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ORIGINAL PRE-CLINICAL SCIENCE

Low-flow support of the chronic pressure–overloaded right ventricle induces reversed remodeling

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KEYWORDS:
Pulmonary arterial hypertension;
right ventricular failure;
pressure-overloaded right ventricle;
right ventricular mechanical support

BACKGROUND: Mechanical right ventricular (RV) support in pulmonary arterial hypertension patients has been feared to cause pulmonary hemorrhage and to be detrimental for the after-load–sensitive RV. Continuous low-flow pumps offer promise but remain insufficiently tested.

METHODS: The pulmonary artery was banded in 20 sheep in this study. Eight weeks later, a Synergy micro-pump (HeartWare International, Framingham MA) was inserted in 10 animals, driving blood from the right atrium to the pulmonary artery. After magnetic resonance imaging, hemodynamics and RV pressure–volume loop data were recorded. Eight weeks later, RV function was assessed in the same way, followed by histologic analysis of the ventricular tissue.

RESULTS: During the 8 weeks of support, RV volumes and central venous pressure decreased significantly, whereas RV contractility increased. Pulmonary artery pressure increased modestly, particularly its diastolic component. RV contribution to total right-sided cardiac output increased from $12 \pm 12\%$ to $41 \pm 9\%$ ($p < 1 \times 10^{-4}$). After pump inactivation, and compared with 8 weeks earlier, RV volumes had significantly decreased, tricuspid valve regurgitation had almost disappeared, and RV contractility had significantly increased, resulting in significantly increased RV forward power (0.25 ± 0.05 vs 0.16 ± 0.06 W, $p = 0.014$). Fulton index and RV myocyte size were significantly smaller, and without changes in fibrosis, when compared with controls.

CONCLUSIONS: Prolonged continuous low-flow RV mechanical support significantly unloads the chronic pressure–overloaded RV and improves cardiac output. After 8 weeks, RV hemodynamic recovery and reverse remodeling begin to occur, without increased fibrosis.

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Pulmonary arterial hypertension (PAH) is caused by a pathologic increase in pulmonary vascular resistance (PVR) and leads to right ventricular (RV) failure.[1] Even with modern therapy, mortality is still 15% within 1 year and

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median survival remains limited to 5 to 6 years, with insufficient functional improvement in many survivors.[2] Bilateral lung transplantation (bLTx) remains the only curative option. Unfortunately, most patients are unlikely to survive until transplantation.

PAH-associated RV failure is potentially reversible as RV function generally recovers after bLTx.[3] Therefore, surgical strategies to increase cardiac output (CO) and reduce RV wall stress should be elaborated. Atrial septostomy for PAH unloads the RV and improves cardiac index, but procedural mortality approaches 16%.[4] Right ventricular assist devices (RVADs) could offer the same advantages, but would actively support the RV without arterial oxygen desaturation. Pulsatile device use often results in pulmonary hemorrhage and death.[5] Continuous-flow devices have been successful for acute pressure–overloaded RVs.[6] However, such devices, with relatively high flow rates, may also result in increased pulmonary pressures and lung injury.[7] Smaller devices with lower flow capacities may therefore be more appropriate. We recently demonstrated the feasibility and advantages of mechanically supporting acute and chronic pressure overloaded RVs with low flows.[8,9] Our next goal is to assess the effects of prolonged low-flow RVAD support on chronic pressure–overloaded RVs.

Methods

Animal preparation

This study was approved by the animal ethics committee of KU Leuven (P127/2011). The female sheep (Swifter–Charolais) used for the study received humane care in compliance with the "Principles of Laboratory Animal Care" (National Society for Medical Research) and the *Guide for Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, National Institutes of Health). Twenty animals were included (weight 47.3 ± 4.8 kg and age 10.4 ± 0.8 months). After sedation with intramuscular ketamine 15 mg/kg, anesthesia was induced and maintained with isoflurane (2% to 3%). A volume-controlled respirator (Dräger Cicero; Lübeck, Germany) was used for ventilation. Buprenorphine hydrochloride 0.3 mg and meloxicam 0.5 mg/kg intravenously were used for analgesia.

Pulmonary artery banding

Arterial blood pressure (ABP) and central venous pressure (CVP) were measured in an ear artery and a jugular vein, respectively. A Swan–Ganz catheter measured distal pulmonary artery (PA) pressure. After left thoracotomy, a band around the distal pulmonary trunk was tightened as much as hemodynamically tolerated; that is, the ends of the band were fixed together at their end by a clip, resulting in a drop in ABP to a new stable level. Additional clips were placed to increasingly tighten the band around the PA. A new, lower ABP was achieved with each clip. Once the ABP showed continued decline without signs of stabilization, the last clip was removed. A flowmeter (TS420; Transonic Systems Europe BV, Maastricht, The Netherlands) around the proximal PA measured right ventricular cardiac output (RVCO). Pressure lines in the left atrium, just proximal and distal to the band, served to measure corresponding pressures.

Intervention at 8 weeks

Animals were scanned with 3.0-Tesla magnetic resonance imaging (MRI) (Magnetom, Trio Tim; Siemens Medical Solutions, Erlangen, Germany), with a phased-array body coil over the heart. Cine images were acquired with electrocardiogram gating during suspended respiration, in vertical and horizontal long- and short-axis planes.

In addition to PA-banding instrumentation, an 18-mm balloon (Reliant; Medtronic, Minneapolis, MN) was inserted in the left jugular vein and then docked in the inferior caval vein 1 day later. In 10 sheep, a Synergy micro-pump (HeartWare International, Framingham, MA) was inserted to withdraw blood from right atrium to the PA. A flowmeter (Sono TT; Emtec, Gennevilliers, France) measured pump flow. A 7F combined pressure conductance catheter, connected to a Sigma M signal processor (both from CD Leycom, Zoetermeer, The Netherlands), was positioned through a stab wound just below the pulmonary valve toward the apex (Figure 1). Pressure, flow and pressure–volume (PV) loop data were recorded for all animals, just before mechanical support initiation, and then 15 minutes after pump activation (22,000 rpm) in 10 animals. PV loops with pre-load reduction were obtained by balloon inflation, but only in the non-supported condition (pre-load reduction during support generated unusable PV loops).

Evaluation at 16 weeks

Eight weeks later, hemodynamics and PV loop parameters were recorded. MRI was performed on the following day. In RVAD animals, pumps were deactivated and their subcutaneous metal housings were removed 15 minutes before MRI. Subsequently, animals were euthanized using 20 ml KCl (14.9%) intravenously after reassurance of adequate anesthesia. During autopsy, the Fulton index [RV / (left ventricle (LV) + septum) weight] was calculated.

Histology

RV and LV free wall mid-ventricular samples were fixed in 4% paraformaldehyde in phosphate-buffered saline and processed and

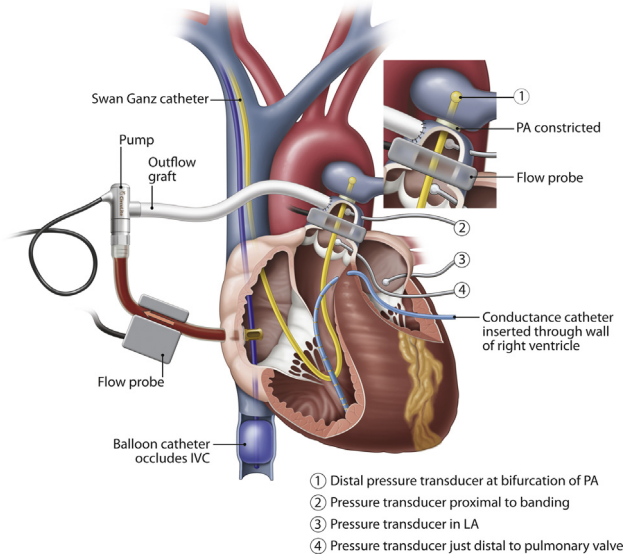

Figure 1 Schematic overview of the experimental set-up. PA = pulmonary artery; LA = left atrium; IVC = inferior vena cava.