Acute *In Vivo* Testing of an Intravascular Respiratory Support Catheter

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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 pulsated 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 CO_2 exchange rate occurred at the highest pulsation rate and averaged 56 ± 3 ml/min, or 327 ± 15 ml/min per m^2 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.[1] Management of ARF requires immediate blood oxygenation to sustain adequate oxygen delivery to the tissues, and CO_2 removal to minimize respiratory acidosis and other problems associated with excessive hypercapnia.[1–3] Mechanical ventilation (MV) is often the first strat-

egy for augmenting gas exchange in an ARF patient, but MV exposes the lung to high volumes and high pressures of inspired air or oxygen. Ventilator induced trauma (VIT)[4] can arise from overdistention of the healthier, more compliant lung regions (volutrauma) and from the positive end-expiratory pressure required to prevent alveolar collapse (barotrauma).[2] Despite significant improvements in ventilatory management, VIT remains a persistent clinical problem[4] and highlights a clear need for providing supplemental gas exchange independent of the lungs.

Intravenous respiratory support is a potential method for providing extrapulmonary gas exchange in ARF patients,[5] or in patients with acute exacerbations of a chronic respiratory condition. The technique involves the introduction of hollow fiber membranes (HFMs), as used in standard blood oxygenators, into the vena cava through insertion at the femoral vein. The fiber bundle is connected to an external console that pulls pure oxygen through the HFMs, thus, producing extrapulmonary venous gas exchange, as oxygen diffuses out of the HFMs and CO_2 diffuses into the HFMs and is swept out by the oxygen flow stream (sweep gas). We have been developing an intravenous respiratory support catheter,[6–8] the Hattler catheter (HC, known previously as the IMO), which uses pulsation of a central balloon within the fiber bundle to improve blood convection past the HFMs and, thereby, to augment gas exchange by reducing diffusional boundary layers on the fiber surfaces.[9] Active balloon pulsation of the HC distinguishes it from the IVOX catheter developed by Mortenson,[10] which relies on passive gas exchange. In clinical trials, the IVOX improved blood gas tensions and allowed some reduction in ventilatory support, accomplishing an average of 28% of the metabolic needs for O_2 supply and CO_2 removal.[11] One conclusion from the IVOX clinical trials, however, was that greater gas exchange might be needed for improved clinical efficacy of intravenous respiratory support.[12] A principal development goal for the Hattler catheter is increased gas exchange performance compared with that accomplished by the IVOX.

This report describes recent experiments on the Hattler catheter implanted acutely within the vena cava of calves. The principal goals of these experiments were to establish the level of gas exchange provided by the catheter *in vivo*, and to evaluate any hemodynamic impact associated with the catheter during short-term implantation and operation in an animal. These *in vivo* studies complement our recently reported *ex vivo* studies of the HC,[8] in which the catheter was evaluated within a mock vena cava vessel (a Silastic tube) that was attached to an extracorporeal circuit on a calf. In these studies, balloon pulsation significantly increased gas exchange, the extent of which depended on blood flow rate. At maximum

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

Animal	Device	Weight (kg)	IVC OD (mm)	SVC OD (mm)	Jugular Vein OD (mm)
E035	9–2	94	25.09	17.32	12.5
E036	9–3	102	26.25	22.25	14.3
E037	9–1	110	25.81	18.55	15.4
E038	9–6	92	27.13	21.17	13.2
Average		99.5	26.1	19.8	13.9
SD		8.2	0.9	2.3	1.3

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

balloon pulsation across the range of blood flow rates, the HC exchanged approximately 74 ml/min and 63 ml/min of CO_2 and O_2, respectively, or 350 ml/min per m^2 and 300 ml/min per m^2, respectively, when normalized to the 0.21 m^2 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 monitoring catheter was placed in the right femoral vein and advanced 30 cm to the common iliac vein. A 16 g PVC (Arrow, Reading, PA) catheter was placed directly into the femoral artery. These catheters were attached to fluid-filled pressure transducers (Baxter Health care Corp., Irvine, CA) connected to a pressure and electrocardiograph monitor (Hewlett-Packard, Andover, MA). The left lateral cervical region was incised to expose the internal and external jugular veins. A 7 Fr. Swan-Ganz thermodilution catheter (Baxter Health Care Corp.) connected to a cardiac output monitor (SAT-2, Baxter Health care Corp.) was placed in the left internal jugular vein and advanced to the pulmonary artery. Central venous pressure (CVP) was also obtained from this catheter. Blood gases were acquired every half hour throughout the experiment and measured with a blood gas analyzer (ABL 505, Radiometer, Copenhagen, Denmark) and co-oximeter (482, Instrumentation Laboratory, Lexington, MA). Anticoagulation was monitored by measuring the activated clotting times (ACT) (Hemachron Jr., International Teledyne Corp., Edison, NJ).

Baseline hemodynamic data was collected, including mean arterial pressure, CVP, femoral vein pressure, and cardiac output. Baseline blood samples were also collected, including blood gases from the femoral vein, right atrium, and femoral artery, as well as platelet counts, white blood cell counts, total blood chemistry, plasma free hemoglobin fibrinogen concentrations, ACT, and hematocrit. During the next 10 to 15 minutes, the animals were volume loaded with lactated Ringer's

solution (15 ml/kg), to maximize vessel size for insertion.[13] 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% O_2) 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 O_2 and CO_2 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-
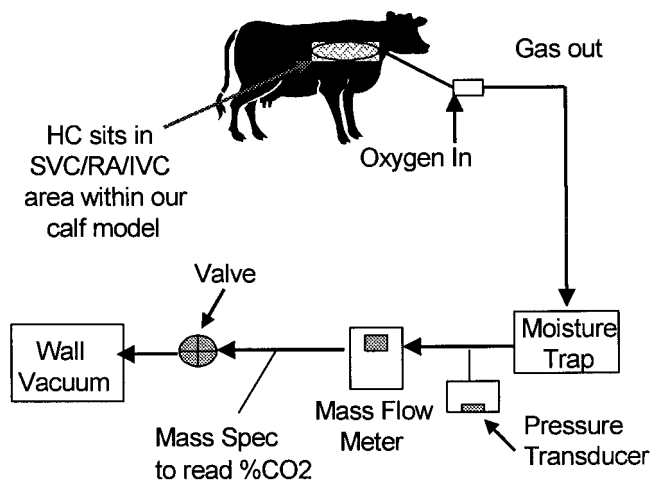
Figure 1. Experimental setup for acute animal implant tests of the Hattler catheter (HC). SVC/RA/IVC, superior vena cava/right atrium/inferior vena cava.

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 CO_2 exchange rate, which can be determined with acceptable accuracy (within 5%) from gas side measurements. The CO_2 gas exchange rate was calculated based on the exit CO_2 gas fraction, FCO_2, measured with the mass spectrometer according to:

$$\dot{V}_{CO_2} = Q_{out}^{stp} F_{CO_2}$$

where Q_{out}^{STP} represents the mass flow rate (STP conditions) of the sweep gas exiting the catheter. The CO_2 exchange rate depends on the venous blood pCO_2 in contact with the fiber bundle,[8] which can differ among experiments and animals even with appropriate ventilatory adjustments. Accordingly, we also determined a CO_2 exchange rate normalized to a venous pCO_2 of 50 mm Hg for a more direct comparison between devices when blood pCO_2 differed. The normalized CO_2 exchange rate was determined according to:

$$\dot{V}_{CO_2}^{Normalized} = \dot{V}_{CO_2} * \frac{50}{pCO_2^{Venous}}$$

where pCO_2^{venous} was determined using samples from the femoral vein catheter (with tip in the iliac vein), which best represented the venous pCO_2 of blood contacting the catheter. Results are presented in both un-normalized and normalized CO_2 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 O_2 exchange from gas-side analysis is problematic because O_2 exchange is the difference between O_2 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 O_2 and CO_2 exchange rates). This difference is important in the mass balance used to determine O_2 exchange but is small and cannot be determined reliably using typical mass flow meters. Blood-side measurements of O_2 gas exchange in the vena cava are also problematic, in part because of the multiple inflows of venous blood into the cava.[14] One approach used by others is to measure pulmonary artery blood saturation and O_2 tension with gas flow to the device turned off (*i.e.,* no gas exchange) then turned back on (*i.e.,* gas exchange). O_2 exchange rate is then computed from cardiac output and the difference in the O_2 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 O_2 exchange determined using the device on/off method was too large to reliably determine O_2 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 m^2. 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 CO_2 exchange rate measured for each HC implanted is shown in **Figure 3** over a range of pulsation rates, where
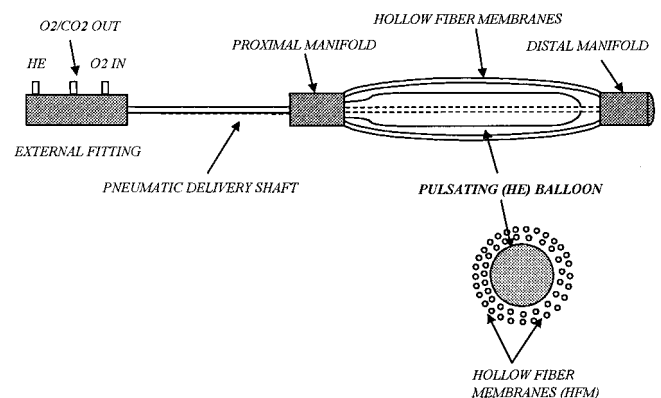

Figure 2. Schematic of the Hattler catheter tested in the acute implants. HE, helium.
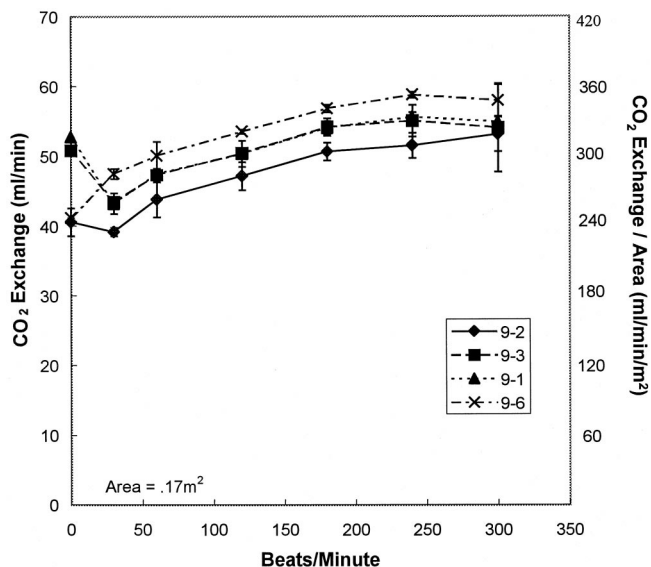
Figure 3. CO_2 exchange rate for all devices tested *in vivo*. Absolute gas exchange on left ordinate, area-normalized gas exchange on right ordinate.
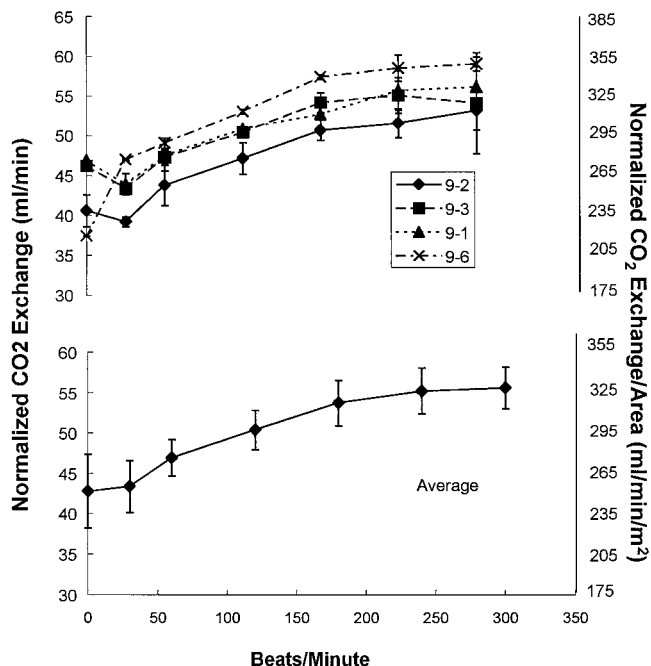

Figure 4. CO_2 exchange rates normalized to a venous pCO_2 of 50 mm Hg. The top panel shows individual devices, whereas the bottom panel shows the average and standard deviation for all four devices.

exchange rates are not normalized for venous PCO_2. 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 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 pCO_2) 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 CO_2 exchange rate for each catheter shown previously is normalized to a venous pCO_2 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 CO_2 exchange for all catheters. The normalization of CO_2 exchange to a venous pCO_2 of 50 mm Hg reduces the standard deviation across the four experiments (results not shown). The maximum normalized CO_2 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 m^2. The HC devices without balloon pulsation averaged a CO_2 exchange rate of 42.5 ± 4.4 ml/min (or 250 ± 26 ml/min per m^2). Thus, balloon pulsation *in vivo* increased CO_2 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
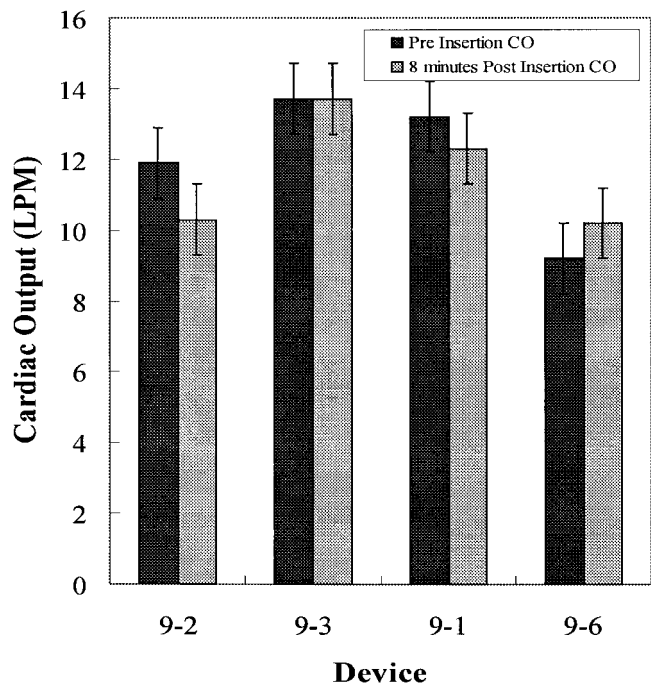

Figure 5. Preinsertion and postinsertion cardiac outputs determined using the thermodilution technique. The error bars shown represent the nominal standard error reported by manufacturers for thermodilution determination of cardiac output.

Table 2. Venous Pressure Changes with Catheter Insertion and Operation

Device	Femoral Pressure (mm Hg)		Central Venous Pressure (mm Hg)	
	Preinsertion	Postinsertion	Preinsertion	Postinsertion
9-2	12	10	8	1
9-3	13	15	10	9
9-1	14	15	10	6

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 CO_2 exchange. The maximum CO_2 exchange rate, normalized to a venous pCO_2 of 50 mm Hg, averaged 56.1 ± 2.6 ml/min, or 330 ± 15 ml/min per m^2, 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

Table 3. Plasma Free Hemoglobin Levels (mg/dl)

Device	Pre	Mid	End
9-2	4.9	9.6	13.8
9-3	5.3	8.9	8.6
9-1	3.1	4.9	5
9-6	11.9	8.1	8.4

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.[15] 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,[8] 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 m^2 fiber surface area and 33 ml balloons. The maximum CO_2 exchange rate, normalized for comparison to a venous pCO_2 of 50 mm Hg and to membrane surface area, averaged 330 ml/min per m^2 in the acute calf implantations as compared with 350 ml/min per m^2 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 4. Gas Exchange in Hattler Catheter vs. IVOX

Device	Absolute CO_2 Exchange (ml/min)	Normalized CO_2 Exchange (ml/min/m²)
IVOX (SA = 0.21m²)	40.2 ± 10.5	191.4 ± 50.0
HC (SA = 0.17m²)	55.6 ± 2.6	327.0 ± 15.3

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,[12] 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.[3,16] As with the Hattler catheter, the IVOX caused no significant drop in cardiac output nor lowering of mean arterial pressure with insertion and operation.[3,17] The CO_2 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 insertional size and membrane area of only 0.17 m² but accomplished 55.6 ± 2.6 ml/min of CO_2 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 found in our *ex vivo* studies, in which the HC accomplished approximately 50–300% greater CO_2 exchange, depending on blood flow rate, than the CO_2 exchange rate reported in the *ex vivo* tests of the IVOX.[18]

Acknowledgment

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