OBJECTIVES: The aim of this manuscript is to describe the first year of our experience using extracorporeal membrane oxygenation support.

METHODS: Ten patients with severe refractory hypoxemia, two with associated severe cardiovascular failure, were supported using venous-venous extracorporeal membrane oxygenation (eight patients) or veno-arterial extracorporeal membrane oxygenation (two patients).

RESULTS: The median age of the patients was 31 yr (range 14–71 yr). Their median simplified acute physiological score three (SAPS3) was 94 (range 84–118), and they had a median expected mortality of 95% (range 87–99%). Community-acquired pneumonia was the most common diagnosis (50%), followed by P. jiroveci pneumonia in two patients with AIDS (20%). Six patients were transferred from other ICUs during extracorporeal membrane oxygenation support, three of whom were transferred between ICUs within the hospital (30%), two by ambulance (20%) and one by helicopter (10%). Only one patient (10%) was anticoagulated with heparin throughout extracorporeal membrane oxygenation support. Eighty percent of patients required continuous venous-venous hemofiltration. Three patients (30%) developed persistent hypoxemia, which was corrected using higher positive end-expiratory pressure, higher inspired oxygen fractions, recruitment maneuvers, and nitric oxide. The median time on extracorporeal membrane oxygenation support was five (range 3–32) days. The median length of the hospital stay was 31 (range 3-97) days. Four patients (40%) survived to 60 days, and they were free from renal replacement therapy and oxygen support.

CONCLUSIONS: The use of extracorporeal membrane oxygenation support in severely ill patients is possible in the presence of a structured team. Efforts must be made to recognize the necessity of extracorporeal respiratory support at an early stage and to prompt activation of the extracorporeal membrane oxygenation team.

KEYWORDS: Extracorporeal Membrane Oxygenation; Respiratory Failure; Mechanical Ventilation; Patient Care Team; Intensive Care Unit.
Acute or acute-on-chronic pulmonary disease, $= 1$ for at least 1 hour, with or $\text{P/F}$ ratio $2$.

Possibility of disease reversion

Murray’s score (lung injury score) was set to 0.6. In

METHODS

The ECMO group comprised nurses, respiratory thera-
pists, and physicians. The care for ECMO-supported patients was delivered by one physician, one nurse, two nursing assistants, and one respiratory therapist, all of whom were also in charge of three additional critically-ill patients.

ECMO support was indicated based on individual judgment of the following objective criteria (20):

Major criteria (both required):
- Acute or acute-on-chronic pulmonary disease
- Possibility of disease reversion

Complementary criteria (at least one required):
- $\text{P/F}$ ratio $\leq 50$ with $\text{FiO}_2 \geq 1$ for at least 1 hour, with or without rescue maneuvers
- $\text{P/F}$ ratio $\leq 50$ with $\text{FiO}_2 \geq 0.8$ for at least 3 hours, despite rescue maneuvers
- Hypercapnia with $\text{pH} \leq 7.2$ using a respiratory rate of at least 35 breaths per minute, with a tidal volume of 4–6 mL/kg of ideal body weight and a plateau pressure $\leq 30$ cmH$_2$O
- Murray’s score (lung injury score) $> 3.0$ with the patient presenting a clinical deterioration

ECMO support was not administered to patients with severe chronic illness without the possibility of improve-
ment of their quality of life.

The canulation of patients was performed percutaneously at the bedside with the Seldinger technique using femoral and jugular canulae (Edward Lifesciences, Irvine, CA, EUA). In the three patients who were transferred from other hospitals, we initiated the ECMO support before the patient was transported. We primed the ECMO circuit with 600 mL of normal saline solution at room temperature. A centrifugal magnetic pump with a polymethylpentene oxygenation membrane (Rotaflo/Josta Quadrox - D, Maquet Cardio-pulmonary AG, Hirrlingen, Germany) was used for all patients.

Initially, the blood flow was maintained at 500 mL per minute until the system was filled with blood. Blood flow and sweep (gas) flow were subsequently increased to 2000 mL per minute when using the venous-venous (VV) configuration. The blood flow and sweep flow were then elevated in a 1:1 ratio, with a peripheral oxygen saturation target of at least 90%. When using the veno-arterial (VA) configuration, the blood flow was gradually elevated to 5000 mL per minute, and the sweep flow was set at 5 L per minute. The ECMO support settings were adjusted based on the arterial blood gases (in the VV configuration) or on the arterial blood pressure, vasopressor requirement, and serum lactate levels (in the VA configuration).

No prophylactic antibiotics were administered. Anticoa-
gulation with heparin was initiated at the team’s discretion, beginning with 1000 IU per hour without bolus and adjusted to reach an activated partial thromboplastin time ratio of 1.5–2.5.

Mechanical ventilation was adjusted to a positive end-expiratory pressure (PEEP) of 10–15 cmH$_2$O, an inspired fraction of oxygen ($\text{FiO}_2$) of 0.3 or the least possible value, a driving pressure of less than 10 cmH$_2$O, and, if necessary, a respiratory rate of 10 breaths per minute (5). The parameters checked daily included arterial blood gases, clots in the system visible through translumination, pump cannula auscultation, and flowmeter lubrication to maintain a good signal quality. The ECMO blood flow was adjusted to maintain a $\text{PaO}_2$ greater than 55 mmHg, and the sweep flow was adjusted to keep the $\text{pH}$=7.3 (through the $\text{PaCO}_2$ modulation). Typical sedatives and analgesics were used if necessary to reach a Richmond agitation sedation scale (RASS) score of zero with no pain. Body temperature was kept between 36 and 37 degrees Celsius with an external apparatus adapted to the ECMO system.

A test to evaluate whether a patient could be weaned from ECMO support was carried out daily. The mechanical ventilation settings remained constant in patients with pressure support ventilation; in patients under controlled ventilation, the tidal volume was raised to 6 mL/ideal body weight or was maintained at a level sufficient to keep the plateau pressure $< 25$ cmH$_2$O and the driving pressure $< 15$ cmH$_2$O. In both situations, the $\text{FiO}_2$ was set to 0.6. In the VV configuration, the test consisted of stopping the sweep flow. In the VA configuration, the test consisted of reducing both the blood flow and sweep flow to 1,000 mL per minute, with an ECMO $\text{FiO}_2$ of 0.21. The weaning test was interrupted if the patient presented a mean arterial blood pressure $< 65$ mmHg, peripheral oxygen saturation $< 85\%$, or respiratory distress (respiratory rate $> 35$ breaths per minute, accessory muscle use, abdominal muscle contraction, diaphoresis, hypertension, or intense complaints of dyspnea). After 1 hour, the patient was considered able to have the ECMO support removed (positive removal associated with low-frequency ventilation com-
pared with conventional treatment (4). The trial was stopped early due to futility. Mechanical ventilation with suboptimal settings and high airway pressures in the CO$_2$ removal arm may have been associated with the negative final result. In 2009, the CESAR trial demonstrated a reduction in mortality and disability at six months among severe ARDS patients using a combined strategy of ECMO and protective mechanical ventilation compared with conventional protective mechanical ventilation (5).

The renewed interest in the use of ECMO was also fostered by the 2009 epidemic of severe pneumonia due to influenza-A H1N1(6–13). Young patients with refractory hypoxemia were common among those affected by this disease, and respiratory rescue with ECMO was carried out with excellent outcomes in Australia (14), the United Kingdom (15), and Italy (16). These data suggest a survival benefit of using ECMO in addition to conventional support (15). In Brazil, many patients with influenza-A H1N1 required mechanical ventilation (17), and some of them developed severe hypoxemia, in whom the case mortality reached 11.6% (11). The absence of centers in Brazil that specialize in ECMO limited the availability of adequate support for those patients (18).

We implemented an ECMO service in two hospitals in São Paulo, Brazil. We followed a stepwise approach, which included theoretical training of ECMO, the use of wet lab practice with ECMO in animals in the research facility, and finally the use of ECMO in patients at the bedside. The aim of this manuscript is to describe the first year of our experience using ECMO support in patients with severe hypoxemic respiratory failure.
weaning test) if he or she was hemodynamically stable without elevations in inotropics or vasopressors, without respiratory distress, with a PaO\textsubscript{2}/FiO\textsubscript{2}=55 mmHg and a pH=7.30. The decanulation was performed at the bedside in the venous-venous configuration after the reversal of anticoagulation. In the veno-arterial configuration, the arterial canulae withdrawal was performed in the surgical room.

Data are presented as medians (minimum–maximum), which were obtained using the R – free source statistical package (Vienna, Austria, 2009) (21).

RESULTS

During a one-year period, ten patients with severe respiratory and/or cardiac dysfunction were supported with ECMO. The general characteristics of patients are shown in Table 1. The patients were young and had extremely severe disease, as demonstrated by their high expected mortality rate (Table 1). The most common etiology of the acute cardiopulmonary dysfunction was community-acquired pneumonia, and six of the ten patients were transferred from outside ICUs.

The patients’ support and clinical statuses prior to ECMO are shown in Table 2. They had low partial pressure of oxygen to inspired fraction of oxygen (P/F) ratios, as well as elevated PEEP and plateau pressures. At least one rescue therapy strategy for refractory hypoxemia had been performed on each patient prior to the initiation of ECMO. We used five sets of 20 French canulae (five long venous and five short arterial canulae) and five sets of 22 French canulae to administer ECMO.

Data regarding the monitoring and physiological variables associated with ECMO support are shown in Tables 3 and 4. ECMO support enabled a significant reduction in tidal volume and FiO\textsubscript{2} during its use.

Table 1 - Characteristics of patients supported by ECMO.

<table>
<thead>
<tr>
<th>General Characteristics</th>
<th>(n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td>31 (14–71)</td>
</tr>
<tr>
<td>Gender – MF – n (%)</td>
<td>5 (50)/5 (50)</td>
</tr>
<tr>
<td>Weight – kg</td>
<td>59 (46–84)</td>
</tr>
<tr>
<td>Pre-ECMO LOS – days *</td>
<td>9 (1–40)</td>
</tr>
<tr>
<td>SAPS 3 score #</td>
<td>94 (84–118)</td>
</tr>
<tr>
<td>Expected mortality – (%)</td>
<td>95 (87–99)</td>
</tr>
<tr>
<td>Duration of pre-ECMO hypoxemia (h)</td>
<td>9 (2–20)</td>
</tr>
</tbody>
</table>

Etiologic diagnosis

- Community-acquired pneumonia: 5 (50)
- P. jiroveci pneumonia + AIDS #: 2 (20)
- Alveolar hemorrhage + SLE #: 1 (10)
- Traumatic pulmonary contusion: 1 (10)
- Nosocomial pneumonia: 1 (10)

Comorbidities

- Hypertension: 2 (20)
- Diabetes: 1 (10)
- Heart failure: 1 (10)
- Atrial fibrillation: 1 (10)

Transfer

- No transfer: 4 (40)
- By in-hospital transportation: 3 (30)
- By ambulance: 2 (20)
- By helicopter: 1 (10)

Quantitative data are shown as medians (minimum, maximum).

# SAPS denotes simplified acute physiological score.

#: SLE denotes systemic lupus erythematosus.

Table 2 - Pre-ECMO clinical status and support §.

<table>
<thead>
<tr>
<th>Arterial blood gases</th>
<th>(n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO\textsubscript{2} – mmHg</td>
<td>50 (36–56)</td>
</tr>
<tr>
<td>PaCO\textsubscript{2} – mmHg</td>
<td>57 (31–142)</td>
</tr>
<tr>
<td>P/F ratio</td>
<td>50 (36–56)</td>
</tr>
</tbody>
</table>

Mechanical ventilation

- PEEP – cmH\textsubscript{2}O: 15 (10–23)
- FiO\textsubscript{2}: 1 (1–1)
- Respiratory rate – breaths/minute: 28 (18–90)
- Tidal volume – mL: 275 (130–400)
- Plateau pressure – cmH\textsubscript{2}O: 31 (25–46)

Pre-ECMO respiratory rescue maneuvers

- Alveolar recruitment – n (%): 7 (70)
- Neuromuscular blockade – n (%): 6 (60)
- Corticosteroids – n (%): 4 (40)
- High frequency ventilation – n (%): 3 (30)
- Tracheal gas insufflation – n (%): 1 (10)

Hemodynamics

- Norepinephrine – n (%)/dosage (mcg/kg/minute): 10 (100)/0.64 (0.28–5.12)
- Epinephrine – n (%)/dosage (mcg/kg/minute): 2 (20)/0.44 (0.19–0.70)
- Dobutamine – n (%)/dosage (mcg/kg/minute): 3 (30)/15 (4–20)
- Vasopressin – n (%)/dosage (mcg/minute): 1 (10)/0.03
- Mean arterial blood pressure – mmHg: 63 (30–94)
- Heart rate – beats/minute: 145 (109–180)

Metabolic

- Temperature - °C: 37.4 (36.6–41.2)
- Lactate – mEq/L: 2.8 (1.6–4.1)
- pH: 7.17 (6.9–7.41)
- SBE – mEq/L #: -2.3 (–21.9–5.6)

Sedation, analgesia and neuromuscular blockers

- SAS: 1.5 (1.0–3.0)
- Midazolam - n (%)/dosage (mg/kg/hour): 4 (40)/0.16 (0.11–0.42)
- Propofol - n (%)/dosage (mg/kg/hour): 4 (40)/0.73 (0.21–1.69)
- Fentanyl - n (%)/dosage (mcg/kg/hour): 7 (70)/2.25 (0.85–6.28)
- Thiopental - n (%)/dosage (mg/kg/hour): 1 (10)/3
- Atracurium - n (%)/dosage (mg): 5 (50)/50 (50–50)
- Cisatracurium - n (%)/dosage (mg): 1 (10)/20

All quantitative data are presented as medians (minimum, maximum).

§ ECMO denotes extracorporeal membrane oxygenation.

High-frequency ventilation denotes high-frequency positive pressure ventilation (HPPV).

# SBE denotes standard base excess.
**DISCUSSION**

In these severely injured patients with an expected survival of less than 13%, this study demonstrated a survival of 40% when using ECMO for respiratory and/or cardiovascular support. Another interesting aspect of this study was the enrollment of patients with acquired immunodeficiency syndrome (AIDS), who are not candidates for ECMO support in classical ECMO referral centers due to their high morbidity and mortality rates (22). Of note, the two AIDS patients included in our study died; one death was due to meningitis and the other was due to severe liver failure, and both occurred after the removal of ECMO support. One of these AIDS patients required 32 days of ECMO support and died 11 days after ECMO weaning. However, AIDS is a common condition among the patients in the Brazilian public health care services (23), and the use of ECMO support for those patients cannot be denied a priori until it is evaluated in a prospective trial.

The high SOFA and simplified acute physiological score (SAPS) 3 scores at the beginning of ECMO support in our patients suggest late enrollment and late initiation of ECMO support. This issue could be corrected by the early recognition of severe ARDS and the early activation of the ECMO team. To this end, promoting the awareness of the methodology and the existence of a referral center within the local medical community is likely an important step.

The VV configuration has lower oxygen-transfer efficacy compared with the VA configuration due to recirculation and the local medical community is likely an important step.

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Table 4 - Hematological, metabolic, infection and sedation support and monitoring of patients during extracorporeal membrane oxygenation.

<table>
<thead>
<tr>
<th>Hematological support</th>
<th>First day</th>
<th>Throughout support</th>
<th>Last day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin - g/dL</td>
<td>7.6 (4.7–11.5)</td>
<td>7.5 (4.7–11.5)</td>
<td>7.0 (6.0–8.5)</td>
</tr>
<tr>
<td>Platelet count – platelets/mm³</td>
<td>120000 (41000–400000)</td>
<td>84000 (7000–40000)</td>
<td>67000 (19000–254000)</td>
</tr>
<tr>
<td>Patients on heparin therapy – n (%)</td>
<td>7 (50)</td>
<td>6 (60)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Heparin dosage – (IU/h)</td>
<td>1000 (500–1000)</td>
<td>1000 (500–1200)</td>
<td>1000 (500–1000)</td>
</tr>
<tr>
<td>APTT ratio ¹</td>
<td>1.7 (0.8–3.0)</td>
<td>1.3 (0.8–3.3)</td>
<td>2.1 (1.9–2.1)</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.5 (1.3–4.0)</td>
<td>1.3 (1.1–4.4)</td>
<td>1.4 (1.1–3.0)</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>1882 (1111–16173)</td>
<td>2281 (491–31413)</td>
<td>2175 (1322–31143)</td>
</tr>
<tr>
<td>Indirect bilirubin – mg/dL</td>
<td>0.23 (0.01–2.27)</td>
<td>0.29 (0.01–3.10)</td>
<td>0.38 (0.10–1.38)</td>
</tr>
<tr>
<td>Packed red cell transfusion – n (%)/units/patient</td>
<td>1 (10)/2</td>
<td>4 (40)/4 (3–11)</td>
<td>1 (10)/2</td>
</tr>
<tr>
<td>Plasma transfusion – n (%)/units/patient</td>
<td>0 (0)/0</td>
<td>3 (30)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Platelet transfusion – n (%)/units/patient</td>
<td>0 (0)/0</td>
<td>6 (60)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic support</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral energy intake – kCal</td>
<td>0 (0–475)</td>
<td>825 (0–1200)</td>
<td>638 (0–1200)</td>
</tr>
<tr>
<td>Enteral protein intake - g</td>
<td>0 (0–19)</td>
<td>36 (0–48)</td>
<td>26 (0–48)</td>
</tr>
<tr>
<td>Temperature - °C</td>
<td>36.4 (35.0–41.2)</td>
<td>36.4 (33.1–41.2)</td>
<td>36.2 (34.2–37.9)</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (7.11–7.51)</td>
<td>7.39 (7.11–7.51)</td>
<td>7.37 (7.29–7.47)</td>
</tr>
<tr>
<td>SBE – mEq/L ¹</td>
<td>-5.0 (18.9–8.4)</td>
<td>4.4 (1.1–17.3)</td>
<td>1.6 (-13.3–11.1)</td>
</tr>
<tr>
<td>Serum lactate – mEq/L</td>
<td>4.4 (1.1–17.3)</td>
<td>3.1 (0.8–19.7)</td>
<td>2 (1.2–17.0)</td>
</tr>
<tr>
<td>Renal replacement therapy administration – n (%)</td>
<td>7 (70)</td>
<td>8 (80)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Renal replacement therapy mode – n (%)</td>
<td>CVVHD 1(10)/CVVHF 6 (60) ¹</td>
<td>CVVHF 8 (80) ¹</td>
<td>CVVHF 7 (70) ¹</td>
</tr>
<tr>
<td>Adenosine citrate dextrose (ACD-A 2.2%) administration – n (%)</td>
<td>2 (20)</td>
<td>5 (50)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Fluid balance – mL</td>
<td>1203 (-1028–7564)</td>
<td>428 (-4997–8612)</td>
<td>200 (-1355–3037)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection support</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients using antibiotics – n (%)</td>
<td>9 (90)</td>
<td>10 (100)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>C-reactive protein – mg/dL</td>
<td>177 (43–465)</td>
<td>165 (8–465)</td>
<td>167 (40–336)</td>
</tr>
<tr>
<td>Leukocytes – leucocytes/mm³ ¹</td>
<td>13620 (2510–60350)</td>
<td>13620 (2510–60350)</td>
<td>11995 (7000–41980)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sedation</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SAS ²</td>
<td>2 (1–5)</td>
<td>4 (1–6)</td>
<td>3 (1–4)</td>
</tr>
<tr>
<td>Patients receiving sedatives/analgesics – n (%)</td>
<td>9 (90)</td>
<td>9 (90)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Fentanyl – n (%)/mcg/kg/h ²</td>
<td>8 (80)/1.0 (0.4–6.3)</td>
<td>8 (80)/1.0 (0.3–6.3)</td>
<td>5 (50)/0.8 (0.3–2.3)</td>
</tr>
<tr>
<td>Propofol – n %(mg/kg/h ²</td>
<td>3 (30)/0.8 (0.5–2.1)</td>
<td>3 (30)/0.9 (0.2–2.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Midazolam – n %(mg/kg/h) ²</td>
<td>1 (10)/0.08</td>
<td>1 (10)/0.10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dexamethasone – n %(mcg/kg/h) ²</td>
<td>1 (10)/0.5</td>
<td>2 (20)/0.2 (0.2–0.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

¹This is the maximum dosage used during the analyzed period.
²FF and VA denote the venous-venous and veno-arterial ECMO configuration, respectively.
³This is the median dosage during the analyzed period.
⁴CVVHF denotes continuous venous-venous hemofiltration, and CVVHD denotes continuous venous-venous hemodialysis.
⁵ECMO denotes extracorporeal membrane oxygenation.
⁶APTT denotes activated partial thromboplastin time.
⁷SBE denotes standard base excess.
⁸SAS denotes sedation agitation score.

Blood flowmeter, and the other occurred due to meningitis. Three patients underwent brain death; one case was due to a trauma-related carotid dissection, one was due to meningitis and one was due to severe and prolonged hypoxemia (~12 h) prior to ECMO administration. The former patient also developed severe hypoxia-related rhabdomyolysis and hypoxic hepatitis, and he was the only patient who was determined to be brain dead while receiving ECMO support, which is a staff configuration that can potentially reduce the costs of ECMO support.

Our patients were allowed to awaken after the ECMO installation and transport. Their comfort was maintained despite their severe lung injuries. Some patients presented respiratory compliances as low as 6 mL/cmH₂O; however, when the membrane sweep flow was sufficiently high, those patients were usually comfortable while alert and oriented.

Only one patient was anticoagulated during the entire ECMO support. The coexistence of bleeding or severe coagulopathy in the remaining patients resulted in the contraindication of anticoagulation (22). The new ECMO systems have a heparin-bound surface, which allows the ECMO support to proceed with minimal or no anticoagulation (29). In addition to the surface technology, the use of a high blood flow through the system is likely associated with the preservation of the ECMO circuits.

Renal replacement therapy is frequently applied through the ECMO circuit (30). Eighty percent of our patients required continuous venous-venous hemofiltration, which was applied through an individual catheter, a choice we made to minimize manipulations of the ECMO system.
Hypoxic hepatitis was diagnosed when alanine transaminase and all patients were discharged free from dialysis and oxygen support.

The pneumothoraces occurred at the end of ECMO support in all.

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ECMO denotes extracorporeal membrane oxygenation.

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