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Systolic and diastolic unloading by mechanical support of the acute vs the chronic pressure overloaded right ventricle

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KEYWORDS:
right ventricular pressure overload;
low-flow support;
right ventricular assist device;
pulmonary hypertension

BACKGROUND: Right ventricular (RV) mechanical support is well described in cases of sudden increase in RV afterload. In cases of chronic RV pressure overload (e.g., pulmonary arterial hypertension), it has rarely been described.

METHODS: The pulmonary artery was banded in 18 sheep. In the acute group ($n = 9$), we immediately implanted a Synergy Pocket Micro-Pump. Blood was withdrawn from the right atrium to the pulmonary artery. In the chronic group ($n = 9$), this pump was implanted 8 weeks after banding. Hemodynamics and pressure-volume loops were recorded before and 15 minutes after pump activation.

RESULTS: Low-flow RV mechanical support significantly improved arterial blood pressure in both groups, but cardiac output only in the acute group. Intrinsic RV contractility was not affected. The RV contribution to the total right-sided cardiac output was 54% ± 8 in the acute group vs 10% ± 13 in the chronic group ($p < 1.10^{-5}$), indicating a more profound unloading in the latter. Diastolic unloading (reflected by decreases in central venous pressure, end-diastolic pressure and volume, and ventricular capacitance) was successful in both groups. Decreases in pressure-volume area and RV peak pressure reflected successful systolic unloading only in the chronic group.

CONCLUSIONS: Low-flow RV mechanical support improved arterial blood pressure in both conditions but caused a more profound unloading in the chronic group. Diastolic unloading was successful in both groups, but systolic unloading was successful only in the chronic group. The potential use of low-flow mechanical support for a chronic pressure overloaded right ventricle warrants further research to assess its long-term effects.

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Right ventricular failure (RVF) resulting from an increased afterload occurs in 2 populations: (1) patients with a sudden increase in afterload immediately leading to RVF (e.g., heart transplant recipients or patients with acute respiratory distress syndrome) and (2) patients with pre-existing chronic pulmonary hypertension in whom the right ventricle went through phases of adaptive hypertrophy and dilatation before clinical failure emerged. In these settings, RVF refractory to medical treatment may benefit from

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mechanical support. Clinically, this has been successful for an acute pressure overloaded right ventricle.[1,2] Few and variable results have been reported for a chronic pressure overloaded right ventricle.[3,4] It is feared that devices that provide relatively high flow rates might result in increased pulmonary pressures and lung injury.[5] Therefore, smaller mechanical circulatory assist devices with lower flow capacities might be more appropriate for right ventricular (RV) support. Low-flow ventricular support resulted in significant hemodynamic benefits in selected cases of left ventricular failure.[6,7] Accordingly, this concept has been proposed for use in patients with RVF secondary to pressure overload.[8]

Our group demonstrated the feasibility and hemodynamic benefits of low-flow RV mechanical support in cases of acute RV pressure overload.[9] Our next goal is to assess the utility of right ventricular assist devices (RVADs) for patients with a chronic pressure overloaded right ventricle (e.g., pulmonary arterial hypertension [PAH]). As a first step, we aimed to compare the short-term hemodynamic effects of low-flow RVADs in an acute pressure overloaded right ventricle and a chronic pressure overloaded right ventricle.

Methods

A more detailed description of methods has been provided before.[9]

Animal preparation

This study was approved by the KU Leuven animal ethics committee (P127/2011). 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, Bethesda, MD). The study included 18 ewe (Swifter-Charolais, University of Leuven, Belgium), 44.3 kg ± 4.6, 10.2 months ± 0.7 old. After sedation with intramuscular ketamine 15 mg/kg, anesthesia was induced with isoflurane. After intubation, the animals were ventilated with a volume-controlled respirator (Cicero; Dräger). Anesthesia was maintained with isoflurane (2%–3%) in a gas mixture consisting of 80%–100% oxygen supplemented with room air. Intravenous buprenorphine 0.3 mg and meloxicam 0.5 mg/kg were used for analgesia.

Instrumentation

Pressure lines in the left ear artery and the left jugular vein served to measure arterial blood pressure (ABP) and central venous pressure (CVP), respectively. A Swan-Ganz catheter measured distal pulmonary artery pressure (PAP). In all animals, a left thoracotomy through the fourth intercostal space was performed. In 9 sheep, a band was placed around the distal pulmonary trunk and tightened as much as was hemodynamically tolerated to create RV pressure overload (chronic group). In this group, a TS420 flowmeter (Transonic Systems Europe B.V., Maastricht, Netherlands) around the proximal pulmonary artery (PA) measured cardiac output (CO) generated by the right ventricle (right ventricular cardiac output [RVCO]). Pressure lines in the left atrium and just proximal to the band served to measure left atrial pressure and PAP just proximal to the band, respectively (Figure 1). Hemodynamics were measured 5 minutes before and 5 minutes after PA banding.

Eight weeks later, all animals were prepared and instrumented as described before. The left thoracotomy was retaken. In sheep

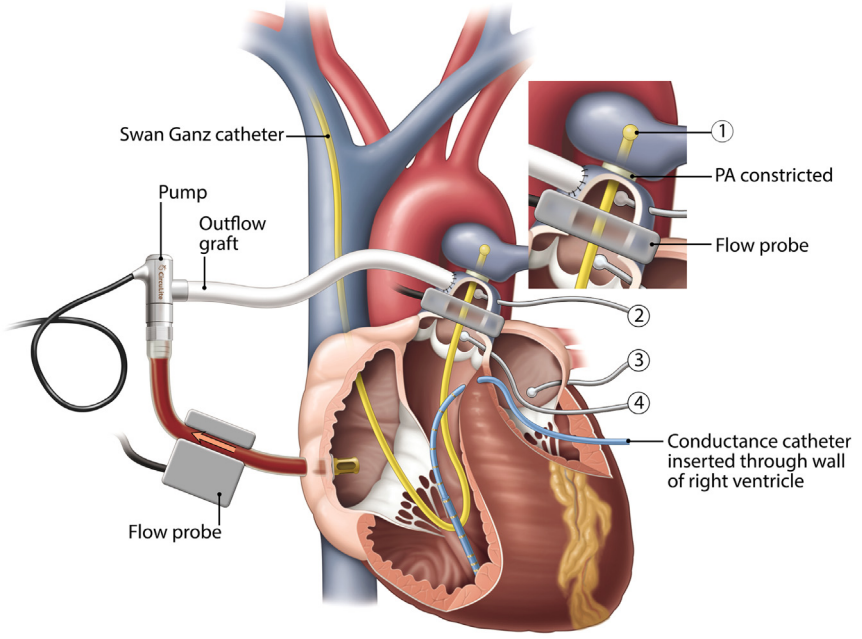

Figure 1 Schematic overview of the experimental set-up. LA, left atrium.

without pulmonary banding, a band was placed, and hemodynamics were measured as described before (acute group). In all sheep, a Synergy Micro-Pump (HeartWare, Framingham, MA) was inserted to withdraw blood from the right atrium to the PA. A Sono TT flowmeter (Emtec, Gennevilliers, France) around the pump's tubing system measured pump flow. The TS420 flowmeter around the proximal PA, proximal to the pump's outflow graft, measured RVCO. Pressure lines in the left atrium, in the PA between the pulmonary valve and the Transonic flowmeter, and just proximal to the band served to measure left atrial pressure, proximal PAP, and PAP just proximal to the band. Finally, a 7F combined pressure-conductance catheter was connected to a Sigma M signal processor (both CD Leycom, Zoetermeer, Netherlands). This catheter was positioned in the right ventricle through a stab wound just below the pulmonary valve and positioned toward the apex.

Pressures, flows, and pressure-volume (PV) loops were recorded at zero pump speed and 15 minutes after activating the pump at low flow (22,000 rpm). Finally, the animals were sacrificed by means of 20 ml potassium chloride (14.9%) administered intravenously after reassurance of adequate anesthesia.

Data analysis

Total CO was calculated by adding intrinsic RVCO and pump flow. RV power was calculated as mean proximal PAP * pulmonary flow * 0.0022, and total power was calculated as mean PAP just before the band * total CO * 0.0022. PV loop analysis was performed using CD Leycom and Matlab R2013a (MathWorks, Natick, MA) software. The end-systolic PV relationship (ESPVR) was determined by using a single beat estimation method by means of a sine curve fitting (A * sin(Bt + C) + D) in which parameters A to D are calculated by the Levenberg-Marquardt procedure in Matlab.[10–12] From this ESPVR, the slope (end-systolic elastance) and volume axis intercept (V_0) were determined. As both end-systolic elastance and V_0 varied in different directions of contractility, ESPVR V_{30}, the volume at an end-systolic pressure of 30 mm Hg, was calculated and served as an additional index of contractility.[13] The end-diastolic PV relationship (EDPVR) was determined using computational single beat methods.[14,15] From these curves ($P = \alpha V^{\beta}$), EDPVR V_{30}, the volume at which diastolic pressure equaled 30 mm Hg, was calculated and served as an index of capacitance. To compare these curves of compliance, the curve-fit expressions were linearized using a logarithmic transformation (ln) of pressure and volume data.[13] This resulted in β as slope and in $(-\ln(\alpha)/\beta)$ as V_0.

Data are presented as mean ± SD. Statistical analysis was performed using STATISTICA 10.0 (StatSoft, Inc., Tulsa, OK) software. For procedural dependent comparison between supported and non-supported RV function of each animal, Wilcoxon matched pairs test was used. For comparison between the 2 experimental groups, data were subjected to Mann-Whitney *U*-test. A p-value < 0.05 was considered statistically significant.

Results

Hemodynamics and PV loop parameters are depicted in Tables 1–5. Banding the PA caused the same acute hemodynamic changes in both groups. In the chronic group, all animals developed clinical signs of RVF. Tachypnea developed from the first post-operative day. Abdominal sonography confirmed the presence of large amounts of ascites. Animals that presented too dyspneic were treated with furosemide and ascites drainage.

Description of 2 conditions

After 8 weeks of chronic pressure overload, RV end-diastolic volume (EDV) had significantly increased compared with the acute group (Figure 2A). Also, end-systolic volume (ESV) had a tendency to be higher ($p = 0.0531$). This caused a rightward and downward shift of the EDPVR, with a decreased slope (β) and an increased V_0 of the linearized EDPVR, implying an increased RV compliance

Table 1 Hemodynamics Before and After Banding the Pulmonary Artery

		Pre-banding	Post-banding	*p*-value
Weight, kg	Acute ($n = 9$)	45.8 ± 3.7		
	Chronic ($n = 9$)	42.8 ± 5.0		
Age, months	Acute ($n = 9$)	10.1 ± 0.8		
	Chronic ($n = 9$)	10.3 ± 0.7		
mABP, mm Hg	Acute ($n = 9$)	59.4 ± 2.9	48.2 ± 6.7	$<1.10^{-4}$
	Chronic ($n = 9$)	59.0 ± 3.9	48.8 ± 5.4	$<1.10^{-5}$
mPAP proximal band, mm Hg	Acute ($n = 9$)	15.4 ± 3.2	32.1 ± 5.3	$<1.10^{-5}$
	Chronic ($n = 9$)	16.0 ± 3.2	32.4 ± 4.9	$<1.10^{-7}$
mPAP distal band, mm Hg	Acute ($n = 9$)	15.4 ± 3.2	13.6 ± 3.3	<0.001
	Chronic ($n = 9$)	16.0 ± 3.2	14.2 ± 3.4	<0.001
CVP, mm Hg	Acute ($n = 9$)	7.8 ± 1.9	12.2 ± 1.9	<0.001
	Chronic ($n = 9$)	8.1 ± 1.9	12.9 ± 1.9	$<1.10^{-6}$
LAP, mm Hg	Acute ($n = 9$)	4.6 ± 1.5	6.0 ± 1.9	<0.001
	Chronic ($n = 9$)	4.2 ± 1.4	5.8 ± 1.7	<0.01
CO, liter/min	Acute ($n = 9$)	3.70 ± 0.72	2.79 ± 0.83	$<1.10^{-7}$
	Chronic ($n = 9$)	3.72 ± 0.62	2.70 ± 0.69	$<1.10^{-5}$
Resistance across banding,[a] dyne · sec · cm^{-5}	Acute ($n = 9$)		572 ± 194	
	Chronic ($n = 9$)		567 ± 137	

CO, cardiac output; CVP, central venous pressure; LAP, left atrial pressure; mABP, mean arterial blood pressure; mPAP, mean pulmonary arterial pressure.
[a]Resistance across banding = 80 · (mPAP proximal band − mPAP distal band)/CO. No statistically significant differences were found between the acute and chronic group.

Table 2 Pressures and Flows

	Acute ($n = 9$)		Chronic ($n = 9$)	
Banding	No support	Pump on	No support	Pump on
mABP, mm Hg	48.2 ± 6.7	56.7 ± 11.6[a]	60.1 ± 17.3	69.1 ± 14.2[a]
mPAP proximal, mm Hg	32.1 ± 5.3	40.0 ± 6.5[a]	27.2 ± 3.6[b]	32.7 ± 6.4[a,b]
Systolic	51.3 ± 8.9	55.1 ± 9.2[a]	41.2 ± 7.5	42.1 ± 7.9[b]
Diastolic	22.6 ± 5.1	32.3 ± 7.5[a]	18.9 ± 4.8	27.8 ± 6.9[a,b]
mPAP distal, mm Hg	15.8 ± 2.6	18.1 ± 2.4[a]	18.1 ± 3.1	21.8 ± 6.6[a]
mCVP, mm Hg	12.2 ± 1.9	10.7 ± 2.1[a]	14.4 ± 2.3[b]	13.6 ± 2.1[a,b]
HR, beats/min	96 ± 11	93 ± 10	98 ± 15	87 ± 17[a]
mLAP, mm Hg	6.0 ± 1.9	7.3 ± 1.9[a]	6.8 ± 3.2	9.2 ± 4.2[a]
Pump flow, liter/min	0 ± 0	1.69 ± 0.56[a]	0 ± 0	2.74 ± 0.19[a,b]
RVCO, liter/min	2.79 ± 0.83	1.96 ± 0.41[a]	2.64 ± 0.79	0.37 ± 0.46[a,b]
Total CO, liter/min	2.79 ± 0.83	3.65 ± 0.82[a]	2.64 ± 0.79	3.11 ± 0.41

CO, cardiac output; distal, distal to the band; HR, heart rate; mABP, mean arterial blood pressure; mCVP, mean central venous pressure; mPAP, mean pulmonary arterial pressure; mLAP, mean left atrial pressure; proximal, just proximal to the band; RVCO, right ventricular cardiac output.

[a]Significant difference with no support in the same condition.

[b]Significant difference with the same pump status in the other condition.

and capacitance (V_{30}) in the chronic group. Although these animals compensated CO and ABP by increasing preload (increased CVP, stroke volume [SV], and EDV), the right ventricle generated lower peak pressures, end-systolic pressures (ESPs), and PAPs compared with the acute group. As contractility and ventriculoarterial coupling also seemed to worsen, the right ventricle was in a clearly worse condition compared with the acute group.

Heart rate * SV equaled the measured CO in the acute group but largely overestimated the measured CO in the chronic group. This can theoretically be explained by the presence of tricuspid valve regurgitation, caused by massive RV dilatation.

Activating mechanical support in the acute vs the chronic group

Pump activation caused significant increases of ABP, left atrial pressure, PAPs, and afterload (arterial elastance) and significant decreases of CVP, RVCO, RV power, EDV, SV, ejection fraction, and stroke work (SW) in both groups (Figure 2B and C). Total CO and power increased in both groups; this was significant only in the acute group. Pump activation in the acute group caused RV peak pressure and ESP to increase, whereas end-diastolic pressure (EDP) remained constant. However, in the chronic group, these 3 parameters decreased. Mechanically supporting the right ventricle had tendencies to cause ESV increases (p 0.0575) in the acute group but ESV decreases ($p = 0.0600$) in the chronic group. Pressure-volume area (PVA) decreased significantly only in the chronic group. In both groups, contractility was not affected. The leftward shift of the EDPVR and the significant decreased RV capacitance were more distinct in the chronic group. The slope (β) of the linearized EDPVR did not change in the acute group but decreased significantly in the chronic group, whereas V_0 of the linearized EDPVR significantly decreased in both groups.

Mechanical supported right ventricle

The supported right ventricle in the acute group generated a significantly higher PAP, ESP, and RV peak pressure and

Table 3 Pressure-Volume Loop Pressures and Volumes

	Acute ($n = 9$)		Chronic ($n = 9$)	
Banding	No support	Pump on	No support	Pump on
Peak RV pressure, mm Hg	53.1 ± 10.2	60.3 ± 9.7[a]	40.4 ± 7.8[b]	31.6 ± 8.3[a,b]
EDP, mm Hg	16.1 ± 3.6	16.0 ± 3.9	10.0 ± 3.9[b]	7.8 ± 3.4[a,b]
ESP, mm Hg	50.6 ± 9.0	59.0 ± 7.4[a]	38.7 ± 8.3[b]	30.8 ± 8.3[a,b]
EDV, ml	103.3 ± 8.7	98.5 ± 9.0[a]	128.9 ± 30.4[b]	96.3 ± 39.1[a]
ESV, ml	73.9 ± 8.8	76.4 ± 7.9	94.8 ± 28.8	83.9 ± 37.1
SV, ml	29.5 ± 6.8	22.1 ± 4.5[a]	34.1 ± 13.7[b]	12.5 ± 5.2[a,b]
EF, %	29 ± 6	22 ± 4[a]	27 ± 10	14 ± 7[a,b]

EDP, end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; RV, right ventricular; SV, stroke volume.

[a]Significant difference with no support in the same condition.

[b]Significant difference with the same pump status in the other condition.

Table 4 Work and Power

	Acute ($n = 9$)		Chronic ($n = 9$)	
Banding	No support	Pump on	No support	Pump on
SW, ml × mm Hg	1,023 ± 520	808 ± 414[a]	954 ± 408	223 ± 210[a,b]
PVA, ml × mm Hg	2,192 ± 939	1,851 ± 1,022	2,229 ± 924	672 ± 494[a,b]
RV power, W	0.19 ± 0.06	0.12 ± 0.03[a]	0.16 ± 0.06	0.02 ± 0.03[a,b]
Total power, W	0.19 ± 0.06	0.32 ± 0.06[a]	0.16 ± 0.06	0.23 ± 0.05[b]

PVA, pressure-volume area; RV, right ventricular; SW, stroke work.
[a]Significant difference with no support in the same condition.
[b]Significant difference with the same pump status in the other condition.

worked with a significantly higher SV and ejection fraction, resulting in significantly higher SW and PVA compared with the chronic group (Figure 2B and C [compare red and orange loops]). This caused the right ventricle to generate a significantly higher intrinsic output and power while on support in the acute group, whereas total CO and power were only slightly higher (but not significant) compared with the chronic group. As such the pump flow is significantly lower in the acute group (Figure 3). This means that the right ventricle generated 54% ± 8 vs 10% ± 13 of the total CO in the acute vs the chronic group ($p < 1.10^{-5}$).

Sub-group analysis of the chronic pressure overloaded group

In 5 of 9 sheep, RVCO was 0 liter/min (no output sub-group) while on mechanical support (Figure 2D). In the 4 remaining sheep, RVCO of 0.78 liter/min ± 0.4 was measured (output sub-group). Total CO did not increase significantly in the chronic group or in 1 of the 2 sub-groups. The significant decreased RV peak pressure, EDP, and ESP after activating the pump were seen only in the no output sub-group. In the output sub-group, these parameters did not decrease or increase (they did increase in the acute group). In the output sub-group, RVCO was 22% ± 10 of the total CO. Baseline characteristics of the 2 unsupported sub-groups did not show any significant differences, although there was a tendency of having a more dilated right ventricle in the no output group compared with the output group (EDV, 142 ml ± 27 vs 113 ml ± 29; $p = 0.1669$).

Discussion

We aimed to assess the hemodynamic effects of low-flow mechanical support of an acute vs a chronic pressure overloaded right ventricle. RVF resulting from sudden increases in afterload was mimicked by PA banding, as has been described before.[9] RVF resulting from chronic pressure overload was mimicked by banding the PA 8 weeks before. Subjected to chronic pressure overload, the right ventricle initially adapted by hypertrophy.[16] However, the persistent elevated EDP eventually led to a further increase of EDV with resulting tricuspid valve regurgitation and a decreased RVCO. The resulting decreased left ventricular preload, together with the leftward displaced interventricular septum, caused a decreased left ventricular CO and further impairment of

Table 5 Contractility, Relaxation, and Ventriculoarterial Coupling

		Acute ($n = 9$)		Chronic ($n = 9$)	
Banding		No support	Pump on	No support	Pump on
Contractility					
ESPVR	Ees	1.14 ± 0.59	2.20 ± 1.21[a]	0.60 ± 0.24[b]	1.35 ± 0.85[a]
ESPVR	V_0	17.3 ± 36.4	32.4 ± 39.7	22.0 ± 33.6	50.6 ± 39.5[a]
ESPVR	V_{30}	53.4 ± 15.3	56.3 ± 17.4	79.2 ± 34.0	82.8 ± 38.2
Compliance					
EDPVR	V_{30}	115.2 ± 11.6	110.2 ± 13.2[a]	157.5 ± 32.0[b]	121.7 ± 43.3[a]
ln (EDPVR)	β	6.11 ± 0.19	6.11 ± 0.21	5.84 ± 0.16[b]	5.77 ± 0.14[a,b]
ln (EDPVR)	V_0	4.2 ± 0.1	4.1 ± 0.1[a]	4.5 ± 0.22[b]	4.1 ± 0.45[a]
Ventriculoarterial coupling					
Ea		1.78 ± 0.42	2.73 ± 0.46[a]	1.23 ± 0.41[b]	2.76 ± 1.31[a]
Ees/Ea		0.63 ± 0.29	0.80 ± 0.47	0.50 ± 0.15	0.49 ± 0.25

Ea, arterial elastance; EDPVR, end-diastolic pressure-volume relationship; Ees, end-systolic elastance; Ees/Ea, ventriculoarterial coupling; ESPVR, end-systolic pressure-volume relationship; P_x, pressure intercept for a given volume x ml; V_x, volume intercept for a given pressure of x mm Hg.
[a]Significant difference with no support in the same condition.
[b]Significant difference with the same pump status in the other condition.

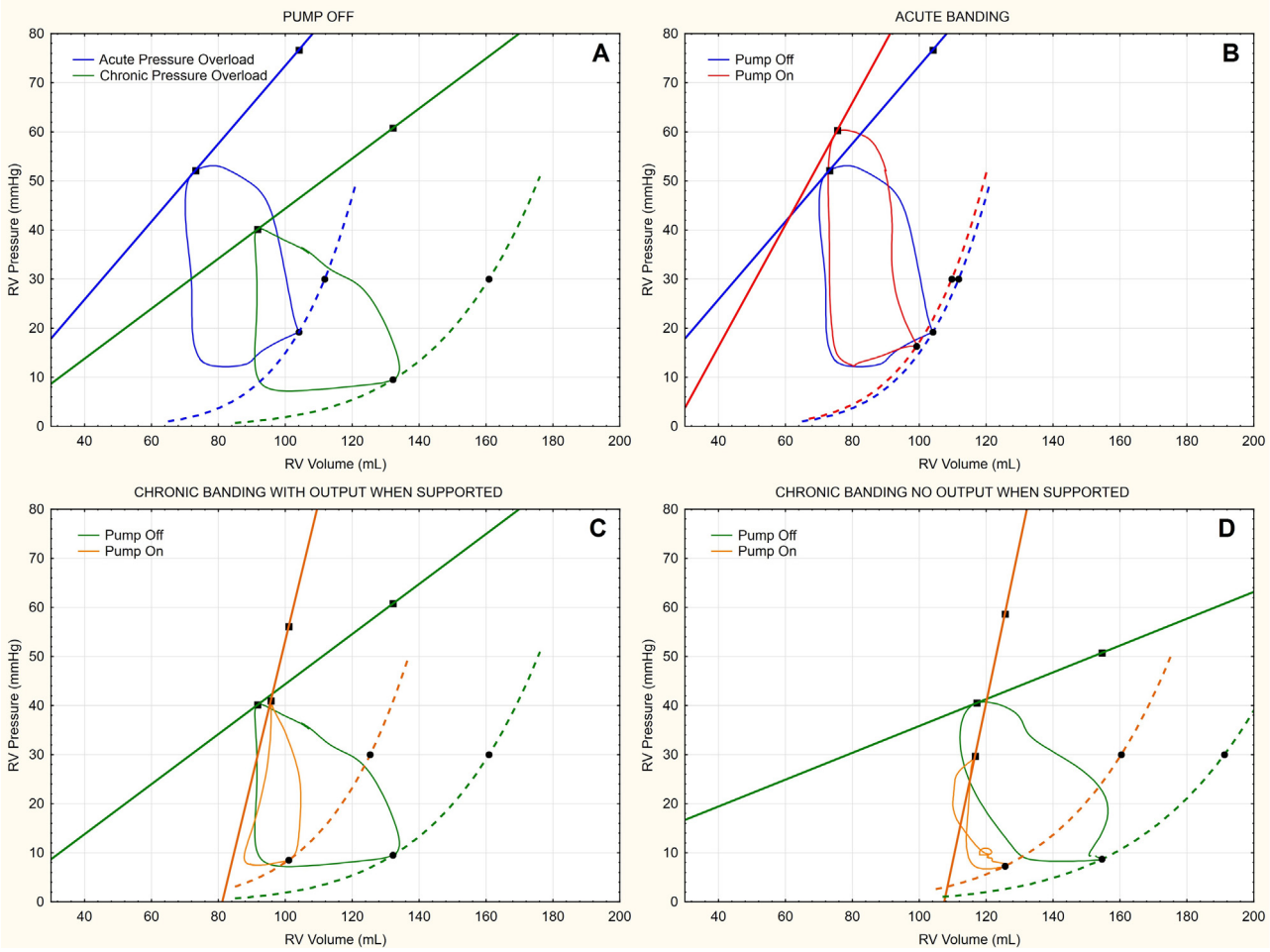

Figure 2 (A) PV loops of the unsupported right ventricle in the 2 conditions. (B) PV loops in the acute banding condition. (C) PV loops in the chronic banding condition. (D) PV loops in the chronic banding condition when the supported right ventricle does not generate any output. Squares indicate end-systolic point on the PV loop and maximum pressure point through which the ESPVR is drawn. Circles indicate end-diastolic point on the PV loop through which the EDPVR is drawn and the point on this EDPVR at a pressure of 30 mm Hg.

organ and coronary perfusion.[17] In our chronic group, these changes progressively continued, and true RVF emerged, manifested by a significant lower RV peak pressure, ESP, and PAP. The significant decreased slope (β) and significant increased V_0 of the linearized EDPVR indicated increased compliance and dilated cardiomyopathy.

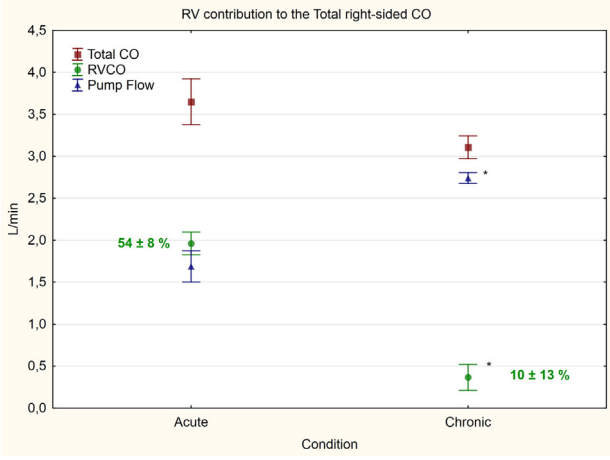

Figure 3 Contribution of the right ventricle to the total CO. *Statistically significant difference with acute group.

Despite the introduction of medical therapies such as epoprostenol and bosentan for patients with PAH, their only hope for long-term, disease-free survival is organ transplantation. However, organ availability is limited. Isolated permanent RVAD implantation has been described as a novel and promising strategy for patients with isolated right heart failure, although more experience is needed to identify patients who could benefit from this technology.[18] The first incentive to use a low-flow assist device for patients with PAH is based on the good results of these devices in selected cases of left ventricular failure.[6,7] However, in left ventricular failure, an inherently abnormal left ventricle commonly faces a normal circulation that is supported, whereas supporting RVF in PAH involves an inherently normal right ventricle facing an abnormal circulation. This explains the ability of the right ventricle to recover after bilateral lung transplantation for PAH. We wonder if it also will recover due to RVAD support. The second incentive is based on survival in patients with PAH that is linked to CO. Experimentally, dogs with chronic RV hypertension showed improved exercise performance and survival after atrial

septostomy (AS).[19,20] Clinically, patients with PAH and a patent foramen ovale or PAH and Eisenmenger syndrome live longer and have less RVF than patients with PAH without shunting.[21–23] The hemodynamic consequences of right-to-left shunting created by AS are an increased left ventricular CO and a decrease in right atrial pressure. However, arterial saturation is also reduced.[24–26] Moreover, AS has been associated with mortality rates of up to 16%, especially in patients with impending death and with severe RVF on maximal cardiorespiratory support.[27] An RVAD could offer the same advantages as an AS, but the fall in oxygen saturation should not occur, and an RVAD might be offered later in the course of the disease. A major challenge to test this hypothesis is the establishment of a clinically representative large animal model. Although the primary focus of this study is a pressure overloaded right ventricle, represented by PA banding, our model does not represent the primary pathophysiology in the pulmonary arterioles causing RVF in PAH. However, to the best of our knowledge, no large animal model exists of PAH that provides sufficient RV pressure overload or increase in pulmonary vascular resistance (PVR) to such an extent as PA banding. Therefore, we used sheep with a chronically fixed banded PA. The hemodynamic maximal tolerated PA banding caused mean PAPs that reached 67% of mean systemic pressures. This clearly distinguishes our model from the near-systemic PAPs that are progressively reached in end-stage PAH. Therefore, plainly extrapolating our findings to clinical RVF in PAH should be done cautiously.

At the present time, there is no durable ventricular assist device on the market that delivers low flow against high afterload pressures as may be encountered in patients with PAH. The previously tested Synergy micro-pump offered promise in this regard but had a too high rate of thrombosis. That experience suggests that the development of a durable device for such an application may be challenging. However, the present results indicate that it is worthwhile to test new pump designs under such conditions and for industry to consider development of a device specifically for this application.

In the clinic, our first target group would be patients with medically refractory RVF secondary to PAH. In these patients, the RVAD could serve as a bridge to bilateral lung transplantation, with the potential of recovery of the right ventricle while on the waiting list. In patients who are not deemed suitable for bilateral lung transplantation, an RVAD could be used as destination therapy. Although the right ventricle might recover, the RVAD probably could not be removed in these cases, as RVF would develop again when the right ventricle continues to face the fixed PVR. In theory, patients with untreated PAH presenting with cardiogenic shock could also benefit from an RVAD as temporary RV support independent of RV recovery.

The case described by Gregoric et al [4] seems to confirm the occurrence of complications that some fear. RVAD implantation resulted immediately in supra-systemic PAH, with subsequent pulmonary hemorrhage. However, RVAD flow rates were not mentioned, and the diagnosis of true PAH was questioned.[5] We think these drawbacks can be avoided by the low-flow concept for several reasons: (1) We previously showed that RVAD-caused increases of PAP and of systolic afterload are flow dependent. At low flows, the hemodynamics improved toward similar values measured in a not-banded, unsupported condition.[9] (2) In the natural course of PAH, PAP increases to a new "set-point" and remains fixed thereafter. In end-stage PAH, decreasing CO, and not increasing PAP, causes the PVR to increase in this setting.[28] Therefore, CO increases toward levels that were tolerated by the lungs before should not increase PAP that much and should even lower PVR again. (3) In both conditions of this experiment, PAP increases are mainly determined by increases in diastolic pressures, whereas increases in systolic pressures are limited. Moreover, PAP increases in the chronic group are limited toward levels that were previously easily tolerated. This low-flow RV mechanical support concept has been proven to work, as described by Rajdev et al.[3] In this case, severe PAH complicated by cardiogenic shock was supported by an RVAD running at 1.9 liter/min. This caused a modest PAP increase but a significant increase of CO and a significant decrease of PVR. The RVAD was implanted for 56 hours without evidence of pulmonary hemorrhage.

The goals of mechanically supporting a pressure overloaded right ventricle are 2-fold: improving end-organ perfusion (reflected by total CO and ABP) and unloading the right ventricle (decreasing RV pressure, CVP, PVA, and EDV) to improve coronary perfusion and prevent (or even reverse) any maladaptive ventricular remodeling that has occurred. Activating the pump caused an improvement of ABP and CVP but an increase in pulmonary pressures. Total CO increased; this was significant only in the acute group. Compared with the acute group, the higher CVP and lower PAP in the chronic group resulted in a smaller pressure gradient across the pump. This enabled the pump to generate higher flows at the same pump speed. As a consequence, the contribution of the right ventricle to the generation of the total CO was significantly lower, with 5 sheep in this group having no native RVCO at all. In this setting, the low-flow pump actually delivered full support. The resulting decreased SW and RV power were significantly lower in the chronic group. This indicates that the intrinsically worse condition of a chronic pressure overloaded right ventricle allows for more profound unloading compared with an acute pressure overloaded right ventricle, independent of pump RPMs. The significantly increased RV peak pressures in the acute group were caused by the RVAD continuously pumping blood from the right atrium to the PA during diastole. Because RV peak pressures did not increase in the chronic group and the resulting PAPs were significantly lower than PAPs in the acute group, one might argue to increase pump speed in the chronic group to increase CO and to optimize end-organ perfusion. However, in a long-term support setting, the right ventricle might recover with resulting higher PAPs and the need to reduce the pump speed again. This potential RV recovery in a long-term support setting could also increase total right-sided CO and as such would cause a significant improvement of end-organ perfusion in the chronic group.

CVP and EDV significantly decreased in the acute group; together with the leftward shifting EDPVR and the decreasing ventricular capacitance, this indicates a successful diastolic unloading. These changes were also obvious in the chronic group. However, as PVA and RV peak pressure also significantly decreased, there is not only a diastolic but also a successful systolic unloading in the chronic group, enhancing the potential to recover in case of long-term support. The effects of long-term low-flow mechanical support on a chronic pressure overloaded right ventricle with regard to hemodynamic recovery, tricuspid insufficiency, pump thrombosis, and possible reverse remodeling are the subject of further experimental research. In addition to the current clinical use of RVADs in patients awaiting heart transplants and patients with acute lung injury or acute respiratory distress syndrome, these results encourage further research into the potential use of RVADs at low flow rates in cases of medically refractory RVF in PAH.

Limitations

First, only a small number of animals was studied, which may impact the significance and interpretation of the results in this work. Second, our animal model is not completely clinically representative, as it does not model the primary pathophysiology in the PA tree. Third, this banding is fixed, whereas PVR is fixed only in end-stage disease. Although our aim for a chronic pressure overloaded right ventricle is to use this technology in end-stage disease with a fixed PVR, the PVR still may vary for an acute pressure overloaded right ventricle. Also, the adaptive hypertrophy and dilatation resulting from a fixed banding might be different from hypertrophy and dilatation caused by a progressive inflatable banding, which may better mimic a chronic pressure overloaded right ventricle, as PVR is fixed only at end-stage disease.

Conclusions

The short-term hemodynamic effects of mechanical RV support at low flows include an improvement in ABP in both an acute and a chronic pressure overloaded right ventricle, whereas CO significantly improves only in the acute group. RV unloading is more profound in the chronic group. In addition to successful diastolic unloading in both groups, low-flow mechanical support provides successful systolic unloading in the chronic group. Therefore, the potential use of RVADs at low flow rates for a chronic pressure overloaded right ventricle (e.g., medically refractory RVF in PAH) warrants further research to assess its long-term effects.

Disclosure statement

D.B. is Vice-President Medical Science at HeartWare. B.M. is a medical consultant for HeartWare.

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