0.18). The extension of consolidation was a discriminating criterion: forty-three percent of patients with pneumonia had more than 3 examined regions characterized by 3 versus 12% of patients without pneumonia (P = 0.006). An intrapulmonary shunt present within a consolidation (cf Fig. 1B) was found in 47% of the patients and was significantly associated with the diagnosis of pneumonia (66% in patients with pneumonia versus

15% in patients without pneumonia, $P = 0.0000043$). An air bronchogram was visualized in 47 patients (67%). The dynamic nature of the air bronchogram was found in 50% of the patients with pneumonia ($N = 20$) and only in a single patient in the group without pneumonia ($P = 0.00024$). The median lung ultrasound aeration score was 15 [11–20] with significantly more aeration loss in the pneumonia group: LUS = 17 [12–20] versus 12 [10–14], $P = 0.0070$ (Table 2). The higher LUS in the pneumonia group was associated with the presence of consolidation in more than three examined regions (43% vs 12%, $P = 0.006$). In the group of patients with pneumonia, 64% had a combination of intrapulmonary shunt and a dynamic air bronchogram, compared to 15% of patients in the group without pneumonia ($P = 0.000009$). The combination of an intrapulmonary shunt and a dynamic air bronchogram yielded an AUC of 0.76 for the diagnosis of pneumonia (Table 3). As shown in Fig. 3, the diagnostic performance of LUS-sCPIS, was significantly better than that of sCPIS: AUC 0.77 [0.67 to 0.88] and AUC 0.65 [0.52 to 0.78] respectively ($P = 0.004$).

Table 2
Comparison of lung ultrasound patterns between groups with and without pneumonia.

Lung ultrasound patterns	Total (n = 70)	Pneumonia		P
		No (n = 26)	Yes (n = 44)	
Consolidation (%)	66 (94)	25 (96)	42 (95)	1
Unilateral	16 (23)	10 (38)	7 (16)	0.072
Bilateral	50 (61)	15 (58)	35 (80)	0.051
Intrapulmonary shunt(%)	33 (47)	4 (15)	29 (66)	0.0000043
Air bronchogram (%)				
Static	26 (37)	10 (38)	16(36)	0.7
Dynamic	21 (30)	1 (4)	20(45)	0.00024
Intrapulmonary shunt + dynamic air bronchogram (%)	32 (46)	4 (15)	28 (64)	0.000009
Juxta pleural consolidation(%)	41 (59)	12 (29)	29 (71)	0.1
Lung ultrasound aeration score	15 [11–20]	12 [10–14]	17 [12–20]	0.007
Quantitative variables are expressed as median [Interquartile range] and qualitative variables as number and percentage (%).				

Table 3
Diagnostic accuracy of lung ultrasound signs.

	Se	Sp	VPP	VPN	AUC
Intrapulmonary shunt	0.66 [0.51–0.78]	0.85 [0.66–0.94]	0.88 [0.77–0.99]	0.60 [0.44–0.75]	0.75 [0.65–0.85]
Dynamic air bronchogram	0.46 [0.32–0.60]	0.96 [0.79–1.00]	0.95 [0.86–1.00]	0.51 [0.37–0.65]	0.71 [0.66–0.79]
LUS-sCPIS	0.64 [0.49–0.76]	0.77 [0.56–0.89]	0.82 [0.61–0.90]	0.56 [0.39–0.72]	0.77 [0.67–0.88]
sCPIS	0.59 [0.44–0.72]	0.65 [0.46–0.80]	0.74 [0.60–0.88]	0.49 [0.33–0.64]	0.65 [0.52–0.78]
LUS-sCPIS and sCPIS in detection of VAP. Se = sensivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value, AUC = area under the curve, sCPIS = simplified Clinical Pulmonary Infection Score, LUS-sCPIS = Lung ultrasound-simplified Clinical Pulmonary Infection Score, where the "chest radiography" criterion is replaced by the presence or not of an intrapulmonary shunt within a consolidation, visualized using color Doppler					

Discussion

This study, performed in cardiac patients on VA ECMO shows several important findings: 1) consolidation of lower lobes was present in 94% of patients with acute respiratory failure 2) diffuse pulmonary edema was present on top of consolidation in 30% of patients with pneumonia and 15% of patients without pneumonia 3) Bedside chest radiography was not discriminating for pneumonia 4) The presence of an intrapulmonary shunt within consolidations, detected by color Doppler ultrasound, was highly suggestive of pneumonia 5) the diagnostic performance of the Lung Ultrasound Score sCPIS, where color Doppler replaces bedside chest radiography, was higher than the conventional sCPIS.

Components of sCPIS and LUS-sCPIS: Diagnostic Value in Patients on VA ECMO

HAP diagnosis is known to be difficult in postoperative cardiac surgery patients.[25] We hypothesized that the criteria usually used to diagnose pneumonia may not be discriminating in VA ECMO patients, as the extracorporeal circulation generates an inflammatory response, and the interpretation of chest radiography is complicated by the frequent presence of cardiogenic pulmonary edema.

As expected, clinical criteria as body temperature and leucocyte count were comparable in both groups. The level of vasopressor support was not discriminating. The difficulty of establishing the diagnosis using the conventional approach resulted in a high rate of inappropriate probabilistic antibiotic therapy in the non-pneumonia group (46%). Taking into consideration specificities of surgical cardiac patients, and

specifically patients on VA ECMO, is a prerequisite to improve diagnostic performance at the bedside. Dureau et al.[14] showed that the LUS-sCPIS is much more performant than the sCPIS for the early diagnosis of postoperative pneumonia in cardiac patients. Intra-operative cardiopulmonary bypass-induced inflammatory reaction is a confounding factor jeopardizing the diagnostic value of bio-clinical and radiological parameters of the conventional sCPIS. Passive atelectasis of dependent lung regions is a common postoperative feature, resulting from diaphragm paralysis. The presence of an intrapulmonary shunt within the atelectatic areas (consolidations) is likely characteristic of an inflammatory/infectious process, a mechanism that likely explains why the LUS-sCPIS was more discriminating for pneumonia diagnosis. Intrapulmonary shunt has been reported in community-acquired pneumonia[17,26], ventilator-associated pneumonia[19], postoperative pneumonia[16], obstructive pneumonia caused by endobronchial tumor[17,27], and acute respiratory distress syndrome[18,28]

Few studies have specifically addressed pneumonia in VA ECMO patients[5] and our work is the first to investigate the LUS diagnostic performance. Lung ultrasound is easy to learn.[29] In acute respiratory failure, it provides an immediate and accurate assessment of the patient's respiratory status and can guide a rapid clinical decision. The presence of a pulmonary blood flow within a consolidation is significantly associated with the diagnosis of pneumonia. Incorporating the intrapulmonary shunt into the LUS-sCPIS yielded an AUC of 0.77, compared with 0.65 for the conventional sCPIS.[23] Confirming a previous statement¹³, the dynamic air bronchogram was significantly associated with the diagnosis of pneumonia with a positive predictive value of 95% and a specificity of 96% %. As fibroaspiration was not systematically performed before lung ultrasound examination, the true incidence of dynamic air bronchogram may have been underestimated [30], explaining the low sensitivity of 46%. The presence of juxta pleural condensation were not discriminating, contrasting with previous studies performed in patients with ventilator-associated pneumonia.[13,31] In comparison, only the abundant and purulent character of the tracheal secretions was discriminating, against none of the radiological criteria.

The poor performance of the chest radiography is easily explained by the high incidence of bilateral posterobasal consolidations (94% in our study) in mechanically ventilated patients following cardiac surgery.[32] As previously reported¹⁹, bilateral radiological infiltrate and coalescent B2 lines due to hydrostatic pulmonary edema were present in 30% of our patients on ECMO VA [33], complicating the chest radiography interpretation. These results support the concept that combining ultrasound and clinical criteria is more discriminating than combining radiological and clinical criteria for the diagnosis of pneumonia in patients on VA ECMO.

Limits

The first limitation of our study is its monocentric nature, with a number of patients limited transplantations (26%). This recruitment bias, linked to the specific characteristics of our center (first heart transplant center in France), may explain the high rate of pneumonia among included patients (63%). Cardiac transplantation and the postoperative context of cardiac surgery are indeed well-known risk factors for HAP.[34,35] The exact prevalence of pneumonia in our VA ECMO patients is difficult to

estimate, as not all consecutive patients admitted to our department were included. Second, the lack of a gold standard for the diagnosis of HAP, resulting in heterogeneous diagnostic criteria used in most studies, as well as the nonconsecutive recruitment of our patients depending on the presence of a LUS experts, may have led to biases. Despite these elements, the rate of pneumonia found in our study remains comparable to the highest incidences reported in the literature, estimated between 60% and 70%.[4,5,36] to 70. Most of them were cardiac surgery patients (71%), including a large proportion of heart

The sensitivity of color Doppler intrapulmonary shunt to detect pneumonia was only 66%, compared with 92% in the study by Dureau et al.¹⁴ The AUC of LUS-sCPIS was also relatively low (0.77). Physiologically, it is expected that a shunt within a consolidation will be detected in pneumonia because of the inhibition of hypoxic vasoconstriction due to local inflammation.[26] In VA ECMO patients, Doppler visualization of an intrapulmonary shunt could be compromised by the modification of transpulmonary blood flow related to the shunting of the cardiac chambers resulting from ECMO. Other parameters may also modify the intrapulmonary shunt, such as vasoactive support or mechanical ventilation settings.

Clinical implication

Any delay in diagnosis and antibiotic treatment of pneumonia in VA ECMO patients, who are already weakened by their critical condition, worsens the prognosis. Conversely, overexposure to unwarranted antibiotic treatment in uninfected patients favors the emergence of bacterial resistance.

Our study shows that in presence of acute respiratory failure complicating VA ECMO, the detection of an intrapulmonary shunt and/or a dynamic air bronchogram within a consolidation should alert the clinician to the possible diagnosis of pneumonia. The LUS-sCPIS score, which was previously described in cardiac surgery patients [14], is also more accurate than sCPIS in diagnosing pneumonia. Both ultrasound findings should incite to perform microbiological sampling and could help to identify patients who should receive empirical antibiotic therapy.

Conclusion

Our study demonstrates that lung ultrasound is a useful tool as initial imaging modality for the diagnosis of pneumonia in patients on VA ECMO. LUS is rapid and easy to perform at the bedside, in addition to being non-invasive and relatively inexpensive. The presence of an intrapulmonary shunt visualized using color Doppler is significantly associated with the presence of pneumonia in these patients. LUS-sCPIS is also more accurate than sCPIS in diagnosing pneumonia and may be a useful tool for the appropriate management of patients on VA ECMO with a suspected pneumonia.

Abbreviations

AUC: Area under Curve

BAL: Bronchoalveolar lavage

BMI: Body Mass Index

CPIS: Clinical Pulmonary Infection Score

FiO₂: Fraction of Inspired Oxygen

FmO₂: Fraction of delivered oxygen in the sweep gas on VA ECMO

HAP: Hospital-Acquired Pneumonia

LUS: Lung Ultrasound

LVAD: Left Ventricular Assist Device

PCT: Procalcitonin

PTP: Plugged Telescopic Catheter

Se: Sensitivity

sCPIS: Simplified Clinical Pulmonary Infection Score

SIRS: Systemic Inflammatory Response Syndrome

SOFA: Sepsis-related Organ Failure Assessment

Sp: Specificity

LUS-sCPIS = Lung ultrasound-simplified Clinical Pulmonary Infection Score, where the "chest radiography" criterion is replaced by the presence or not of an intrapulmonary shunt within a consolidation, visualized using color Doppler

NPV: Negative Predictive Value

PPV: Positive Predictive Value

VA ECMO: Veno-Arterial Extra Corporeal Membrane Oxygenation

Declarations

Ethics approval and consent to participate: CERAR (Ethics Committee of the Société Française d'Anesthésie et de Réanimation, IRB 00010254 - 2019 - 174).

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

Guarantor: AB is the guarantor of the content of the manuscript, including the data and analysis.

Authors' contribution

JP contributed substantially to the acquisition of data, to the statistical analysis and interpretation of the data, drafted the article and provided final approval of the version submitted for publication.

PD contributed substantially to the conception and design of the study, the acquisition of data, the analysis and interpretation of the data, provided critical revision of the article and provided final approval of the version submitted for publication.

JP and PD contributed equally to this work and should be considered as co-first authors.

JJR contributed to the analysis and interpretation of the data, contributes to the illustration of the article and provided critical revision for important intellectual concept

AB contributed substantially to the conception and design of the study, the analysis and interpretation of the data, provided critical revision of the article and provided final approval of the version submitted for publication.

GA, VL, BD participated to the acquisition of data, interpretation of the data and approved the version submitted for publication.

GH, GL provided critical revision of the article and approved the version submitted for publication. GH reviewed and approved the statistical analysis.

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Figures

Figure 1

A) Color Doppler lung ultrasound in the consolidated left lower lobe in a 54 years old patient without pneumonia on veno-arterial extracorporeal membrane oxygenation. The extracorporeal membrane oxygenation was initiated 2 days before and pneumonia was ruled out by a bronchoalveolar lavage retrieving 2.102 orophayngeal flora. Color signals are diffuse and changing resulting from interferences caused by respiratory movements and heart beats. Corresponding to Video 1A (Additional file 1) B)

Intrapulmonary shunt detected in the consolidated right lower lobe of a 43 years old patient with pneumonia on veno-arterial extracorporeal membrane oxygenation. The extracorporeal membrane oxygenation was initiated 12 days before for a cardiogenic shock and pneumonia was confirmed by a bronchoalveolar lavage retrieving 104 *Escherichia coli*. The blood flow in a vessel is seen as a color signal persisting in the same location during the respiratory cycle with a tubular, curvilinear, or branching distribution on real-time images. When blood flow signals are detected, pulse-wave Doppler can identify their spectral waveform.¹⁹ Corresponding to Video 1B (Additional file 2) C) Dynamic air bronchogram in a 79 years old patient with pneumonia on veno-arterial extracorporeal membrane oxygenation. The extracorporeal membrane oxygenation was initiated 5 days before for a cardiogenic shock and pneumonia was confirmed by a bronchoalveolar lavage retrieving 6.106 *Hafnia alvei*. Corresponding to Video 1C (Additional file 3)

Figure 2

Flow chart. ECMO = Extracorporeal Membrane Oxygenation; LUS = lung ultrasound; VA = veino arterial;
ICU = intensive care unit

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