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

Daniele Camboni, MD, Begum Akay, MD, Joshua R. Pohlmann, MS, Kelly L. Koch, MS, Jonathan W. Haft, MD, Robert H. Bartlett, MD, and Keith E. Cook, PhD

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)

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Pulmonary arterial hypertension has a prevalence of approximately 15 per million in both the United States and Europe.[1,2] The prognosis of this disease is poor, with approximately 15% mortality within 1 year on modern therapy[2] and 60% 2-year mortality if untreated.[3] This patient population is routinely listed for lung transplantation when refractory to conventional medical therapy. However, because of a lack of available donor organs, a high number of patients die on the waiting list or become unsuitable candidates for lung transplantation. The impact of organ shortage can be estimated by the high number of approximately 2500 patients who have died on the waiting list in the United States over the last 5 years.[4] A major contributing factor to morbidity and mortality on the transplantation waiting list is right ventricular (RV) failure. Therefore, RV dysfunction is one of the most important prognostic factors in pulmonary hypertension.[5] As a result, intensive efforts are made to develop new therapeutic modalities for combined lung and RV support. This has led to several novel drugs and therapies entering clinical practice to facilitate bridging patients to lung transplantation with considerable success. To date, a poorly understood treatment option has been an atrial septostomy.[6,7] The reported success rates of atrial septostomies for bridging patients to lung transplantation range from 30% to 40%.[6] These low success rates can be

From the Extracorporeal Life Support Laboratory, Department of Surgery, University of Michigan Medical School, Ann Arbor, Mich.

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Address for reprints: Daniele Camboni, MD, Extracorporeal Life Support Laboratory, Department of Surgery, University of Michigan, B560-B Medical Science Research Building II, 1150 West Medical Center Drive, Ann Arbor, MI 48109 (E-mail: dcamboni@arcor.de).

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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

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 veno-venous 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.[8,9] Several large series now report improved survival for patients with acute severe respiratory failure treated with VV ECMO.[10,11] The results obtained by the CESAR-Trial indicate a possible advantage for ECMO over conventional treatment for reversible severe pulmonary failure.[12,13] 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.[14] 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 P_{CO_2} between 35 and 45 mm Hg with a peak inspiratory pressure less than 30 cm H_2O. 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 (Abbot 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 given 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 extracardial 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 (ØTI).

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 O_2 at 100% F_{IO_2} 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 norepinephrine (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