Veno-venous extracorporeal membrane oxygenation with interatrial shunting: A novel approach to lung transplantation for patients in right ventricular failure

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Objective: This study evaluated the effectiveness of an atrial septostomy with veno-venous extracorporeal membrane oxygenation in alleviating high afterload right ventricular dysfunction while providing respiratory support. This technique could be applied as a bridge to lung transplantation.

Methods: Sheep (56 ± 3 kg) underwent a clamshell thoracotomy and hemodynamic instrumentation, including right ventricular pressure and cardiac output. Sheep with and without tricuspid insufficiency (n = 5 each) were examined. While sheep were on extracorporeal membrane oxygenation, right ventricular failure was established by banding the pulmonary artery until cardiac output was 40% to 60% of baseline. An extracardiac atrial shunt was created with modified vascular grafts to examine the effect of shunt flow on hemodynamics. Hemodynamic data were thus collected at baseline, during right ventricular failure, and for 1 hour at 100% (fully open), 70%, 50%, and 30% of baseline shunt flow.

Results: Cardiac output was returned to baseline values (tricuspid insufficiency: 5.2 ± 0.2 L/min, without tricuspid insufficiency: 5.3 ± 1.2 L/min) with 100% shunt flow (tricuspid insufficiency: 4.8 ± 1.1 L/min, without tricuspid insufficiency: 4.8 ± 1.0 L/min; P = .15) but remained significantly lower than baseline at 70% to 30% shunt flow. At 100% shunt flow, tricuspid insufficiency shunt flow was 1.4 ± 0.8 L/min and without tricuspid insufficiency shunt flow was 1.7 ± 0.2 L/min. Right ventricular pressure was significantly elevated over baseline values at all shunt flows (P < .001). In the group without tricuspid insufficiency, all sheep died beginning at the 70% shunt condition, whereas all animals with tricuspid insufficiency survived the entire experiment. Normal arterial blood gases were maintained under all conditions.

Conclusions: An atrial septostomy accompanied by veno-venous extracorporeal membrane oxygenation is capable of eliminating right ventricular failure while maintaining normal arterial blood gases if sufficient shunt flows are achieved. The presence of tricuspid insufficiency improves the efficacy of the shunt. (J Thorac Cardiovasc Surg 2011;141:537-42)
explained by an oftentimes unpredictable decrease in arterial oxygen saturation. Therefore, patients with severe gas exchange physiology are not suitable candidates for this approach, which has limited the application of atrial septostomies as a bridge to transplantation. These patients would then require extracorporeal blood oxygenation with venovenous extracorporeal membrane oxygenation (VV ECMO). Reports on the use of ECMO alone as a bridge to lung transplantation are isolated, and the outcomes remain mixed because of the low sample size of patients. However, recent major technical advances in ECMO enable patients to be supported with relative safety for several weeks up to months, facilitating even extubation until donor organs become available. Several large series now report improved survival for patients with acute severe respiratory failure treated with VV ECMO. The results obtained by the CESAR-Trial indicate a possible advantage for ECMO over conventional treatment for reversible severe pulmonary failure. Therefore, the use of VV ECMO for severe, refractory lung failure can be expected to increase in the near future.

To date, there is no published evidence to support the effectiveness of an atrial septostomy and VV ECMO at treating concomitant respiratory and RV failure. This study was designed to evaluate the feasibility of this new approach as a potential novel bridge to lung transplantation and the hemodynamic factors affecting its success. This study uses an extra-anatomic interatrial shunt in a large animal model to assess the effect of the shunt flow rate (Q_{shunt}) and tricuspid insufficiency (TI) on RV function and arterial blood gases.

### MATERIALS AND METHODS

All animals received care compliant with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences and published by the National Institutes of Health. The study was approved by the University of Michigan Committee on Use and Care of Animals.

### Surgical Instrumentation

Adult male sheep (56 ± 3 kg) were anesthetized using a standard protocol as previously described and used by our laboratory. The ventilator (Narkomed 600; North American Draeger, Telford, Pa) was set initially at a tidal volume of 10 mL/kg and a frequency of 12 to 15 breaths/min. It was adjusted as needed to maintain the arterial PCO2 between 35 and 45 mm Hg with a peak inspiratory pressure less than 30 cm H2O. Arterial and venous accesses were established by carotid and jugular catheterization using PVC tubing (Abbott Critical Care Systems, North Chicago, Ill). The arterial catheter was connected to a fluid coupled pressure transducer (Abbott Critical Care Systems) to monitor arterial pressure, which was displayed continuously (Marquette Electronics, Milwaukee, Wis).

A clamshell thoracotomy was performed, entering the chest cavity through the fourth intercostal space. A 60 mg dose of intravenous ketorolac (Hospira, Inc, Lake Forest, Ill) was injected before the transverse sternotomy. After opening the pericardium, a 16F angiocatheter (Becton, Dickinson Infusion Therapy Systems Inc, Sandy, Utah) was inserted into the right atrium and connected to a fluid-coupled pressure transducer to measure right atrial pressure (RAP). A 6F micromanometer tipped pressure probe (Millar Instruments, Inc, Houston, Tex) was inserted into the conus region of the RV free wall to measure RV pressure (RVP). An ultrasonic perivascular flow probe (T206 Flowmeter; Transonic Systems, Ithaca, NY) was placed around the ascending aorta to measure continuous cardiac output (CO). Heparin (100 U/kg, intravenously; Baxter Healthcare Corporation, Deerfield, Ill) was administered to maintain activated clotting times greater than 400 seconds.

Right to left interatrial shunting was realized with a custom-made extracardial shunt consisting of 40-cm 31F long tubing (Fisher Scientific Company, Pittsburgh, Pa) and 2 right-angled metal 31F cannulas on both ends (Figure E1). The interatrial shunt was introduced through purse-string sutures into the right and left atrial appendages. To measure the flow rate through the interatrial shunt, Q_{shunt}, an ultrasonic tubing flow probe was attached (Transonic Systems). In one group of sheep (n = 5), TI was created by introducing a custom-made fenestrated 16F cannula through the right atrium into the right ventricle. After introducing the cannula, it was secured in place. TI was verified by significant pulsatile backflow in the jugular vein (Cannon-V waves). In another group (n = 5), TI was not created (OTTI).

### Cardiopulmonary Bypass and Extracorporeal Membrane Oxygenation

The ECMO circuit consisted of a centrifugal pump (Biomedicus 520 D; Medtronic Minneapolis, Minn), heater unit (ECMO-Temp, Zimmer, Dover, OH), oxygenator (Capiox SX; Terumo, Ann Arbor, Mich), and 30F Tygon tubing. The circuit was primed with 800 mL Lactated Ringer solution mixed with 50 mL of bicarbonate solution. ECMO was established with standard techniques for VV ECMO by drainage from the iliac vein with an 18F cannula (TenderFlow; Terumo Cardiovascular, Ann Arbor, Mich) and reinfusion into the superior vena cava with an 18F straight cannula introduced through the right jugular vein (L-Series; Terumo Cardiovascular). Before initiating ECMO, 500 mg of methylprednisolone (0.5 g intravenously; Pfizer, New York, NY) was administered to reduce the inflammatory response to the foreign surfaces of the circuit. ECMO flow was kept between 2.5 and 3.5 L/min, and O2 at 100% FIO2 was delivered at a flow rate of 2 to 6 L/min based on arterial blood gases. On initiation of ECMO, the ventilator rate was changed to 8 breaths/min. Low doses of nor-epinephrine (Sicor, Irvine, Calif; 0.05–0.1 μg/min/kg intravenously) were administered to keep mean arterial pressure greater than 50 mm Hg before the establishment of ECMO to reduce the vasodilatory effects of the inflammatory response.

### Experimental Procedure and Data Collection

After initiating ECMO, 10 minutes were allowed for equilibration and a baseline data set was acquired. A complete data set consisted of RAP, RVP, pulmonary artery pressure, CO, and Q_{shunt}. At each data acquisition point, all parameters were collected manually using Excel (Microsoft, Redmond, Wash). RVP was also acquired digitally at 250 Hz using Labview 7.0.

### Abbreviations and Acronyms

- CO = cardiac output
- ØTI = without tricuspid insufficiency
- Q_{shunt} = shunt flow rate
- RAP = right atrial pressure
- RV = right ventricular
- RVP = right ventricular pressure
- TI = tricuspid insufficiency
- VV ECMO = veno-venous extracorporeal membrane oxygenation

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538
and 30
P <
%
Significantly lower at 70
groups (TI: 4.3/C6 4.8
than baseline in both groups (TI: 4.8
group (Figure E2), and CO was not significantly different
difference between TI and ØTI groups (Figure E3). There was no significant difference between TI and ØTI groups (P = .77).

Results for mean pulmonary artery pressure followed similar trends as mean RVP (Table 1), with significantly elevated values at the RV failure condition (P < .001) and all shunt flows (P < .001–.05) with the exception of 50%, which approaches significance (P = .08). Once again, there was no significant difference between TI and ØTI groups (P = .48). Mean RAP was also significantly elevated at the RV failure condition (P < 10^-5) and at all shunt flows (P < .001–.05). However, unlike mean RVP, mean RAP decreased with increasing shunt flow, suggesting improved right to left blood flows. In the TI group, this effect is less pronounced, with

Statistical Evaluation
All data are presented as mean ± standard deviation collected in each experimental condition. All manually collected data from survivors and nonsurvivors were compared using the mixed-model analysis within SPSS 17 (SPSS Inc, Chicago, Ill). On comparison of the hemodynamic variables, the experiment number was the subject variable and the shunt condition was the experiment number. All manually collected data from survivors and nonsurvivors were compared using the mixed-model analysis within SPSS 17 (SPSS Inc, Chicago, Ill). On comparison of the hemodynamic variables, the experiment number was the subject variable and the shunt flow condition and TI group were independent variables. Multiple comparisons confidence intervals were adjusted according to the Bonferroni method to minimize type I errors. To compare the effect of TI group on hemodynamics or gas exchange, the subject and dependent variables remain the same, but baseline and RV failure data were excluded to focus on the effect of TI during ECMO and interatrial support.

RESULTS
Survival
Right to left atrial shunting successfully eliminated complete RV failure under all shunt conditions when TI was present. On the other hand, animals with a competent tricuspid valve (ØTI) experienced complete RV failure and death. One animal died at the end of the 70% shunt flow period; another animal died at 50% shunt flow; 2 animals died during the 30% shunt flow period; and the remaining last ØTI animal died immediately after completion of the 30% period of 60 minutes.

Hemodynamics
Baseline CO was similar in both groups with 5.2 ± 0.2 L/min in the TI group and 5.3 ± 1.2 L/min in the ØTI group (Figure 1). After RV failure was established, CO decreased to 2.2 ± 1.1 L/min in the TI group and 2.3 ± 0.4 L/min in the ØTI group (P < 10^-10). With 100% shunt flow, Qshunt = 1.4 ± 0.8 L/min in the TI group and 1.7 ± 0.2 L/min in ØTI group (Figure E2), and CO was not significantly different than baseline in both groups (TI: 4.8 ± 1.0 L/min; ØTI: 4.8 ± 1.1 L/min; P = .74). Thereafter, CO diminished significantly with decreasing shunt flow. CO became significantly lower at 70% compared with baseline in both groups (TI: 4.3 ± 1.04 L/min; ØTI: 4.5 ± 0.8 L/min; P < .01) and was significantly lower than baseline at 50% and 30% (P < 10^-7 and P < .001). There was no significant difference between TI and ØTI groups (P = .60).

Mean RVP increased significantly from 12.7 ± 1.2 mm Hg at baseline to 24 ± 2 mm Hg at the imposed RV failure condition in the TI group and from 11.3 ± 1.5 mm Hg to 24 ± 7 mm Hg in the ØTI group at the same conditions (Figure 2; P < 10^-7). Mean RVP at full shunt flow (TI: 25 ± 7 mm Hg; ØTI: 23 ± 10 mm Hg) was significantly higher than at baseline in both groups (P < .01) and remained significantly elevated at all shunt flows (P < .001–.01). Typical examples of RVP tracings are shown in Figure E3. There was no significant difference between TI and ØTI groups (P = .77).

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TABLE 1. Pulmonary artery, radial artery, and left artery pressures (mm Hg)

<table>
<thead>
<tr>
<th>Condition</th>
<th>BL</th>
<th>Right ventricular failure</th>
<th>100% shunt</th>
<th>70% shunt</th>
<th>50% shunt</th>
<th>30% shunt</th>
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<tbody>
<tr>
<td>Mean PAP</td>
<td></td>
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<td></td>
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<tr>
<td>TI</td>
<td>15.4 ± 2.3</td>
<td>26.6 ± 4.3</td>
<td>26.8 ± 5.1</td>
<td>26.5 ± 5.2</td>
<td>24.9 ± 6.4</td>
<td>30.9 ± 13.3</td>
</tr>
<tr>
<td>ØTI</td>
<td>12.6 ± 5.8</td>
<td>25.4 ± 5.7</td>
<td>25.2 ± 6.9</td>
<td>23.1 ± 7.7</td>
<td>21.8 ± 6.3</td>
<td>24.0 ± 6.9</td>
</tr>
<tr>
<td>Mean RAP</td>
<td></td>
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</tr>
<tr>
<td>TI</td>
<td>3.6 ± 2.5</td>
<td>7.6 ± 2.7</td>
<td>7.1 ± 2.2</td>
<td>7.3 ± 2.1</td>
<td>8.7 ± 1.8</td>
<td>8.8 ± 1.5</td>
</tr>
<tr>
<td>ØTI</td>
<td>4.4 ± 1.9</td>
<td>11.2 ± 2.7</td>
<td>7.6 ± 1.8</td>
<td>8.9 ± 3.7</td>
<td>8.3 ± 4.4</td>
<td>10.3 ± 5.0</td>
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</tbody>
</table>

RL, Baseline; PAP, pulmonary artery pressure; TI, tricuspid insufficiency; ØTI, without tricuspid insufficiency; RAP, right atrial pressure.

DISCUSSION

The surgical exclusion of the failing right ventricle is reported to be an effective management in patients with post-operative refractory RV dysfunction. Therefore, volume unloading the failing right ventricle has proven successful. In the setting of severe primary pulmonary hypertension, early experimental studies in the mid-1960s and clinical observations in the mid-1980s have suggested that an interatrial shunt may be beneficial for the treatment of RV failure. The atrial septal defect allows right to left shunting and a resultant increase in systemic CO. This leads to an increase in systemic oxygen delivery despite a decrease in systemic arterial saturation. Thus, atrial septostomies are occasionally performed either as a sole treatment for refractory RV failure or to bridge patients to lung transplantation. However, patients with severe gas exchange deficiency are not suitable candidates for this approach. Therefore, our hypothesis was that the combination of an atrial septostomy with extracorporeal gas exchange by VV ECMO could be a successful approach to support these patients.

Various pulmonary devices have entered clinical practice to treat respiratory failure, but only a few devices and management concepts also treat ventricular failure. Of these, the
paracorporeal artificial lung is a promising innovation for pulmonary and ventricular support. This artificial lung is attached between the pulmonary artery and the left atrium, thereby improving gas exchange while reducing RV afterload.\textsuperscript{14,21,22} However, this approach requires an invasive thoracotomy in critically ill patients, exposing them to the risk of anesthesia and major surgery. In addition, the artificial lung attachment results in technically more difficult lung transplantation because of induced native lung and heart adhesions.

In contrast, an atrial septostomy is performed percutaneously, oftentimes requiring only sedation rather than general anesthesia. This diminishes the risk associated with anesthesia and technically difficult major thoracic surgery.\textsuperscript{7} Furthermore, ECMO does not necessarily require sedation, and it is perfectly feasible in an alert, extubated, spontaneously breathing patient, the ideal transplant candidate.\textsuperscript{23} Novel technical achievements, such as the 2009 Food and Drug Administration-approved double-lumen cannula for veno-venous gas exchange, facilitate the use of ECMO as a percutaneously introduced portable paracorporeal lung.\textsuperscript{24} This new cannula for adult ECMO support is introduced into the jugular vein draining from both vena cavae and reinfusing into the right atrium directly through the tricuspid valve into the right ventricle. It may be that this novel cannula will improve flows of oxygenated blood to the left atrium in the setting of a combined ECMO and atrial septal defect support. On the other hand, ECMO causes larger activation of blood components than paracorporeal artificial lungs because of its large circuit and mechanical pump. Thus, the resulting systemic inflammatory response and thrombogenicity are greater.

The study presented was designed to examine the effectiveness of right to left atrial shunting with VV ECMO at treating high-afterload RV failure. Our results indicate that right to left atrial shunting is capable of treating acute severe RV failure, here defined by a 40% to 60% decrease in CO. This degree of RV failure would otherwise be fatal. The necessary amount of right to left atrial shunt flow needed to treat this degree of acute RV failure seems to be as low as approximately 8% of baseline CO to avoid RV failure when TI is present but ideally greater than 20% to maintain baseline CO. However, the animals of this study did not have the typical hypertrophic ventricle present in patients with chronic lung disease. The required shunt fraction in a hypertrophied RV may be lower because the RV is already adapted to high afterloads.

All animals with TI survived the entire experiment, but sheep without TI required a $Q_{\text{Shunt}}$ greater than 13% of baseline CO to avoid complete RV failure and death. The insufficient tricuspid valve likely acts as a “pop off valve,” allowing a slightly greater blood flow through the atrial septal defect (Figure E2) in the TI group. This result is not fully explained by the hemodynamic data from this study, because statistical comparison did not find significant differences between the TI and ØTI groups for all measured parameters. The cause of this is that ØTI animals with poorer hemodynamics died earlier in the course of the experiment, leaving only animals with better RV function. Thus, small differences in shunt flow between the groups at 100% $Q_{\text{Shunt}}$ disappeared at lower shunt flows as weaker members of the ØTI group died. Finally, because stable hemodynamics were maintained regardless of the presence of TI, a combined VV ECMO and interatrial shunt support might be applicable for both group of patients.

The shunt was able to unload the right ventricle sufficiently to allow increased CO but not sufficiently to reduce RVP. As the shunt resistance decreased, the overall resistance of the right ventricle to left atrial flow pathway was reduced. This led to greater volume unloading of the RV and a small, statistically insignificant decrease in RAP. There were no RV volume measurements in this study, but it is likely that RV end-diastolic volume was also reduced. Such a reduction leads to a reduction in the ventricular work necessary to pressurize blood before ejection, and this work was likely used instead to generate more productive stroke work. Thus, CO increased with increasing shunt flow, and as a result, mean RVP remained elevated despite the volume unloading. Because CO was returned to a normal value at 100% $Q_{\text{Shunt}}$, further increases in shunt flow would likely have no effect on CO and thus result in lower RVP. This may be possible with a less resistant atrial septal defect created via septostomy.

These results are comparable to a similar study conducted by Zierer and colleagues.\textsuperscript{25} In that study, low versus high atrial shunt flow was compared in dogs with chronic right heart failure after 3 to 4 months of progressive pulmonary artery banding. The role of the tricuspid valve in atrial shunting was not considered. The authors reported that CO increased beyond baseline with a shunt flow equal to 15% of CO. On the other hand, a shunt flow of 29% of CO did not increase CO beyond baseline. The authors concluded that high flows seem to exceed an ideal shunt fraction. In comparison, our results indicate that a shunt fraction between 20% and 30% of baseline CO is capable of treating RV failure, and a shunt fraction less than 20% of baseline CO results in decreased CO. The reason for this discrepancy is explained by a different study design. The animals of the present study had normal hearts without RV hypertrophy and a more severe, acute RV failure, perhaps diminishing the CO increase at small shunt flows, but also provided gas exchange, allowing better function at high shunt flows.

**Study Limitations**

The present study was designed to examine a bridge to transplantation for patients with chronic pulmonary hypertension caused predominantly from pathologies in the peripheral vascular tree and consecutive RV failure. However, our study more closely resembles acute RV failure...
similar to a severe pulmonary embolism. Despite this, the proposed bridge is designed for critically ill patients who have had an acute-on-chronic event (eg, acute pneumonia) leading to a severe deterioration of pulmonary hypertension and RV failure. The presented animal model simulates this clinical scenario for the most part. Nonetheless, improved results may be achieved using animals with chronic pulmonary hypertension and a partially compensated right ventricle.

CONCLUSIONS
Right to left atrial shunting of oxygenated blood with VV ECMO is capable of eliminating acute, severe, normally lethal RV failure while maintaining normal arterial blood gases. The presence of TI seems to improve RV function during application of this potentially novel technique to bridge patients to lung transplantation.

References
FIGURE E1. Right to left atrial shunting was simulated with a custom-made 31F extracardiac shunt introduced into the atrial appendages.

FIGURE E2. Q_{Shunt} at each shunt condition in TI and ØTI groups. RV, Right ventricular; TI, tricuspid insufficiency; ØTI, without tricuspid insufficiency; Q_{Shunt}, shunt flow rate.

FIGURE E3. Typical examples of RVP tracings at each condition. RV, Right ventricular.