Acute In Vivo Testing of an Intravascular Respiratory Support Catheter

JOSEPH F. GOLOB,* WILLIAM J. FEDERSPIEL,*‡§ THOMAS L. MERRILL,* BRIAN J. FRANKOWSKI,* KENNETH LITWAK,* HEIDE RUSSIAN,* and BRACK G. HATTLER*

Current treatment for acute respiratory failure (ARF) includes the use of mechanical ventilation and/or extracorporeal membrane oxygenation, both of which can exacerbate lung injury. Intravenous respiratory support, using hollow fiber membranes placed in the vena cava, represents an attractive potential treatment for ARF, which could help reduce or eliminate ventilator induced trauma and/or other problems. Our group has been developing a respiratory support catheter (the Hattler catheter [HC]) that consists of a constrained hollow fiber bundle with a centrally located balloon. The balloon can be pulsed rapidly to increase blood flow across the fibers and decrease diffusional transfer resistance there, thus increasing gas exchange. The purpose of this study was to evaluate the HC in acute animal implants and to compare performance with that achieved in previous ex vivo studies. The HC was implanted into four calves by means of the external jugular vein and placed in the superior and inferior vena cava spanning the right atrium. Gas exchange, hemodynamics, and hematologic parameters were assessed over a range of balloon pulsation rates from 30 to 300 beats/minute. A <10% reduction in cardiac output was associated with catheter insertion and operation. The maximum CO₂ exchange rate occurred at the highest pulsation rate and averaged 56 ± 3 ml/min, or 327 ± 15 ml/min per m² when averaged to catheter membrane area, a level comparable to that achieved in the previous ex vivo studies. Balloon pulsation did not produce significant levels of hemolysis, as plasma-free hemoglobin remained below 10–15 mg/dl. ASAIO Journal 2001; 47:432–437.

Acute respiratory failure (ARF) describes a broad range of clinical conditions in which the lungs do not perform adequate gas exchange. Medical conditions leading to ARF include COPD, drug overdose, trauma, burns, near drowning, infections, and severe heart failure. Management of ARF requires immediate blood oxygenation to sustain adequate oxygen delivery to the tissues, and CO₂ removal to minimize respiratory acidosis and other problems associated with excessive hypercarpia. Mechanical ventilation (MV) is often the first strat-
balloon pulsation across the range of blood flow rates, the HC exchanged approximately 74 ml/min and 63 ml/min of CO₂ and O₂, respectively, or 350 ml/min per m² and 300 ml/min per m², respectively, when normalized to the 0.21 m² of catheter membrane area. In the in vivo tests described here, the HC reached gas exchange levels comparable to those in the ex vivo studies, without causing any significant hemodynamic problems in the animal.

Materials and Methods

Animal Preparation and Catheter Insertion

The in vivo performance of the HC was studied in four Holstein calves, each weighing 99.5 ± 8.2 kg (see Table 1). Each calf was premedicated with 0.5 mg/kg atropine, injected with approximately 10 mg/kg Brevital (Eli Lilly and Co., Indianapolis, IN), and intubated endotracheally. Isoflurane (1–2.5%) was mixed with low flow oxygen and room air (1:1), and the animal was placed on a volume controlled ventilator (Penlon AM1000, Abingdon, UK). The right femoral and left cervical region were prepped and draped. A fluid-filled pressure catheter manifold in the superior vena cava. The PTFE sheath and guide wire were removed, and purse string sutures were used to hold the catheter in place at the jugular vein.

Table 1. Calf Size and Calf Vessel Size Used in Studies

<table>
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<tr>
<th>Animal</th>
<th>Device</th>
<th>Weight (kg)</th>
<th>IVC OD (mm)</th>
<th>SVC OD (mm)</th>
<th>Jugular Vein OD (mm)</th>
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<td>0.9</td>
<td>2.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 1. Calf Size and Calf Vessel Size Used in Studies

IVC, inferior vena cava; SVC, superior vena cava; OD, outside diameter.

Another set of hemodynamic and hematologic data was then gathered postvolume loading. The animals were anticoagulated with a bolus (400 units/kg) of heparin and a continuous heparin drip (0.5–1.0 mg/kg per hr) was started through the femoral vein. The ACT was determined hourly and maintained above 450 seconds with repeat heparin boluses and adjustments in the IV drip as needed.

The HC device was preloaded into a polytetrafluoroethylene (PTFE) sheath that decreased the insertion size of the fiber bundle to ~11 mm and minimized friction with the vessel wall for insertion. The catheter was soaked in a solution of 500 ml of saline, 60 ml of human albumin, and 8 ml of heparin. An Amplatz Super Stiff guidewire (Boston Scientific, Watertown, MA) was then threaded into the inferior vena cava (IVC) by means of the left internal jugular vein. A venous cut-down of the left external jugular vein allowed for the distal tip of the catheter to be inserted into the vein. Following the guidewire, the catheter was inserted approximately 35 cm. This placed the distal manifold in the IVC approximately at the diaphragm, with the fiber bundle spanning the right atrium and the proximal manifold in the superior vena cava. The PTFE sheath and guide wire were removed, and purse string sutures were used to hold the catheter in place at the jugular vein.

Experimental Setup and Procedure

A schematic of the experimental setup is shown in Figure 1. Sweep gas flow (100% O₂) was delivered through the catheter at 3 L/min under vacuum pressure (~250 mm Hg required) and measured downstream of the catheter with a mass flow meter (Fathom, Georgetown, TX). The sweep gas leaving the catheter traveled through a moisture trap, after which was located a sampling port to a mass spectrometer (MGA 1,100, Marquette Medical Systems, Jupiter, FL) for on-line continuous determination of effluent O₂ and CO₂ fractions (F O₂ and F CO₂). Beat rates were randomly varied at 30, 60, 120, 180, 240, and 300 bpm. After a 5 minute stabilization at each beat rate, F O₂, F CO₂, gas flow rate, and pressure drop were recorded. The HC balloon was pulsated using a laboratory pneumatic drive system, which could pulse the balloon with helium gas at frequencies up to 300 beats per minute.

Every 30 minutes, venous and arterial blood gases were collected, as well as mean arterial, central venous, and femoral pressures. Samples for plasma free hemoglobin and platelet and white cell counts were collected every hour. After the 6 to 7 hour experiment, the animal was deeply anesthetized and euthanized with a bolus of potassium chloride. During nec-
ropsy, all thoracic and abdominal organs were examined, as was the explanted catheter. All animal procedures were conducted under supervision of a staff surgical veterinarian and were in accordance with NIH and University of Pittsburgh guidelines for the care and use of experimental animals in research.

**Determination of Gas Exchange**

The in vivo gas exchange performance of the Hattler catheter was characterized by the CO₂ exchange rate, which can be determined with acceptable accuracy (within 5%) from gas side measurements. The CO₂ gas exchange rate was calculated based on the exit CO₂ gas fraction, FCO₂, measured with the mass spectrometer according to:

$$\dot{V}_{CO_2} = \frac{Q_{out} \cdot F_{CO_2}}{STP}$$

where $Q_{out} \cdot F_{CO_2}$ represents the mass flow rate (STP conditions) of the sweep gas exiting the catheter. The CO₂ exchange rate depends on the venous blood pCO₂ in contact with the fiber bundle, which can differ among experiments and animals even with appropriate ventilatory adjustments. Accordingly, we also determined a CO₂ exchange rate normalized to a venous pCO₂ of 50 mm Hg for a more direct comparison between devices when blood pCO₂ differed. The normalized CO₂ exchange rate was determined according to:

$$\dot{V}_{CO_2 \text{Normalized}} = \dot{V}_{CO_2} \cdot \frac{50}{pCO_2 \text{Venous}}$$

where $pCO_2 \text{Venous}$ was determined using samples from the femoral vein catheter (with tip in the iliac vein), which best represented the venous pCO₂ of blood contacting the catheter. Results are presented in both un-normalized and normalized CO₂ exchange rates for comparison.

The oxygen exchange rate of the Hattler catheter in vivo cannot be determined with sufficient accuracy and is not reported in this study. The measurement of O₂ exchange from gas-side analysis is problematic because O₂ exchange is the difference between O₂ flow rate in and out of the catheter and, as such, represents the difference in two large and similar numbers. The measurement problem is exacerbated because (total) gas flow in and out of the catheter differ (due to generally unequal O₂ and CO₂ exchange rates). This difference is important in the mass balance used to determine O₂ exchange but is small and cannot be determined reliably using typical mass flow meters. Blood-side measurements of O₂ gas exchange in the vena cava are also problematic, in part because of the multiple inflows of venous blood into the cava. One approach used by others is to measure pulmonary artery blood saturation and O₂ tension with gas flow to the device turned off (i.e., no gas exchange) then turned back on (i.e., gas exchange). O₂ exchange rate is then computed from cardiac output and the difference in the O₂ content of PA blood with the device on versus off. For conditions of our study (higher cardiac output range, catheter with smaller membrane area), the variability in O₂ exchange determined using the device on/off method was too large to reliably determine O₂ exchange and was, therefore, not incorporated into our standard protocol.

**Characteristics of Catheters Tested**

*Figure 2* shows a schematic of the HC. The catheters used in these tests were of the 9 mm size family, which refers to the diameter of the manifolds at the proximal and distal ends of the catheter in which the hollow fibers are potted. The fiber bundles consisted of 600 polypropylene hollow fiber membranes (X30–240, Celgard, Charlotte, NC), with inner and outer diameters of 240 μm and 300 μm, respectively. The bundles were fabricated by wrapping a woven fabric of these fibers (54 fibers/inch) in concentric continuous layers around the central balloon. The length of the fiber bundle in the 9 mm HC series is 30 cm, and the total membrane surface area is 0.17 m². All catheters had 25 cc balloons with diameters of 12.5 mm, giving the device an overall fiber bundle diameter of 18.5 mm. For insertion, the fiber bundle is compressed significantly by the PTFE introducer sheath, down to an overall insertional diameter of approximately 11 mm.

**Results**

The CO₂ exchange rate measured for each HC implanted is shown in *Figure 3* over a range of pulsation rates.
exchange rates are not normalized for venous PCO₂. Absolute exchange rate values are shown on the left ordinate, whereas the right ordinate displays the exchange rate normalized to catheter membrane area \((A = 0.17 \text{ m}^2)\). The gas exchange for each catheter increases significantly with increasing balloon pulsation rate. Although the exchange rates for catheters 9-1 and 9-3 with no balloon pulsation (0 bpm) seem comparable with those at maximal balloon pulsation, the 0 bpm exchange values for these catheters seem to deviate from their respective gas exchange versus balloon frequency curves. This most likely reflects different conditions (e.g., increased venous pCO₂) during the measurement period at 0 bpm, because these measurements are done only at the end of a complete experiment on a given catheter, just before its removal. (This is done to avoid problems of thrombus formation within the fiber bundle, and irreversible degradation in gas exchange, due to the blood stasis within the fiber bundle associated with lack of balloon pulsation.)

The CO₂ exchange rate for each catheter shown previously is normalized to a venous pCO₂ of 50 mm Hg in Figure 4 (top panel), whereas the bottom panel of Figure 4 shows the average and standard deviation of the normalized CO₂ exchange for all catheters. The normalization of CO₂ exchange to a venous pCO₂ of 50 mm Hg reduces the standard deviation across the four experiments (results not shown). The maximum normalized CO₂ exchange rate for the four experiments averaged 56.1 ± 2.6 ml/min at 300 beats/min, which corresponds to an area-normalized exchange of 330 ± 15 ml/min per m². The HC devices without balloon pulsation averaged a CO₂ exchange rate of 42.5 ± 4.4 ml/min (or 250 ± 26 ml/min per m²). Thus, balloon pulsation in vivo increased CO₂ gas transfer by 13%.

Cardiac output changed by <10% with insertion and operation of the Hattler catheter, as shown in Figure 5. The cardiac outputs were obtained just before insertion (postvolume loading) and 5 to 8 minutes postinsertion. Each calf had baseline and postinsertion cardiac outputs between 10 and 14 L/min.

The CVP and femoral vein pressure before and after insertion of the HC devices are listed in Table 2 (pressures not measured for catheter 9-6). Preinsertion pressures correspond to those
by the level of CO₂ exchange. The maximum CO₂ exchange demonstrated consistent gas exchange performance, as indicated devices were tested in separate calf implantations and dem-
just before HC introduction, whereas postinsertion pressures were obtained 5 minutes after introduction. Generally, femoral vein pressure increased slightly while CVP decreased, and, thus, the femoral pressure–CVP difference increased by 5 to 6 mm Hg upon catheter insertion and operation. (In catheter 9-2, both pressures decreased, but the pressure difference still increased by 5 mm Hg.) Plasma free hemoglobin values before insertion, at the midpoint of the trial period, and at the end of the trial period for each catheter are listed in Table 3. Plasma free hemoglobin remained below 10–15 mg/dl in all experiments and, in all but one experiment, (catheter 9-2) seemed to level off after an initial postinsertional increase.

### Discussion

Our ultimate goal is an intravascular respiratory support catheter that can be used as an effective extrapulmonary support therapy for patients with acute respiratory failure. Although significant work remains before human clinical trials, the studies described here are the first implantation tests and evaluation of our human sized HC in an acute calf model. The HC used in this study (9 mm series) represents the smallest of the four sizes of respiratory support catheters that have been designed to span the adult human population. Four 9 mm HC devices were tested in separate calf implantations and demonstrated consistent gas exchange performance, as indicated by the level of CO₂ exchange. The maximum CO₂ exchange rate, normalized to a venous pCO₂ of 50 mm Hg, averaged 56.1 ± 2.6 ml/min, or 330 ± 15 ml/min per m², when normalized to membrane surface area. Balloon pulsation increased gas exchange by an average of 13%. Cardiac output did not drop significantly with introduction or pulsation of the HC, and blood hemolysis remained below 10–15 mg/dl, a level not considered problematically elevated, even though pulsation rates up to 300 beats/min were used in these acute studies.

In delivering extrapulmonary gas exchange, an intravenous respiratory support catheter should not adversely impact the cardiovascular system in general nor venous hemodynamics specifically. Significant flow resistance of the HC within the vena cava would impede venous return or potentially divert some venous blood flow through collateral vessels bypassing the cava. In these acute animal implants, our index of venous flow obstruction is cardiac output, which for a given cardiac contractility is affected principally by venous return according to the Frank-Starling relationship. In each animal implant, there was no significant drop in cardiac output postinsertion, which we interpret as an indication that the HC has no appreciable effect on venous return. Nevertheless, the HC does seem to increase the blood side pressure drop past the catheter, defined as the difference in femoral and central venous pressure. For example, femoral vein pressure for catheter 9-2 rose approximately 2 mm Hg, whereas CVP pressure fell approximately 1 mm Hg after insertion. A 4 mm Hg increase in venous pressure drop does reflect an increased blood flow resistance associated with the pulsating catheter, but even so, the increase does not apparently alter venous return or cardiac output. This result may not be entirely surprising in that an increase of venous pressure of 2 mm Hg per se would have little effect on organ perfusion provided mean arterial pressure remains near normal, as it did in our implant studies. Partial diversion of venous return by the catheter around the vena cava through collaterals cannot be directly ruled out.

The performance of the Hattler catheter in these animal implants can also be compared and contrasted with our recent ex vivo studies of the catheter, in which the catheter was placed within a mock vena cava in an extracorporeal circuit run from a calf. The ex vivo experiments tested catheters from the 10 mm series, which have 0.21 m² fiber surface area and 33 ml balloons. The maximum CO₂ exchange rate, normalized for comparison to a venous pCO₂ of 50 mm Hg and to membrane surface area, averaged 330 ml/min per m² in the acute calf implantations as compared with 350 ml/min per m² in the ex vivo studies. Clearly, blood flow conditions and vessel geometry differ between those in the vena cava during acute implantation and those in the mock vena cava during the ex vivo studies. For example, the catheter sees a bidirectional flow at 10–14 L/min in the vena cava position used in the calf implants, whereas the ex vivo studies expose the catheter to unidirectional flow to 4.5 L/min. Despite these differences, the gas exchange levels in vivo versus ex vivo are remarkably comparable, which may be fortuitous but may also reflect behavior of the catheter that can be attributed to balloon pulsation. Our ex vivo studies indicated that, although gas exchange varied significantly with blood flow rate with no balloon pulsation, maximal balloon pulsation eliminated most if not all of the dependence of gas exchange on blood flow rate. This finding occurs because balloon pulsation in the HC generates blood flow across the fibers that is largely independent of native vessel blood flow and can be significantly greater than this flow. As a result, the level of gas exchange accomplished by the catheter becomes partly decoupled from the level of native blood flow in the vessel.

The effect of balloon pulsation on gas exchange may also explain why balloon pulsation enhanced gas exchange more in the ex vivo studies, by 200–300% at the lowest blood flow rate (1.5 L/min) and 50–100% at the upper blood flow rate (4.5 L/min), than it did in the acute implants, in which a 13% increase in exchange occurred due to balloon pulsation. Cardiac output, our index of flow in the vena cava, was relatively high (~10–14 L/min) in the acute implants, which creates greater gas exchange in the absence of balloon pulsation. The

### Table 2. Venous Pressure Changes with Catheter Insertion and Operation

<table>
<thead>
<tr>
<th>Device</th>
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<td>6</td>
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### Table 3. Plasma Free Hemoglobin Levels (mg/dl)

<table>
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<th>Device</th>
<th>Pre</th>
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<td>9-6</td>
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</table>
effect of blood flow rate on gas exchange is diminished, however, with maximal balloon pulsation. Thus, balloon enhancement of exchange would seem reduced, as was seen in the acute implants. This hypothesis suggests that with lower cardiac outputs, as may occur in human clinical implantation, balloon enhancement of gas exchange may be greater than observed in this study, but gas exchange with maximal balloon pulsation may still be comparable to those levels measured in this study. We hope to explore this hypothesis through comparative animal implants using an animal model with lower cardiac output (e.g., sheep).

Finally, as the need for greater gas exchange was one conclusion of the IVOX clinical studies, a comparison between the gas exchange levels observed in this study and those reported for animal implantation of the IVOX is informative (see Table 4). The animal implants of the IVOX characterized gas transfer rates and hemodynamic effects in over 50 sheep weighing 60–70 kg. As with the Hattler catheter, the IVOX caused no significant drop in cardiac output nor lowering of mean arterial pressure with insertion and operation. The CO₂ exchange rate during normocapnia averaged 40.2 ± 10.5 ml/min for the IVOX 7 device, with a membrane surface area of 0.21 m², which corresponds to an area-normalized gas exchange level of 191.4 ml/min per m². The Hattler catheter tested here has a smaller insertion size and membrane area of only 0.17 m² but accomplished 55.6 ± 2.6 ml/min of CO₂ removal, or an area normalized exchange rate of 327 ± 15.3 ml/min/m². The greater gas exchange efficiency (exchange per unit area) of the HC in our implants is consistent with what we observed in our ex vivo studies, in which the HC accomplished approximately 50–300% greater CO₂ exchange, depending on blood flow rate, than the CO₂ exchange rate reported in the ex vivo tests of the IVOX.

Acknowledgment

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References