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First in vivo assessment of RAS-Q technology as lung support device for pulmonary hypertension

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Abstract

Objectives: To assess the in vivo hemodynamic effects on the pressure overloaded right ventricle of RAS-Q® technology, the world's first gas exchanger with a fully integrated compliance.

Methods: In six acute in vivo trials RAS-Q was implanted in sheep between the pulmonary artery and left atrium. Right ventricular pressure overload was induced by pulmonary artery banding. Pressures and flows were recorded in baseline, moderate and severe pulmonary hypertension conditions. In one trial, RAS-Q was benchmarked against the pediatric Quadrox-i®.

Results: With 1.00 and 1.17 L/min, RAS-Q delivered 31% and 39% of the total cardiac output in moderate and severe pulmonary hypertension, respectively. Pulmonary artery pressures and mean pulmonary artery pressure/mean arterial blood pressure ratio successfully decreased, implying a successful right ventricular unloading. Cardiac output was restored to normal levels in both pulmonary hypertension conditions. With both devices in parallel, RAS-Q provided three times higher flow rates and a 10 times higher pressure relief, compared to the pediatric Quadrox-i.

Conclusion: A gas exchanger with a fully integrated compliance better unloads the right ventricle compared to a non-compliant gas exchanger and it can restore cardiac output to normal levels in cases of severe pulmonary hypertension.

Keywords

Pulmonary hypertension, gas exchanger, compliance, oxygenator, right ventricular unloading

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Introduction

For end-stage lung failure, venovenous extracorporeal membrane oxygenation (ECMO) can successfully bridge patients to lung transplantation.[1] However, the commonly used femoral or jugular access inevitably causes an important loss of ambulatory status and quality of life. In patients with pulmonary hypertension (PH), right ventricular (RV) failure also emerges. This often requires venoarterial ECMO to provide both pulmonary and cardiac support. Its use, however, is limited to a run time of approximately 2 weeks due to the significant increase of relevant complications thereafter.[2]

It has been demonstrated that the pressure difference between the pulmonary artery (PA) and left atrium (LA) in PH patients can be used as the driving force to pass blood across a PA-LA cannulated low resistance oxygenator.[3,4] This option is more invasive, but obviates the need of a pump and allows mobilization of the patient. Moreover, it offers the potential to unload the pressure overloaded RV.

However, unloading the RV by reducing its power requirements is determined by more than resistance alone; it is a function of flow rates and time (impedance). Current commercially available oxygenators possess blood flow impedances greater than the natural lungs. In the PA-LA configuration with simultaneous increased RV afterload,

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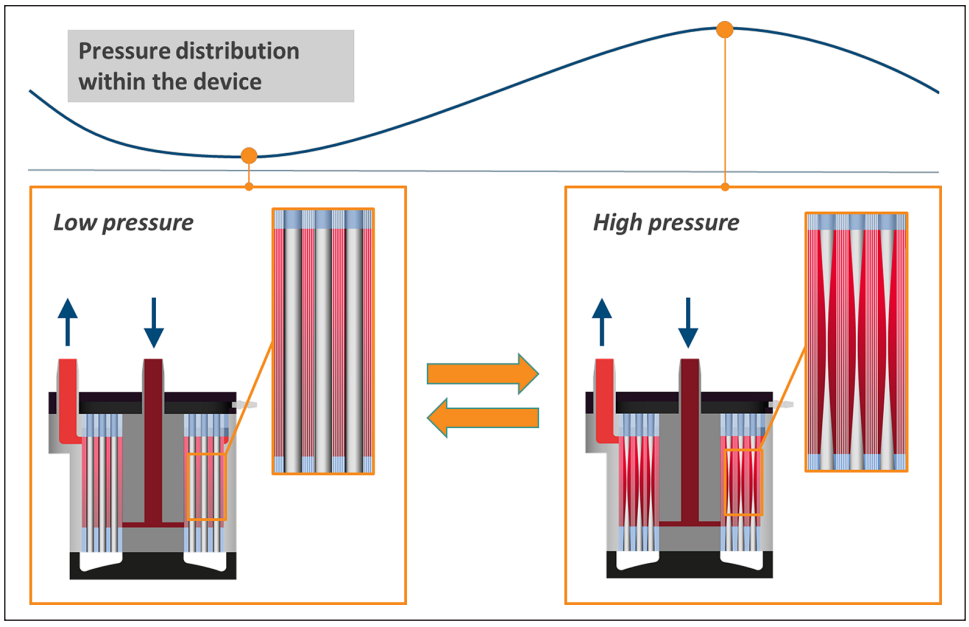

Figure 1. Schematic overview of RAS-Q® technology illustrating the effect of different pressures on the compliance elements (silicone tubes) placed within the polymethylpentene fiber bundle.

such oxygenators might increase PA-pressures (PAPs) even more, which can lead to decreased cardiac output (CO) and exercise tolerance.[5]

Increasing the compliance, defined here as the ability of a device to increase in volume with increasing static pressure, of an oxygenator is the most effective method in lowering the pulmonary inflow impedance.[6] This was first applied by Lick et al., who demonstrated an improved RV function when adding an inflow compliance chamber.[7] Meanwhile, other groups have described oxygenator designs with an expandable housing.[8–10]

Here, we describe the in-vivo hemodynamic effects of RAS-Q® (Enmodes Gmbh, Aachen, Germany), an enabling technology which allows the design of oxygenators with fiber-bundle-integrated compliance.

Material and methods

RAS-Q® technology

The RAS-Q technology combines industry-standard polymethylpentene (PMP) hollow fiber bundles with silicone tubes, acting as compliant elements. These tubes are placed in defined positions inside the wound fiber bundle, providing a pulmonary-mimetic flow environment and low pressure loss at high performance (Figure 1). The RAS-Q prototype used in this study was designed for a blood flow of 1 L/min with a gas exchange surface of 0.6 m^2.

Besides lowering the pressure loss, the flow can also be guided through the fiber bundle, improving the washout behavior.

Compliance measurement

To measure the compliance of each oxygenator, the device was primed with saline solution, and the inlet and outlet were connected with a short 3/8″ PVC tube, including one Luer-connector. The Luer connector was used to add saline solution to the closed device in discrete volumes and to measure the corresponding pressure increase simultaneously.

In-vivo investigations

Animal preparation. This study was approved by the KULeuven animal ethics committee (P210/2015). All animals received humane care in compliance 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 Institute of Laboratory Animal Resources (National Institutes of Health). Six ewes (Swifter) of 53 ± 7 kg, ages 12.4 ± 1.3 months, were included. After sedation with 15 mg/kg intramuscular ketamine, anesthesia was induced with isoflurane. After intubation, the animals were ventilated with a volume-controlled respirator (Dräger, Cicero). Anesthesia was maintained with isoflurane (2%–3%) in a gas mixture consisting of 80% to

100% oxygen supplemented with room air. About 0.3 mg Buprenorphine-hydrochloride and 0.5 mg/kg Meloxicam were administered intravenously for analgesia.

Instrumentation. While the animals were being prepared, the RAS-Q prototype was primed and degassed using saline solution. Briefly, the solution was added to a closed circuit containing the prototype, and after initial extraction of bubbles, the solution was circulated through the prototype for >30 min. The circuit was then inspected once more, and any new bubbles were removed before attaching the circuit to the animal.

A pressure line in the left ear artery served to measure arterial blood pressure (ABP). End tidal CO_2 and blood O_2 saturation were monitored throughout the study. A left thoracotomy through the fourth intercostal space was performed and the heart was exposed in the pericardial cradle. 5000 IU of heparin were administered intravenously. A 14-mm Dacron graft bound to 3/8″ PVC tubing was anastomosed end of graft-to-side of the proximal PA. A 22 Fr cannula (Sorin, Milan, Italy) was inserted through the roof of the LA and connected with 3/8″ silicone tubing. The tubing was subsequently connected with a RAS-Q prototype oxygenator (Enmodes, Aachen, Germany). A Sono TT flowmeter (Emtec, Gennevilliers, France) around the tubing measured the flow through the device. A TS420 flowmeter (Transonic Systems Europe B.V., Maastricht, The Netherlands) around the proximal ascending aorta measured the CO. Pressure lines in the LA and in the PA (proximal to the banding) served to measure LA pressure (LAP) and PAP, respectively.

Experimental conditions. In addition to physiological conditions (NO PH), two pathophysiological conditions mimicking the effects of RV pressure overload were created by artificially banding the PA distal to the oxygenator's inflow tract. The effects of PA banding have been described before.[11] In brief, PA banding increases RV afterload which significantly increases RV dimensions and pressures. The resulting reductions of RV stroke volume and ejection fraction significantly decrease ABP and CO while RV forward delivered power significantly increases.

For the experiments presented here, pressure overload was first induced by tightening the band around the PA until mean (m) PAP/mABP reached 0.5 (MODERATE PH). In the second case, the band was tightened as much as was hemodynamically tolerated (SEVERE PH). After allowing the animal to stabilize for 10 min at each of the three experimental conditions, during which the oxygenator circuit was clamped off from the blood flow, baseline pressures, and flows were recorded. Then the oxygenator circuit was opened, and pressures and flows were recorded again 5 min later. Additionally, blood samples were taken from inlet and outlet of the oxygenator to measure blood gases (epoc®, Siemens Healthineers, Erlangen, Germany). At the end of each experiment, the sheep was sacrificed by means of intravenous injection of potassium chloride (14.9%) after reassurance of adequate anesthesia.

Comparative evaluations. In addition to evaluating the RAS-Q prototype alone, its performance was also compared to a market predicate device. In the first animal, a second parallel circuit containing a Quadrox-i® neonatal and pediatric oxygenator (Maquet Getinge Group, Gothenburg, Sweden) was constructed by including two three-way valves in the RAS-Q circuit. The pediatric device size was chosen (1) to accommodate the sheep's lower CO and (2) to compare the RAS-Q prototype with an oxygenator that has similar dimensions. Quadrox-i and the RAS-Q prototype have an exchange membrane area of 0.8 and 0.6 m^2 and a priming volume of 84 and 77 mL, respectively. Additionally, the Quadrox-i pediatric was regarded as an appropriate comparison device, since it was designed to offer a wide flow range, high gas exchange rates and low blood side flow resistance.[12] In each experimental condition (NO PH, MODERATE PH, SEVERE PH) four subconditions were tested: (1) Baseline, (2) RAS-Q, (3) Quadrox-i pediatric, (4) RAS-Q and Quadrox-i pediatric in two PA-LA separate parallel circuits.

Data-analysis

PA-flow was calculated by subtracting oxygenator flow from flow through the ascending aorta.

Data are presented as mean ± standard deviation. Statistical analysis was performed using Statistica 10.0 (StatSoft, Inc., Tulsa, USA) software. Direct comparisons between the baseline states under the three experimental conditions and between baseline and RAS-Q-supported states at moderate and severe PH were made using Wilcoxon matched pairs test. A p-value of less than 0.05 was considered statistically significant.

Results

This RAS-Q prototype was previously tested in vitro. Pressure loss was very low (5, 8, and 11 mmHg at 1, 1.5, and 2 L/min blood flow, respectively). Gas exchange at 1:1 gas to blood flow rate ratio was sufficient, managing an oxygen exchange of >60 mL/min and carbon dioxide removal of >50 mL/min with a hematocrit of 38.8%, following harmonized standards for oxygenator blood trials (ISO 7199) (previously unpublished results).

The compliance measurements are depicted in Figure 2. Adding an additional volume of 40 mL in the RAS-Q prototype increased the pressure by only 8.3 mmHg. As a comparison, in the Quadrox-i oxygenator, adding only 1 mL increased the pressure by more than 50 mmHg.

Prototype in-vivo performance

Hemodynamics of the different conditions prior to opening the RAS-Q circuit are depicted in Table 1. Moderate banding caused ABP to decrease, and the RV generated higher PAPs to overcome the increased resistance. mPAP/mABP increased from 0.22 ± 0.04 to 0.53 ± 0.20 ($p < 0.05$). CO showed a tendency to decrease ($p = 0.07$). A severe banding caused ABP and CO to significantly decrease further, while PAP also decreased compared to the moderate banding. mPAP/mABP increased further towards 0.83 ± 0.10 ($p < 1.10^{-4}$ vs baseline, $p = 0.06$ vs moderate banding). These changes indicate acute RV-failure.

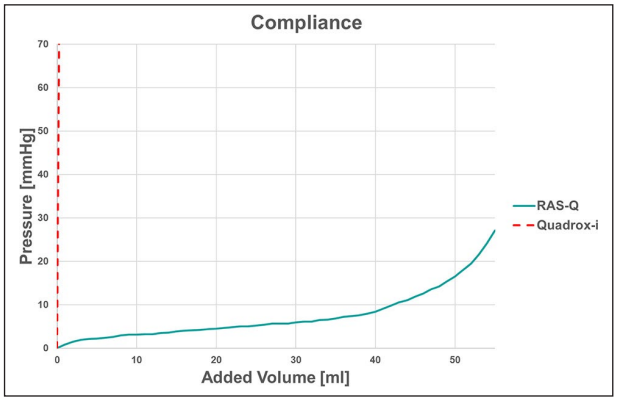

Figure 2. Compliance measurement illustrating the effect of the integrated silicon tubes.

Hemodynamic effects in baseline conditions are depicted in Table 1. The device accommodated 20% of the total CO, but ABP and total CO both decreased significantly, whereas PAPs even increased slightly.

Hemodynamic effects and the influence on blood gas values at moderate banding are depicted in Tables 1 and 2, respectively. With 1.0 L/min of flow, the device delivered 31% of the total CO to the LA. ABP and total CO remained the same, but PAP decreased. mPAP/mABP decreased from 0.53 ± 0.20 to 0.41 ± 0.15 ($p < 0.05$). Blood gas samples showed a decrease of pCO_2 and an increase of pO_2.

Hemodynamic effects and the influence on blood gas values at severe banding are depicted in Tables 1 and 2, respectively. With 1.17 L/min of flow, the device delivered 39% of the total CO to the LA. ABP and total CO significantly increased. PAP increased, but mPAP/mABP decreased from 0.83 ± 0.10 to 0.49 ± 0.20 ($p < 0.05$). Blood gas samples showed a decrease of pCO_2 and an increase of pO_2.

Comparison of RAS-Q versus Quadrox-i support

In all three conditions, the RAS-Q prototype received higher flows than the Quadrox-i (Figure 3(b) vs (d)), resulting in

Table 1. Pressures and flows.

	Baseline	RAS-Q	*p* Value
NO PH ($n = 6$)			
mABP (mmHg)	68.2 ± 13.9	60.2 ± 15.1	<0.05
mPAP (mmHg)	14.5 ± 3.4	15.7 ± 4.0	0.50
mLAP (mmHg)	4.8 ± 1.3	7.0 ± 4.9	0.42
Oxygenator flow (L/min)	0 ± 0	0.68 ± 0.34	<0.01
Pulmonary flow (L/min)	3.77 ± 1.08	2.75 ± 1.03	<0.01
Total CO (L/min)	3.77 ± 1.08	3.43 ± 1.01	<0.05
MODERATE PH ($n = 6$)			
mABP (mmHg)	60.5 ± 10.6^{a}	59.9 ± 14.4	0.70
mPAP (mmHg)	31.8 ± 13.8^{a}	24.0 ± 10.9^{a}	<0.01
mLAP (mmHg)	4.4 ± 3.2	6.8 ± 6.2	0.37
Oxygenator flow (L/min)	0 ± 0	1.00 ± 0.27^{a}	$<1.10^{-3}$
Pulmonary flow (L/min)	3.13 ± 0.89	2.27 ± 0.95	<0.05
Total CO (L/min)	3.13 ± 0.89	3.27 ± 1.17	0.68
SEVERE PH ($n = 5$)			
mABP (mmHg)	$33.6 \pm 10.4^{a,b}$	63.8 ± 17.4	<0.05
mPAP (mmHg)	27.4 ± 6.7^{a}	30.6 ± 16.1	0.69
mLAP (mmHg)	3.3 ± 2.5	3.0 ± 2.6	0.92
Oxygenator flow (L/min)	0 ± 0	$1.17 \pm 0.27^{a,b}$	$<1.10^{-3}$
Pulmonary flow (L/min)	$1.63 \pm 1.11^{a,b}$	1.85 ± 0.70	0.40
Total CO (L/min)	$1.63 \pm 1.11^{a,b}$	3.02 ± 0.77	<0.01

mABP: mean arterial blood pressure; mPAP: mean pulmonary artery pressure; mLAP: mean left atrial pressure; CO: cardiac output; PH: pulmonary hypertension.
[a]Statistical significant difference with NO PH.
[b]Statistical significant difference with MODERATE PH.

Table 2. Blood gas values.

	RAS-Q inlet	RAS-Q outlet	*p* Value
MODERATE PH ($n=4$)			
pH	7.35 ± 0.06	7.41 ± 0.06	0.08
pCO_2	54.6 ± 3.7	45.3 ± 6.2	<0.05
pO_2	43.1 ± 4.8	133.5 ± 49.7	0.08
SEVERE PH ($n=4$)			
pH	7.37 ± 0.06	7.44 ± 0.04	<0.05
pCO_2	55.1 ± 2.1	44.1 ± 2.4	<0.05
pO_2	44.0 ± 5.8	128.8 ± 31.1	<0.01

PH: pulmonary hypertension.

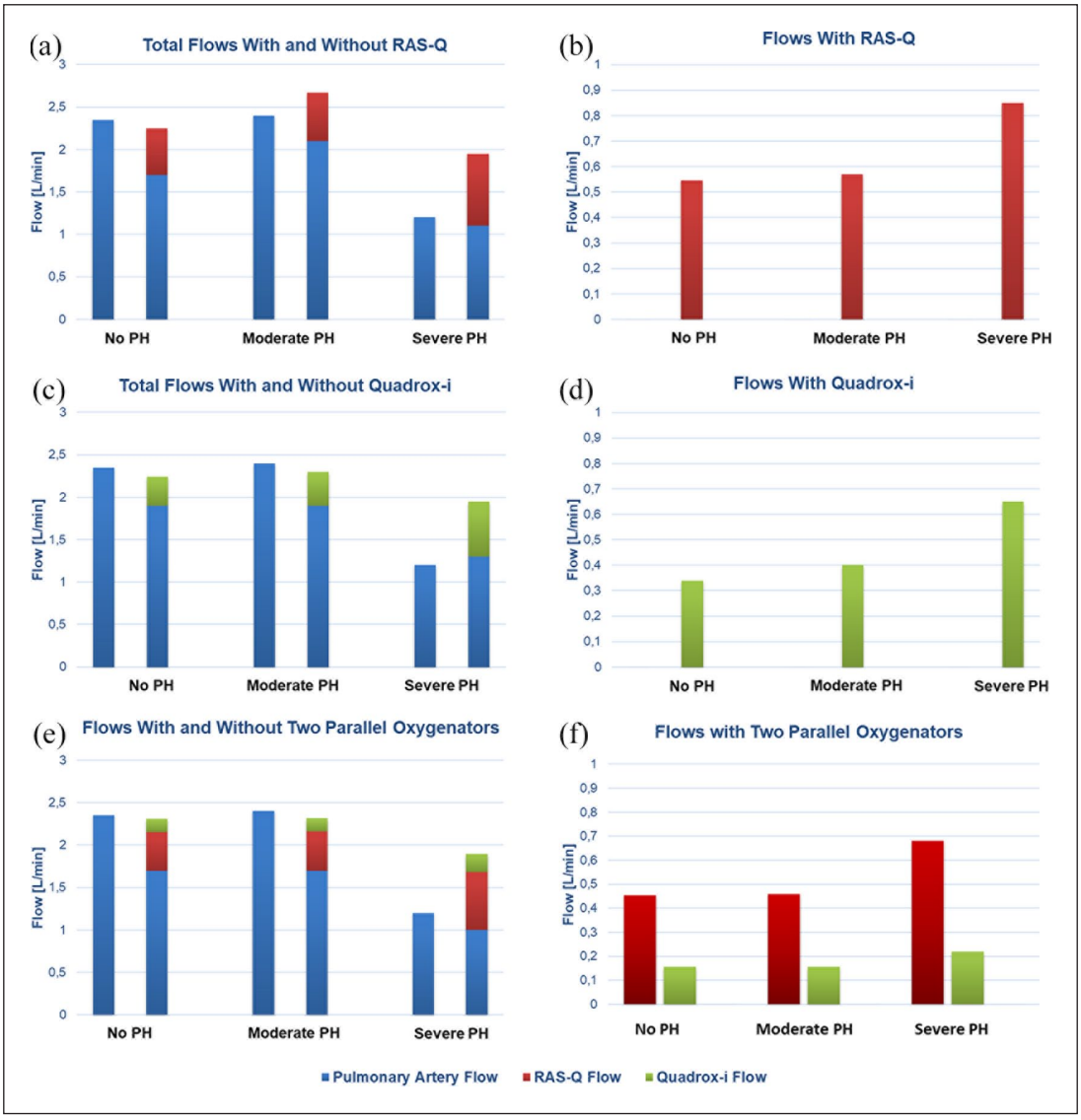

Figure 3. Flow measurements comparing the performance of RAS-Q® with Quadrox-i® in a single animal. (a) Total flows for each condition, left-sided bar = without RAS-Q, right-sided bar = with RAS-Q. (b) Flow through RAS-Q in the three different conditions. (c) Total flows for each condition, left-sided bar = without Quadrox-i, right-sided bar = with Quadrox-i. (d) Flow through Quadrox-i in the three different conditions. (e) Total flows for each condition with both RAS-Q and Quadrox-i opened in two separate parallel circuits, left-sided bar = without opening the parallel circuits, right-sided bar = with RAS-Q and Quadrox-i circuits both opened. (f) Flow through RAS-Q and Quadrox-i when both circuits are simultaneously open in the three different conditions.
PH: pulmonary hypertension.

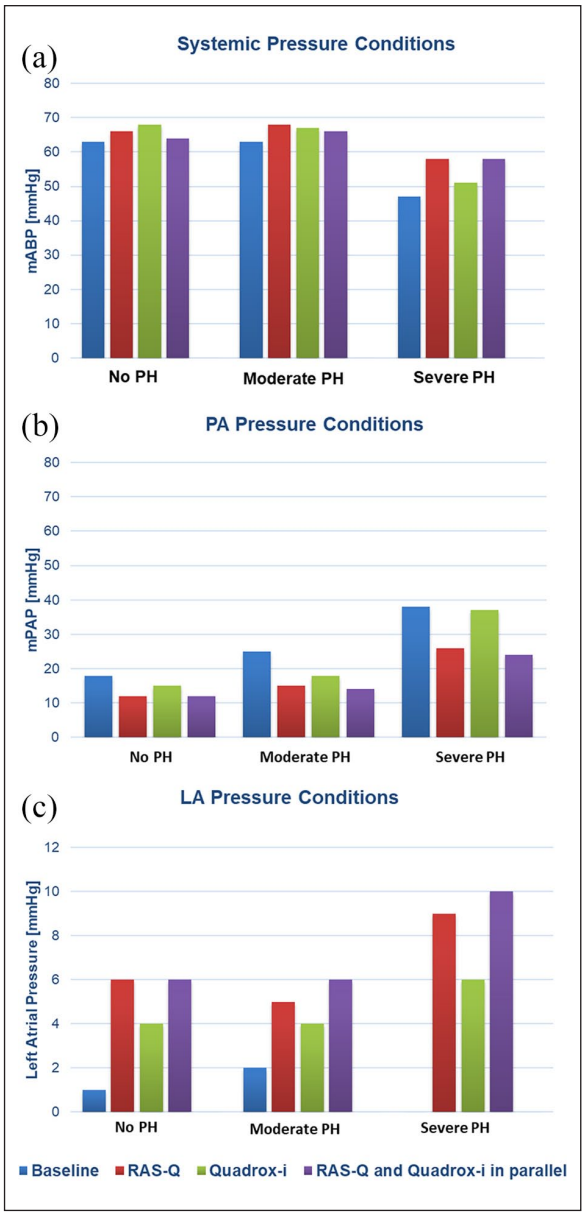

Figure 4. Pressure measurements comparing the performance of RAS-Q® with Quadrox-i® in a single animal.
PH: pulmonary hypertension; mABP: mean arterial blood pressure; PA: pulmonary artery; mPAP: mean pulmonary artery pressure; LA: left atrial.

better LA-filling pressures (Figure 4(c)) and a better total CO in moderate PH (Figure 3(a) vs (c)). This resulted in the delivery of a higher percentage of the total CO (no PH: 24 vs 15%, moderate PH: 21% vs 17%, severe PH: 44% vs 33%, illustrated in Figure 3(a) and (c)) and lower mPAPs (Figure 4(b)) by RAS-Q, while, especially in severe PH, systemic pressures were higher. This resulted in better mPAP/mABP ratio's compared to the Quadrox-i (No PH: 0.18 vs 0.22; moderate PH: 0.22 vs 0.27; severe PH: 0.45 vs 0.73). The most striking difference is seen in severe PH, where mPAPs are reduced from 38 to 26 mmHg by RAS-Q, but only decrease to 37 mmHg by the Quadrox-i.

Opening the two parallel circuits at the same time allowed a direct comparison of the devices. In each condition a 3× higher flow passed through the RAS-Q oxygenator compared to the Quadrox-i (Figure 3(e) and (f)).

Discussion

We have demonstrated here that the unique low pressure loss and integrated compliance of the RAS-Q prototype significantly lowered RV afterload and restored CO in cases of RV-failure due to RV pressure overload. In baseline conditions, the RV was not unloaded; PAP's even increased. At moderate pressure overload, RV unloading was successful as PAP and mPAP/mABP decreased. At severe pressure overload, the decreasing mPAP/mABP signified successful RV unloading while the increasing PAP signified RV recovery from acute RV-failure. Compared to the Quadrox-i device, the RAS-Q prototype delivered a >90% higher relief in pulmonary arterial pressure. This resulted in the delivery of a higher percentage of the CO and in better mPAP/mABP ratio's, indicating a better RV unloading.

Patients with end-stage respiratory failure and an elevated pulmonary vascular resistance or cardiac dysfunction often require veno-arterial ECMO. But in cases of severe PH, the elevated right-side pressures can be used as the driving force for a pumpless oxygenator between PA and LA.[3,4] PAPs reaching systemic levels are most often encountered in end-stage pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease (world health organization (WHO) PH classification group 1 and 1'). These patients will almost certainly benefit the most from this strategy. Aside from that population, the largest group of PH patients who could benefit from this approach are those with PH due to lung diseases and/or hypoxia (WHO PH classification group 3), for example, patients with chronic obstructive pulmonary disease (COPD) or interstitial lung disease, with a so called end-stage "cor pulmonale."[13,14]

RV afterload is determined by several components: (1) mean resistance, or resistance to blood flow during steady state; (2) the compliance, or blood storage capacity of the vascular system; (3) arterial wave reflections that occur as a result of pulsatile blood flow; and (4) the inertance of blood during ejection.[15] Pulmonary artery input impedance is the most comprehensive description of RV vascular load and takes into account all of the four components mentioned above. In the normal pulmonary circulation, pulse wave reflections are minimized by the large surface area and gentle tapering of blood vessels. In addition, the compliant vascular bed slows the speed of wave transmissions. Reflection peaks occur during the diastolic phase of the cardiac cycle, avoiding direct opposition to forward flow.[9] In PH, the compliance of the arterial vessels is lost,

meaning that the reflection peaks occur during systole, directly opposing cardiac ejection. Consequently, the delivered RV power must increase (by increasing RV systolic pressure, resulting in higher systolic PAPs) to exceed this added load or the ventricle becomes unable to completely eject.

The benefit of adding compliance to an artificial lung design in the PA-LA configuration has been nicely demonstrated by Haft et al.[9] In their non-compliant design, a large pulse wave reflection was generated and the stiff conduits resulted in rapid return during the systolic phase of the cardiac cycle. As such, a relatively non-pulsatile flow pattern was seen. Their modified device (with a compliant oxygenator housing) dampened the reflected pressure and delayed its return to the heart until later in the cardiac cycle. The physiological benefit could be seen with the restoration of RV-generated pulsatile flow.

Most oxygenator designs have focused on lowering resistance, which has resulted in many devices whose resistances are equal to or even less than the normal pulmonary vascular resistance. Their impedances, however, remain higher than that of the natural lungs. Although we did not include an impedance recording and analysis in our in-vivo study, the effect of adding compliance was demonstrated by comparing our low resistance design with the low resistance Quadrox-i oxygenator. The RAS-Q prototype received higher flows, which resulted in a higher total CO in moderate PH and a comparable total CO in severe PH. However, in both conditions, mPAP was reduced more with the RAS-Q prototype, with even a $>$90% higher pressure relief in severe PH. This additional RV unloading improves the chances of reversed remodeling and/or recovery as has been demonstrated before with low-flow RV-assist devices (RVADs) in the pressure overloaded RV.[16]

Although a compliant oxygenator only offers passive RV unloading compared to the active, and more profound, unloading of a low-flow RVAD, this strategy has some clear advantages. First, the pulmonary vasculature, which is already heavily challenged during PH, is relieved as well, by providing a parallel oxygenated circuit for the blood. Second, the RV itself serves as the driving force for the blood flow through the oxygenator, omitting the need for a blood pump, external power supply, controllers, etc.

The approach taken in the RAS-Q technology presents some key advantages in comparison to earlier efforts to create compliant oxygenators. Those designs exclusively incorporated a high compliance through some form of "external" measure (e.g. a compliant oxygenator housing or additional flow circuit component). However, adding external compliance to the design of an oxygenator resulted in larger dimensions of the device, making it quite bulky.[7,8,10] The RAS-Q technology, on the other hand, is the first to exhibit a compliance integrated completely within the fiber bundle. This resulted in smaller, more acceptable device dimensions, making it more wearable. It also allowed for the passive manipulation of blood flow across the fiber bundle. In theory, this could reduce the risk of thrombus formation, since these compliant elements can be placed in crucial areas to improve flow conditions. Moreover, compared to veno-venous ECMO, the strategy of using a compact, pumpless system more readily offers the tremendous advantage of making patients mobile again and possibly even to let them go home, as is done today with LVAD-patients.

The improved RV unloading and possibly consequent reversed remodeling could make RAS-Q-based oxygenators an excellent tool to serve as bridge to RV-recovery (in cases of acute RV-failure and COPD exacerbation), bridge to candidacy (from too sick to be transplantable to transplant eligible), bridge to transplant (end-stage PAH and COPD) or even destination therapy (non-transplant candidates).

In the near future, chronic animal trials are planned to: (1) assess the hemocompatibility of the device; (2) assess the effects on the chronic pressure overloaded RV; (3) to asses a larger prototype, designed for a blood flow of 2 L/min as this may be more suitable for clinical application. In parallel, an in vitro experimental circuit will be set up to meet future objectives of the RAS-Q project, with an emphasis on evaluating blood trauma and optimizing perfusion in future devices.

Limitations

First, only a small number of animals was studied. Second, our animal model serves as a model for acute RV pressure overload. Though it also serves to assess the effects of increased PAP, a model of chronic RV pressure overload will be needed to adequately assess the effects of long-term RAS-Q use on the RV in PH. Third, we were only able to compare our device with a commercially available low-resistance, non-compliant oxygenator in one trial.

Conclusion

These in vivo results of the world's first gas exchanger with a low pressure loss and an internally integrated compliance demonstrate its possibilities to better unload the RV compared to non-compliant oxygenators and to restore normal CO in cases of severe PH in a PA-LA configuration.

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