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Safety and efficacy of beta-blockers to improve oxygenation in patients on veno-venous ECMO

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ABSTRACT

Purpose: Beta-blockers (BB) may improve oxygenation in patients on veno-venous extracorporeal membrane oxygenation (V-V ECMO). This study analyzed safety and efficacy of BB in hypoxemic patients on V-V ECMO.
Materials and methods: Retrospective analysis of patients who were treated with BB during V-V ECMO in two centers. The primary safety outcome was a composite of occurrence of bradycardia or hypotension with need for intervention, resuscitation, unexplained rise in serum lactate, and discontinuation of beta-blockers for other reasons than inefficacy or resolution on hypoxemia during the first 5 days of therapy. The main efficacy outcome was increase in oxygen saturation (SaO_2) within 12 h after start of BB.
Results: 33 patients received BB for 4 [3–7] days while on V-V ECMO. Fifteen episodes of adverse events occurred in 13 patients (39%); BB had to be discontinued in only one patient for sustained hypotension. In two other patients, doses were reduced or temporarily withheld due to bradycardia. There was an increase in SaO_2 from 92 [90–96]% to 96 [94–97]% at 12 h, with unchanged mean arterial pressure and norepinephrine doses.
Conclusions: In this study, use of BB in hypoxemic patients on V-V ECMO was safe and associated with a moderate increase in SaO_2.

1. Introduction

Beta-blockers (BB) could improve oxygenation in patients with persistent hypoxemia, by reducing intrapulmonary shunt through a reduction in cardiac output [1]. Vincent et al. showed that intravenous propranolol led to increase in PaO2 in acutely hypoxemic patients. This may also occur in patients on veno-venous extracorporeal membrane oxygenation (V-V ECMO). In some patients, V-V ECMO fails to restore arterial oxygenation saturation (SaO_2) to acceptable targets [2].

Although low SaO_2 thresholds down to 80% may be tolerated [3], clinical tolerance to hypoxemia largely depends on the patient's physiological status. The most important determinant of SaO_2 during V-V ECMO is the ratio of ECMO blood flow to cardiac output (Q_{ECMO}/Q_{CO}): the higher the ratio, the higher the SaO_2. Schmidt et al. demonstrated that a Q_{ECMO}/Q_{CO} >60% was associated with an SaO_2 higher than 90% during V-V ECMO [4]. Another important factor is recirculation of blood into the ECMO circuit, which is influenced by the distance between the drainage and return cannula, but also by Q_{ECMO} [5]. Finally, haemoglobin levels influence total oxygen delivery (DO_2) and may also indirectly influence SaO_2, as a low haemoglobin results in lower venous O_2 saturation in the flow not passing the ECMO circuit [4].

In case of persistent hypoxemia during V-V ECMO, after having excluded recirculation, the main step to increase SaO_2 is to increase Q_{ECMO} as much as possible (i.e. 5–7 L/min). Moreover, it may be necessary to give red blood cell transfusions to increase oxygen delivery [4]. Optimization of residual lung function can also be obtained by recruitment manoeuvres and a more aggressive ventilation strategy, although this might increase the risk of lung over-distension, and prone position, which is not easy to implement during V-V ECMO [6]. BB can be used to improve SaO_2, by decreasing Q_{CO} and thereby increasing Q_{ECMO}/Q_{CO}. However, this approach has been described in only 9 patients, reported in three different studies [7-9]. Safety and efficacy have never been reported in larger numbers of patients, and experts remain sceptical

Abbreviations: ARDS, acute respiratory distress syndrome; BB, beta-blockers; ELSO, extracorporeal life support organization; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; PEEP, positive end expiratory pressure; Q_{ecmo}, ECMO blood flow; Q_{co}, cardiac output; RASS, Richmond agitation and sedation scale; RESP, respiratory ecmo survival prediction; V-V ECMO, veno-venous extracorporeal membrane oxygenation.

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about the use of BB in this setting. Therefore, we explored safety and efficacy of BB during V-V ECMO in a cohort of patients treated in two university centers.

2. Materials and methods

2.1. Study design and population

We reviewed the data of all patients who were treated with BB during V-V ECMO in two ECMO centers (Erasmus MC, University Medical Center Rotterdam, The Netherlands and Cliniques Universitaires de Bruxelles Erasme, Brussels, Belgium) between January 2012 and December 2017. The study protocol was approved by the Ethical Committees of both hospitals. Informed consent was not deemed necessary for this anonymous retrospective study according to local regulations and privacy laws. Patients receiving BB for other indications than V-V ECMO, i.e. arrhythmias or coronary artery disease, or receiving BB before V-V ECMO initiation were excluded.

2.2. Study endpoints

We formulated a composite safety endpoint as primary outcome, which was defined by the occurrence of any of the following during the first 5 days of BB treatment: a) documented bradycardia (heart rate <50/min) with need for intervention (i.e. discontinuation of BB, administration of atropine and/or epinephrine); b) hypotension (mean arterial pressure, MAP<60 mmHg) with need for intervention (i.e. initiation or increase in norepinephrine >0.1 μg/kg/min compared to baseline); c) need for cardiopulmonary resuscitation; d) a rise in serum lactate concentration >1.5 mmol/L (compared to baseline) in the absence of a new episode of documented septic shock; e) any other reason for BB discontinuation other than inefficacy or resolution of hypoxemia. Patients could meet more than one safety endpoint. The secondary endpoint was the change in SaO_2, after the first 12 h of BB compared to baseline.

2.3. Data collection

All parameters were retrieved from the hospital electronic patient file and the ICU Patient Data Management System. Baseline characteristics included gender, age, comorbidities, ECMO configuration, Respiratory ECMO Survival Prediction (RESP) score [10], and indication for V-V ECMO. Characteristics and parameters at start of BB therapy included vasopressor dose, indication for BB, type of BB, sedatives and sedation level (i.e. Richmond agitation and sedation score). The dose of BB over the first 12 h was recorded. Also, HR, MAP, vasopressor dose, ECMO flow, sweep gas flow, ventilator settings, lactate, PaO_2 and $PaCO_2$ were recorded after 1, 3, 6 and 12 h after the initiation of BB treatment. Total duration of BB treatment, total ECMO duration and ICU outcome (i.e. recovery with weaning, bridge to transplantation, death) were also collected.

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 24.0 for Windows. Descriptive statistics were computed for all study variables and normal distribution was assessed using the Kolmogorov–Smirnov test. Data are presented as count (percentage) or median [25th–75th percentiles].

To assess change in SaO_2 and other parameters, values at 12 h were compared with the baseline value (i.e. the last available before BB administration) using the Wilcoxon Signed Rank test. A p value <0.05 was considered significant.

3. Results

Of a total of 274 patients treated with V-V ECMO in the two centers, we retrieved 33 patients (12%) who received BB (18 in Rotterdam and 15 in Brussels). Characteristics of these patients are shown in Table 1. V-V ECMO was initiated 3 [2-7] days after ICU admission; in 23 patients, V-V ECMO configuration was based on double cannulation (with femoral drainage and jugular reinjection), while 8 patients had a right jugular double lumen cannula. Two patients had V-VA ECMO as a result of initial V-A cannulation for cardiogenic shock, with secondary respiratory failure requiring a V-branch when cardiac output improved. The total duration of ECMO was 10 [8-21] days; 16 (48%) patients were successfully weaned from ECMO and all 16 survived to hospital discharge.

BB treatment was initiated after a median of 3 [2-7] days on V-V ECMO. The main reason for initiation of BB was to increase SaO_2 (Table 2). In 9 patients (27%) hypoxemia occurred only at awakening from sedation or during mobilization. Close to three fourth of patients (24/33, 73%) were treated with sedative agents (propofol and/or midazolam), All patients received at least one opioid (remifentanil, fentanyl or morphine), and 11 (33%) received clonidine. The vast majority of patients (30/33, 91%) were on mechanical ventilation at the moment of BB initiation.

The total duration of BB therapy was 4 [3-7] days. Metoprolol was used in 27 patients (82%), orally in 11 patients, preceded by an intravenous loading dose (median dose 5 mg; ranges 5–15 mg) in 4 patients. Median total oral dose in 12 h was 25 mg (ranges 25–50 mg). Sixteen patients received intravenous metoprolol, with a median dose of 4 mg/h (ranges 0–10 mg/h), preceded by a loading dose in 9 patients (median dose 5 mg; ranges 5–20 mg). Five patients received intravenous esmolol (median bolus of 50 mg; ranges: 25–50 mg; median dose of 45 mg/h; ranges 15–100 mg/h). One patient received labetalol (bolus of 25 mg and repeated additional boluses of 10–20 mg over the next hours).

Table 1
Baseline patient characteristics and patient outcome.

	n = 33
Patient demographics	
Age, years	49 (39–56)
Male gender, n (%)	18 (55)
Body weight, kg	74 (62–90)
History of heart failure, n (%)	1 (3)
History of ischemic heart disease, n (%)	3 (9)
Diabetes, n (%)	2 (6)
COPD/asthma, n (%)	6 (18)
Chronic renal disease, n (%)	1 (3)
Liver cirrhosis, n (%)	2 (6)
Apache IV score, median (IQR)	69 (60–86)
Characteristics on the initiation of ECMO	
Respiratory diagnosis:	
Bacterial pneumonia, n (%)	12 (36)
Viral pneumonia, n (%)	2 (6)
Other acute respiratory diagnosis, n (%)	15 (45)
Chronic respiratory and non-respiratory, n (%)	4 (12)
Bridge to transplant, n (%)	9 (27)
Days on mechanical ventilation before ECMO, median (IQR)	4 (1–9)
RESP score, median (IQR)	0 (−2–3)
ECMO configuration:	
Veno-venous, double cannulation, n (%)	23 (70)
Veno-venous, single dual lumen cannula, n (%)	8 (24)
Venous to venous and arterial (VVA), n (%)	2 (6)
Patient outcome	
Days on ECMO, median (IQR)	10 (8–21)
Successful weaning or transplant, n (%)	18 (55)
ICU survival, n (%)	16 (48)
Hospital survival, n (%)	16 (48)

Abbreviations: APACHE, acute physiology and chronic health evaluation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; RESP, Respiratory ECMO survival prediction;

Table 2
Characteristics of beta-blocker treatment and main clinical parameters at the start of the treatment.

	n = 33
Beta-blocker treatment	
Days on ECMO at start of beta-blocker, median (IQR)	3 (2–7)
Indication for beta-blocker:	
Increase SaO_2, n (%)	24 (73)
Low SaO_2 only during waking up/mobilization, n (%)	9 (27)
Days of beta-blocker use during ECMO, median (IQR)	4 (3–7)
Type and dose of beta-blocker:	
Metoprolol oral, n (%)	11 (33)
Iv loading dose, n (%)	4 (12)
Median oral dose per patient in first 12 h (mg)	25 (25–50)
Metoprolol iv, n (%)	16 (45)
Median dose per hour at t = 12 h (mg/h)	4 (0−10)
Esmolol iv, n (%)	5 (15)
Median dose per hour (mg)	45
Labetalol iv, n (%)	1 (3)
Median dose per hour (mg)	15
Parameters at the start of beta-blocker	
Haemoglobin (g/dl)	8.9 (8.4–9.6)
Creatinine (mg/dl)	0.6 (0.5–1.4)
Bilirubin (mg/dl)	0.6 (0.3–1.0)
CRP (mg/dl)	160 (110–249)
RASS score	-3 (−3;-1)
Sedatives and analgesics:	
Propofol infusion, n (%)	15 (45)
midazolam infusion, n (%)	11 (33)
Clonidine infusion, n (%)	11 (33)
Any opioid infusion, n (%)	33 (100)
Mechanical ventilation >16 h/dag, n (%)	30 (91)
Ventilator modus (control/support), n/n	19/11
FiO_2 on ventilator	0.5 (0.4–0.7)
ECMO flow (l/min)	4.4 (3.9–5)
Any kind of mobilization of patient, n (%)	3 (9)

Abbreviations: CRP, C reactive protein; ECMO, extracorporeal membrane oxygenation; iv, intravenous; RASS, Richmond Agitation and Sedation Score.

3.1. Main endpoints

We found 15 safety events in 13 patients (39%) (Table 3). Of those 13 patients, 6 patients were on oral therapy and 7 patients received intravenous BB. One patient needed norepinephrine increase >0,1 μg/kg/min 1 h after an intravenous loading dose of metoprolol, 2 patients on intravenous BB had an increase of norepinephrine within 12 h after BB initiation. All other endpoints occurred after >24 h on beta-blockers. An episode of bradycardia occurred in 2 patients. One patient had sinus bradycardia due to a combination of BB, ivabradine and sedation. The other patient temporarily experienced a Mobitz II AV-block. In both patients BB treatment was not discontinued, but the subsequent dose was temporarily decreased (in the first patient) or withheld (in the second patient). Nine patients required an increase in norepinephrine to maintain MAP, but only in one patient BB treatment was stopped because of clinically relevant hypotension. Two patients had a transient elevation in lactate levels, not followed by any adjustments in BB therapy. No patient needed cardiopulmonary resuscitation. Possible drug-drug interaction in one patient and new onset of severe septic shock on day 4 of treatment in another patient were other reasons to stop BB.

Table 3
Occurrence of primary safety endpoint and its components (in bold) during first 5 days of beta-blocker treatment.

	n = 33
Any potential safety endpoint (composite of below)	**15**
Number of patients affected by any safety endpoint	13
during treatment with oral beta-blocker	6
during treatment with intravenous beta-blocker	7
Heart rate 50/min with need for intervention, n	**2**
Withholding one dose, beta-blocker continued thereafter, n	1
Withholding one dose, dose adjusted, n	1
Need for resuscitation, n	**0**
Need for an increase in norepinephrine, n	**9**
Beta-blocker continued	8
Beta-blocker stopped	1
New rise in lactate levels	**2**
Transient serious ECMO flow problems[a]	1
Episode of severe coughing, dyspnea, agitation	1
Any reason to stop beta-blocker, other than end of indication	**2**
New septic shock[a]	1
Risk for interaction	1

Abbreviations: ECMO, extracorporeal membrane oxygenation.
[a] Patient had need for an increase in norepinephrine dose as well.

Change in hemodynamics, gas exchanges and ECMO related parameters in the first 12 h after the initiation of BB are reported in Table 4 and Fig. 1 and Fig. 2. After initiation of BB, SaO_2 increased from 92 [90–96]% to 96 [94–97]% ($p = 0.01$). Heart rate decreased from 105 [87–116] bpm to 93 [80–104] bpm ($p < 0.01$). Lactate levels, norepinephrine dose, MAP and $PaCO_2$ did not change significantly. ECMO flow and ventilatory conditions were not changed.

4. Discussion

In this retrospective study, we observed that the administration of BB in patients on V-V ECMO significantly increases SaO_2 although the effect was small (i.e. 4%), where baseline SaO_2 values were already relatively high. The intervention was associated with few side-effects, thus presenting a good safety profile. >10% of our total V-V ECMO population was treated with BB in this setting.

Increasing fraction of oxygen on the ventilator (FiO_2) or more aggressive ventilator strategies using recruitment manoeuvres, higher positive end-expiratory pressure (PEEP) and/or higher driving pressures could be effective to improve oxygenation as well, but can result in additional lung injury [11,12]. Furthermore, BB can be administered in awake patients; i.e. patients being bridged to lung transplantation by V-V ECMO.

Although 39% of patients presented with at least one potential side effect, in only one patient BB was stopped due to a clinically relevant problem (hypotension), while in two others the occurrence of another event (i.e. new septic shock and potential drug-drug interaction) induced the clinicians to stop the treatment. Most episodes with need for increase of norepinephrine occurred after >24 h and occurred both in oral and intravenous treated patients. An intravenous loading dose of metoprolol was followed by an increase in norepinephrine dose in one patient. Other potential factors contributing to late increases in norepinephrine dose were attempts for negative fluid balances, or sedation. The main hemodynamic effect we observed in the first 12 h was a reduced heart rate, which underlined that the drug regimen was effective to provide the expected results, i.e. negative chronotropic and inotropic effects.

In previous studies in critically ill patients, BB were generally well tolerated hemodynamically [13]. No major side effects were described either in the small series on short acting BB during V-V ECMO [7-9]. Unfortunately, we did not measure Q_{CO}, which would have provided additional information on the effects of BB on systemic hemodynamics, global tolerance and DO_2. Our population was likely to be selected, after having excluded hypovolemia or severe cardiac dysfunction. Thus, patients' characteristics are an important factor in the selection of the best therapeutic strategy to correct persistent hypoxemia during V-V ECMO.

During V-V ECMO, the extracorporeal trans-membrane oxygen transfer depends primarily on Q_{ECMO} [14]. Nevertheless, arterial blood oxygenation results from a more complex interplay among recirculation, Q_{ECMO}, oxygenator function, Q_{CO} and pulmonary shunting [15]. In particular, any elevation of the Q_{CO}, unaccompanied by equal adjustment in the Q_{ECMO}, will result in a higher fraction of the CO returning deoxygenated to the right heart and to the native lungs and result in arterial desaturation. Increase of Q_{ECMO} is effective in this case but

Table 4
Course of hemodynamics, gas exchanges and ECMO parameters during first 12 h after initiation of BB.

Parameter	Baseline	T = 1 h	T = 3 h	T = 6 h	T = 12 h	P value[a]
Heart rate, bpm	105 (87–116)	94 (76–103)	96 (78–104)	99 (84–105)	93 (80–104)	p < 0.01
MAP, mmHg	88 (74–96)	76 (73–88)	80 (71–92)	76 (69–87)	80 (74–91)	p = 0.34
CVP, mmHg	11 (9–16)	12 (8–16)	12 (8–15)	11 (7–14)	12 (8–16)	p = 0.48
SaO_2, %	92 (90–96)	95 (94–97)	95 (94–97)	95 (94–97)	96 (94–97)	p = 0.01
PaO_2, mmHg	62 (55–74)	72 (64–82)	70 (61–81)	70 (64–88)	71 (59–83)	p = 0.44
$PaCO_2$, mmHg	43 (41–48)	43 (39–46)	41 (38–46)	42 (38–47)	42 (38–46)	p = 0.60
ECMO blood flow, l/min	4.4 (3.9–5.0)	4.5 (4.0–5.0)	4.6 (4.0–5.0)	4.6 (4.0–5.0)	4.6 (4.1–5.0)	p = 0.27
Sweep gas flow, l/min	5 (4–7)	6 (4–7)	5 (4–7)	6 (4–7)	6 (4–8)	p = 0.41
FiO_2 on ventilator[b]	0.5 (0.4–0.6)	0.5 (0.5–0.6)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	p = 0.19
Lactate, mmol/l	1.3 (1.1–1.9)	1.4 (1.0–2.0)	1.5 (1.2–1.9)	1.2 (1.0–1.6)	1.3 (1.1–1.6)	p = 0.58
Norepinephrine dose, μg/kg/min	0.02 (0–0.18)	0.02 (0–0.11)	0.03 (0–0.15)	0.04 (0–0.11)	0.04 (0–0.17)	p = 0.81
Patients on norepinephrine, n (%)	20 (61)	18 (55)	21 (64)	23 (70)	23 (70)	p = 0.45[c]
Dose in pts. receiving nor	0.13 (0.03–0.35)	0.11 (0.05–0.25)	0.11 (0.03–0.26)	0.09 (0.03–0.23)	0.09 (0.04–0.24)	

All values are median (IQR).
Abbreviations: MAP, mean arterial pressure; CVP, central venous pressure; ECMO extracorporeal membrane oxygenation;
[a] P-values at t = 12 h versus baseline calculated using Wilcoxon signed rank test.
[b] Based on 29 patients on mechanical ventilation.
[c] P-value at t = 12 h versus baseline calculated using McNemar test.

could be limited in the maximal values by the ECMO configuration (i.e. oxygenator, pump and cannulas size) or complicated by increased recirculation, haemolysis or collapse of the inferior vena cava. As such, the most effective strategy to improve SaO_2 in this setting without exposing patients to major risks remains still unsolved. Advanced therapies include body cooling or inhaled nitric oxide, although they can potentially increase the risk of infections, bleeding and renal failure [16,17]. As such, BB would be a less invasive and cheaper strategy in this setting. Indeed, in patients with a hyperdynamic circulation, BB may reduce the amount of blood which would not be oxygenated by the extracorporeal membrane, decrease the intra-pulmonary shunt and also provide some myocardial protection [18]. Noteworthy, in their randomised study on esmolol in septic shock patients, Morelli et al. reported an increase in PaO_2/FiO_2 ratio in (non ECMO) patients treated with esmolol, as Vincent et al. showed with propranolol [1,19]. A prospective study could better clarify the contributions of the various potential mechanisms involved.

In contrast to most other measures aiming to increase SaO_2, BB administration may not increase DO_2, as it aims to increase the Qecmo/Qco ratio by reducing cardiac output. The effect of BB on DO_2 can vary and the benefit of a higher SaO_2 in the absence of an increase in DO_2 is speculative. A hyperdynamic circulation is probably driven less by hypoxemia than by sympathetic and inflammatory response [20]. However, severe hypoxemia may be life threatening and hypoxemia during ARDS may be associated with cognitive impairment [21,22]. Also, the impact of transient events (i.e. coughing, unstable ECMO flow) on gas exchange will be much bigger at lower SaO_2 already on the steep portion of the O_2– haemoglobin dissociation curve.

Previous studies reported an effective increase in arterial oxygenation and minimal side effects of intravenous esmolol in a few patients with hypoxemia (PaO2 ≈ 50 mmHg) [7-9]. Our study confirms these findings in a larger patient population, using primarily metoprolol. In general, the doses chosen were low in order to maximize the benefit/risk balance. Although the half-time of metoprolol is longer than esmolol, metoprolol has a β1-selective effect (i.e. myocardial protection and less hypotension), can be easily titrated to avoid significant bradycardia and has almost no accumulation in patients with renal failure, which is common in patients undergoing ECMO [23]. The fact that we rarely found side effects (i.e. hypotension) after intravenous administration with a loading dose, could be affected by patient selection. Although oral metoprolol(tartrate) obtains its maximum effect already at T = 1,5 h, an intravenous loading dose has an immediate effect and warrants caution in critically ill patients, especially in the early phase of their disease when compensatory tachycardia may be present due to vasoplegia or hypovolemia. True hypovolemia was unlikely in our patient population, as this generally limits maximizing V-V ECMO flow. Although hypoxemia may have stimulated tachycardia, a large component of tachycardia was supposedly caused by "sympathetic overshoot" (non-compensatory tachycardia) in critically ill patients or perceived stress in those patients where we aimed for light sedation

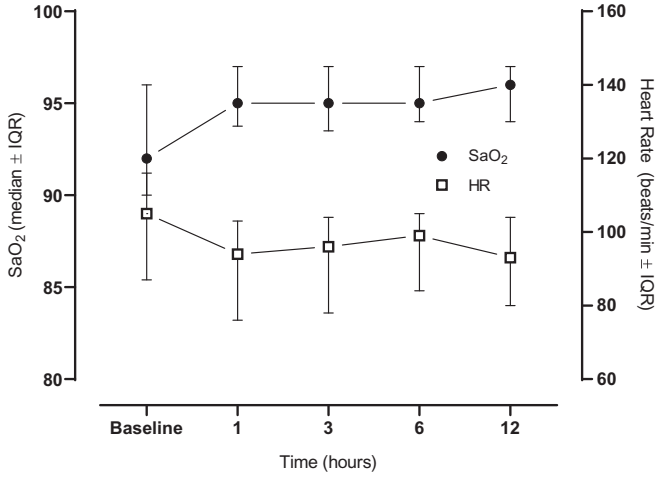

Fig. 1. Arterial oxygen saturation (SaO_2 (%)) and heart rate (beats/min) versus time. Data are presented as median with inter quartile range (IQR).

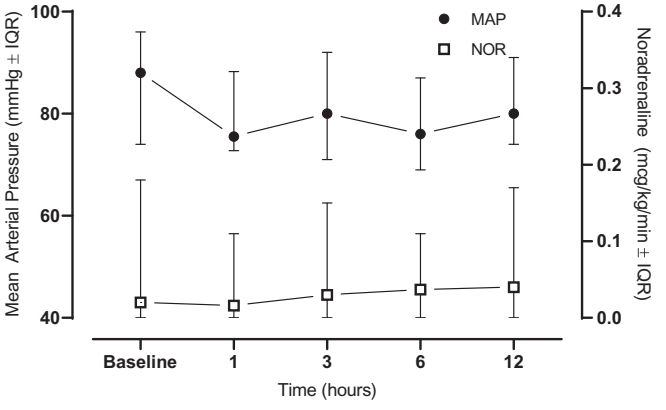

Fig. 2. Mean arterial pressure (mmHg) and norepinephrine dose (μg/kg/min) versus time. Data are presented as median with interquartile range (IQR).

or mobilization. Further studies on the selection of the most effective BB, as well as the optimal dosing and administration strategy (i.e. bolus vs. continuous infusion) are required.

The initial SaO_2 before BB was relatively high (i.e. 92%) in the patients we studied, and one may question the need for an increase of SaO_2 as the main indication for BB in these patients. The extracorporeal life support organization (ELSO) guidelines, recommends a PaO_2 of 6 to 7,3 kPa, resulting in a SaO_2 of 80–85%, or even 75–80% for critically ill ECMO patients [3]. Yet, there is little evidence to support this, as there are no good quality trials comparing these lower SaO_2 targets to a normal SaO_2 (i.e. >90%) strategy in adults [24].

In previous studies, hypoxemic ECMO patients were often sedated and hypoxemia was significantly more relevant (SaO_2 75–80%) [7-9]. Nevertheless, BB still produced large improvement in SaO_2 in these patients. In many patients in our study we found that hypoxemia was often transient, occurring during activities such as washing the patient, or during wake-up calls or attempts to mobilize the patient. These findings suggest a potential benefit of BB in two situations: In the very early phase with significant hypoxemia, or in a later "stable" phase, where hypoxemia may limit general management, including light sedation and mobilization of patients.

The strengths of our study are the relatively large number of patients included, the detailed characterization of the population considered and its multicentric design. However, our study also has limitations. First, the retrospective nature of the study and the absence of control group as well as the lack of some important hemodynamic and echocardiographic data would limit the interpretation of our findings. Secondly, data come from two different ICUs, which have different admission criteria and different guidelines for use of drugs and manage ECMO. Furthermore, there was no predefined SaO_2 or other target of therapy, and individual physicians decided on dose and route of administration, balancing potential risks and benefits. Third, BB therapy was quite safe, but any side effects may have been underestimated in the data collection. Fourth, we used arterial blood gas analysis values in our study, and not pulse oximetry. Although blood gas derived values are more reliable than pulse oximetry values, there were no pre-specified sampling time points and we used the results closest to the desired time point. Hence, the effect of BB on transient hypoxemic episodes could not be assessed reliably.

5. Conclusions

In our experience, BB therapy was well tolerated and resulted in a significant increase in arterial oxygenation in patients on V-V ECMO. Future prospective studies should be performed to clarify the benefit of this strategy in this setting.

Conflicts of interest

None.

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References

[1] Vincent JL, Lignian H, Gillet JB, Berre J, Contu E. Increase in PaO2 following intravenous administration of propranolol in acutely hypoxemic patients. Chest 1985;88(4):558–62.
[2] Combes A, Hajage D, Capellier G, Demoule A, Lavoue S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378(21):1965–75.
[3] ELSO guidelines for cardiopulmonary extracorporeal life support, version 1.4. Ann Arbor, MI, USA: Extracorporeal Life Support Organization, www.elso.org; 2017.
[4] Schmidt M, Tachon G, Devilliers C, Muller G, Hekimian G, Brechot N, et al. Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults. Intensive Care Med 2013;39(5):838–46.
[5] Abrams D, Bacchetta M, Brodie D. Recirculation in venovenous extracorporeal membrane oxygenation. ASAIO J Am Soc Artif Intern Organs 2015;61(2):115–21.
[6] Guervilly C, Hraiech S, Gariboldi V, Xeridat F, Dizier S, Toesca R, et al. Prone positioning during veno-venous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome in adults. Minerva Anestesiol 2014;80(3):307–13.
[7] Guarracino F, Zangrillo A, Ruggeri L, Pieri M, Calabro MG, Landoni G, et al. Beta-blockers to optimize peripheral oxygenation during extracorporeal membrane oxygenation: a case series. J Cardiothorac Vasc Anesth 2012;26(1):58–63.
[8] Pappalardo F, Zangrillo A, Pieri M, Landoni G, Morelli A, Stefani M, et al. Esmolol administration in patients with VV ECMO: why not? J Cardiothorac Vasc Anesth 2013;27(4):e40.
[9] Pinto BB, Siegenthaler N, Tassaux D, Banfi C, Bendjelid K, Giraud R. VV-ECMO and brave heart: a subtle competition? Int J Cardiol 2015;186:45–7.
[10] Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The respiratory extracorporeal membrane oxygenation survival prediction (RESP) score. Am J Respir Crit Care Med 2014;189(11):1374–82.
[11] Serpa Neto A, Schmidt M, Azevedo LC, Bein T, Brochard L, Beutel G, et al. Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis : mechanical ventilation during ECMO. Intensive Care Med 2016;42(11):1672–84.
[12] Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimaraes HP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. Jama 2017;318(14):1335–45.
[13] van Loon LM, van der Hoeven JG, Lemson J. Hemodynamic response to beta-blockers in severe sepsis and septic shock: a review of current literature. J Crit Care 2018;50:138–43.
[14] Park M, Costa EL, Maciel AT, Silva DP, Friedrich N, Barbosa EV, et al. Determinants of oxygen and carbon dioxide transfer during extracorporeal membrane oxygenation in an experimental model of multiple organ dysfunction syndrome. PLoS One 2013;8(1):e54954.
[15] Messai E, Bouguerra A, Harmelin G, Di Lascio G, Cianchi G, Bonacchi M. A new formula for determining arterial oxygen saturation during venovenous extracorporeal oxygenation. Intensive Care Med 2013;39(2):327–34.
[16] Kimmoun A, Vanhuyse F, Levy B. Improving blood oxygenation during venovenous ECMO for ARDS. Intensive Care Med 2013;39(6):1161–2.
[17] Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev 2016;6 (Cd002787).
[18] Lynch JP, Mhyre JG, Dantzker DR. Influence of cardiac output on intrapulmonary shunt. J Appl Physiol Respir Environ Exerc Physiol 1979;46(2):315–21.
[19] Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. Jama 2013;310(16):1683–91.
[20] Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet (London, England) 2005;365(9453):63–78.
[21] Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson LV. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160(1):50–6.
[22] Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med 2012;185(12):1307–15.
[23] Hoffmann KJ, Regardh CG, Aurell M, Ervik M, Jordo L. The effect of impaired renal function on the plasma concentration and urinary excretion of metoprolol metabolites. Clin Pharmacokinet 1980;5(2):181–91.
[24] Gilbert-Kawai ET, Mitchell K, Martin D, Carlisle J, Grocott MP. Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients. Cochrane Database Syst Rev 2014;5 (Cd009931).