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RESEARCH ARTICLE

Efficacy and safety of the Aria pulmonary endovascular device in pulmonary hypertension

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Aims A common feature of various forms of pulmonary hypertension (PH) is progressive decline of pulmonary arterial compliance (C_{PA}), which correlates with reduced survival. In this acute study, we evaluated feasibility, safety and haemodynamic performance of the Aria pulmonary endovascular device in patients with PH associated with left heart disease (PH-LHD) and chronic lung disease (PH-CLD).

Methods and results Eight patients with PH-LHD and 10 patients with PH-CLD were included in this study. The device was placed in the main pulmonary artery via the right femoral vein and was connected by a catheter to a gas-filled reservoir outside the body. During systole, gas shifts from the balloon to the reservoir, leading to deflation of the balloon. In diastole, the gas returns from the reservoir to the balloon, leading to balloon inflation and enhancing diastolic blood flow to the distal pulmonary capillary bed. Haemodynamics were assessed at baseline, and again with device off, device on and device off. The primary safety endpoint was the incidence of serious adverse events through 30 days after the procedure. No complications or investigational device-related serious adverse events occurred. Device activation in PH-LHD and PH-CLD patients decreased pulmonary arterial pulse pressure by 5.6 ± 4.2 mmHg (−12%; $p = 0.003$) and 4.2 ± 2.2 mmHg (−11%; $p < 0.001$), increased C_{PA} by 0.4 ± 0.2 ml/mmHg (+23%; $p = 0.004$) and 0.4 ± 0.3 ml/mmHg (+25%; $p = 0.001$), and increased right ventricular-to-pulmonary vascular (RV-PV) coupling by 0.24 ± 0.18 (+40%; $p = 0.012$) and 0.11 ± 0.07 (+21%; $p = 0.001$), respectively.

Conclusions Temporary implantation of the Aria endovascular device was feasible and safe. Device activation resulted in acute improvement of C_{PA} and RV-PV coupling.

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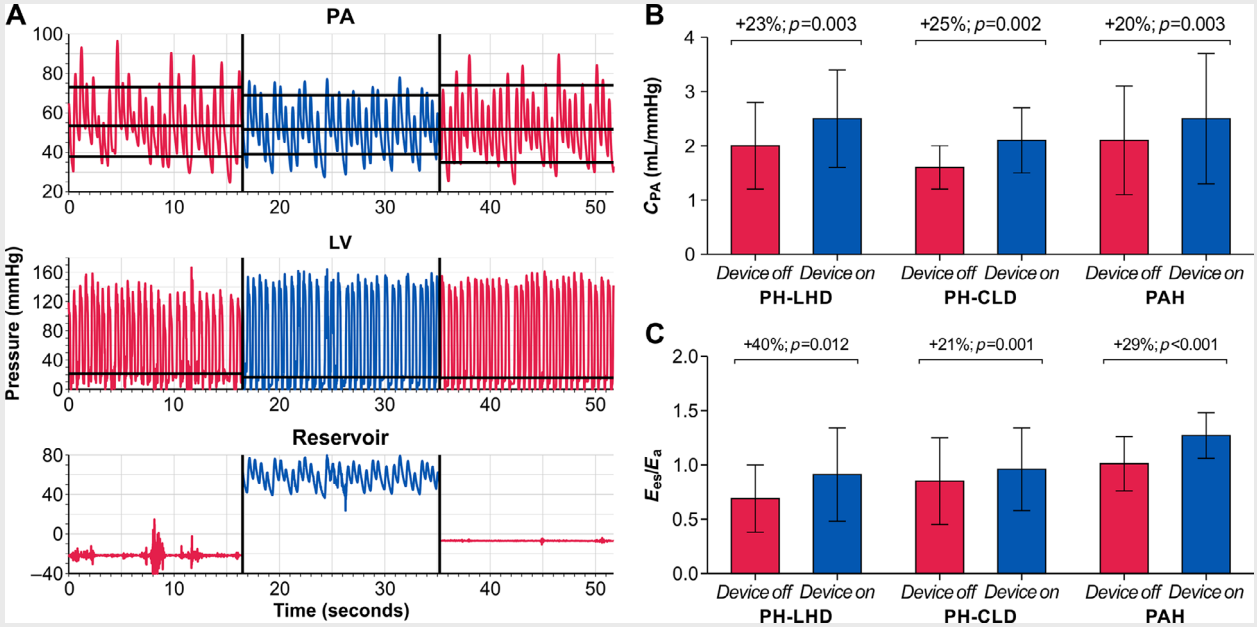
Graphical Abstract



Impact of the Aria pulmonary endovascular device on hemodynamics. Hemodynamics and reservoir pressures are depicted in blue during device activation and in red when the device is deactivated. Panel A demonstrates the effect of temporary device activation on pulmonary arterial (PA) and left ventricular (LV) pressures in a patient with pulmonary hypertension associated with left heart disease (PH-LHD). Panel B shows the effect of the Aria pulmonary endovascular device on pulmonary arterial compliance (CPA) and right ventricular-to-pulmonary vascular coupling assessed by the ratio of right ventricular end-systolic elastance to effective arterial elastance (Ees/Ea) in patients with PH-LHD, PH associated with chronic lung disease (PH-CLD) and pulmonary arterial hypertension (PAH, panel C).

Keywords Device • Pulmonary hypertension • Right ventricular afterload • Pulmonary arterial compliance • Right ventricular-to-pulmonary vascular coupling

Introduction

Pulmonary hypertension (PH) may complicate the majority of cardiovascular and respiratory diseases, and confers a poor prognosis with reduced survival. A common feature of different forms of PH is increased pulmonary arterial stiffness, which increases right ventricular (RV) afterload, leading to right heart failure and death. Widely employed current treatments are vasodilators with limited pulmonary selectivity for pulmonary arterial hypertension (PAH) and interstitial forms of PH associated with chronic lung disease (PH-CLD),[1] and percutaneous and surgical pulmonary vascular interventions for chronic thromboembolic PH. Despite these treatments the disease progresses, and a major unmet need remains elevated RV afterload.[2,3] In addition, vasodilators are not effective in PH associated with left heart disease (PH-LHD) and most forms of PH-CLD, and are currently not recommended in these conditions.[4]

Chronic right heart failure is associated with decreased exercise tolerance, poor functional capacity, decreased cardiac output (CO) and stroke volume (SV), a combination of end-organ venous congestion and hypoperfusion, cachexia and a systemic proinflammatory state. In PH, right heart failure is the result of increased RV afterload which is comprised of steady state and pulsatile components. Steady state load is increased due to remodelling of the distal pulmonary arteries and an increase in pulmonary vascular resistance (PVR). Pulsatile load is increased due to a loss of the elastic properties of the pulmonary arterial tree resulting in a reduction in pulmonary arterial compliance (C_{PA}).[1,5]

C_{PA} (SV/pulmonary arterial pulse pressure [PAPP]) is a predictor of prognosis in various forms of PH.[6–15] The loss of C_{PA} may explain the failure of current medical interventions, which vasodilate and primarily reduce PVR, to dramatically alter prognosis[2] and may better reflect the biologic, structural and mechanical changes that give rise to and maintain PH.[16] Analysis of both animal experiments and human studies have demonstrated a loss of C_{PA} resulting from enhanced adventitial and medial fibrosis, pulmonary arterial smooth muscle cell hypertrophy, loss of small vessel mass, and disruption of vascular elastin fibers.[17] These changes alter the mechanical pressure volume relationships of the pulmonary

circulation, which in turn adversely affect the steady state and pulsatile components of RV afterload. The mismatch between ventricular and pulmonary artery pressure/flow characteristics may result in the 'uncoupling' of the normal relationship between the RV and pulmonary circulation, leading to right heart failure.

In a previous first-in-human pilot study, we hypothesized that a biomechanical intervention in PAH patients consisting of an implanted, compressible balloon within the main pulmonary artery, the volume of which varies passively throughout the cardiac cycle in response to intravascular pressure changes, would augment C_{PA}, reduce PAPP, improve RV-to-pulmonary vascular (RV-PV) coupling and enhance CO independent of heart rate. In that study we have demonstrated that temporary device implantation is safe and device activation improves C_{PA} by 20% at rest and 40% during exercise in PAH patients.[18] Following the same hypothesis as in our previous study, we tested the Aria pulmonary endovascular device system in patients with RV dysfunction due to PH-LHD and PH-CLD. The objective was to evaluate device safety, with a particular focus on stable left ventricular filling pressures and arterial saturations, the performance characteristics of the device, and the impact of cardiac cycle pressure-induced balloon volume changes on key determinants of RV afterload and RV-PV coupling. In addition, haemodynamic performance data were compared with results from our previous study with PAH patients.[18]

Methods

Study population

This study was a single-centre, prospective, non-randomized, single-arm study that was exploratory in nature with descriptive summaries to analyse the feasibility, safety and clinical performance of the device. Eight patients with PH-LHD and 10 patients with severe PH-CLD, who underwent routine clinically-indicated right heart catheterization were included in this study between July 2021 and October 2021.

Eligible patients had confirmed PH-LHD or severe PH-CLD in World Health Organization functional class III with a mean pulmonary artery pressure (mPAP) >30 mmHg, evidence of RV dysfunction on echocardiography, and anatomical suitability for temporary device implantation as determined by preexisting fluoroscopy, echocardiography, computed tomography or magnetic resonance imaging within the past 6 months. Patients were stable on optimal medical therapy. A full list of inclusion and exclusion criteria is provided in the online supplementary *Appendix S1*. Data from our previous first-in-human pilot study in 10 PAH patients on stable PAH-targeted combination therapy were plotted for comparison.[18] The ethics committee of the Medical University of Vienna approved the study and all patients signed informed consent (#1046/2017 and #1160/2021).

Study endpoints

The primary safety endpoint was the incidence of investigational device-related serious adverse events, acutely particularly the effects of the device on left ventricular filling pressures and arterial saturations, and all other events through 30 days post-index procedure. An independent Clinical Events Committee (CEC) was utilized to evaluate adverse events during the study. The role of the CEC was performed by a board-certified cardiac surgeon who was independent of the investigational site and Aria CV. The primary performance endpoints were pulmonary haemodynamics at rest, both when the balloon was deflated ('device off') and also when it was actively cycling ('device on'). Secondary endpoints were all reported adverse events during the study.

Description of the Aria pulmonary endovascular device

The acute Aria pulmonary endovascular device consists of a flaccid gas-filled balloon which operates in the main pulmonary artery, a gas-filled reservoir, and a 14 F catheter which connects the balloon to the catheter and allows gas to move between them. The balloon on the catheter measures 25 by 33 cm with a volume of 25 ml and is manufactured of ChronoflexC, a thin-walled polycarbonate-based thermoplastic polyurethane. The device for acute testing has four catheter lumina. One allows for gas introduction and cycling between the balloon and reservoir in response to cyclic pulmonary artery pressure (PAP) changes. Another provides access for a 0.035″ introducer guide wire to facilitate device delivery and positional stability. The remaining two lumina accommodate 0.014″ pressure wires (Abbott PressureWire X) positioned proximal and distal to the balloon (in the right ventricle and pulmonary artery during use). The reservoir is equipped with two connection ports. One port is used to connect the gas-filled reservoir to the balloon catheter, while the second lumen is connected to a four-way stopcock allowing for attachment to a helium filled syringe for system gas volume adjustments as well as a fluid-filled line to monitor reservoir pressure.

A 14 F right femoral vein approach was utilized. The device was placed in the main pulmonary artery under fluoroscopic monitoring with the tip of the guide wire in the proximal left pulmonary artery to provide stability. All patients were systemically heparinized in accordance with institutional protocols. The balloon was connected to the gas-filled reservoir. When active, the system was filled with enough gas to ensure cycling of the balloon with every cardiac cycle throughout the respiratory cycle based on fluoroscopic and reservoir pressure trace feedback.

The system operates as passive counter pulsation device. During systole, the intrinsic PAP applied to the balloon is greater than the pressure in the reservoir and consequently forces gas to flow from the balloon into the reservoir, mimicking the capacitance effect of normally distensible pulmonary arteries. After closure of the pulmonary valve, the intrinsic PAP falls below the pressure in the reservoir and gas flow reverses, moving back into the balloon during diastole (*Figure 1*; Supplementary Video S1). Balloon inflation and deflation were monitored under fluoroscopy, while haemodynamics were monitored using the two pressure wires. The device was not anchored during the acute testing, but would be stably anchored during permanent implantation. Detailed methods on haemodynamic assessment, haemodynamic definitions and assessment of RV-PV coupling are provided in online supplementary *Appendix S1*.

Statistical analysis

For categorical outcome variables, counts and percentages of patients are provided. No formal sample size estimation was performed. Qualitative variables were described with counts and percentages. Adherence to a Gaussian distribution was determined using the Kolmogorov–Smirnov test. Normally distributed data were described as means ± standard deviations and the independent samples Student's *t*-test was utilized to compare continuous variables between two

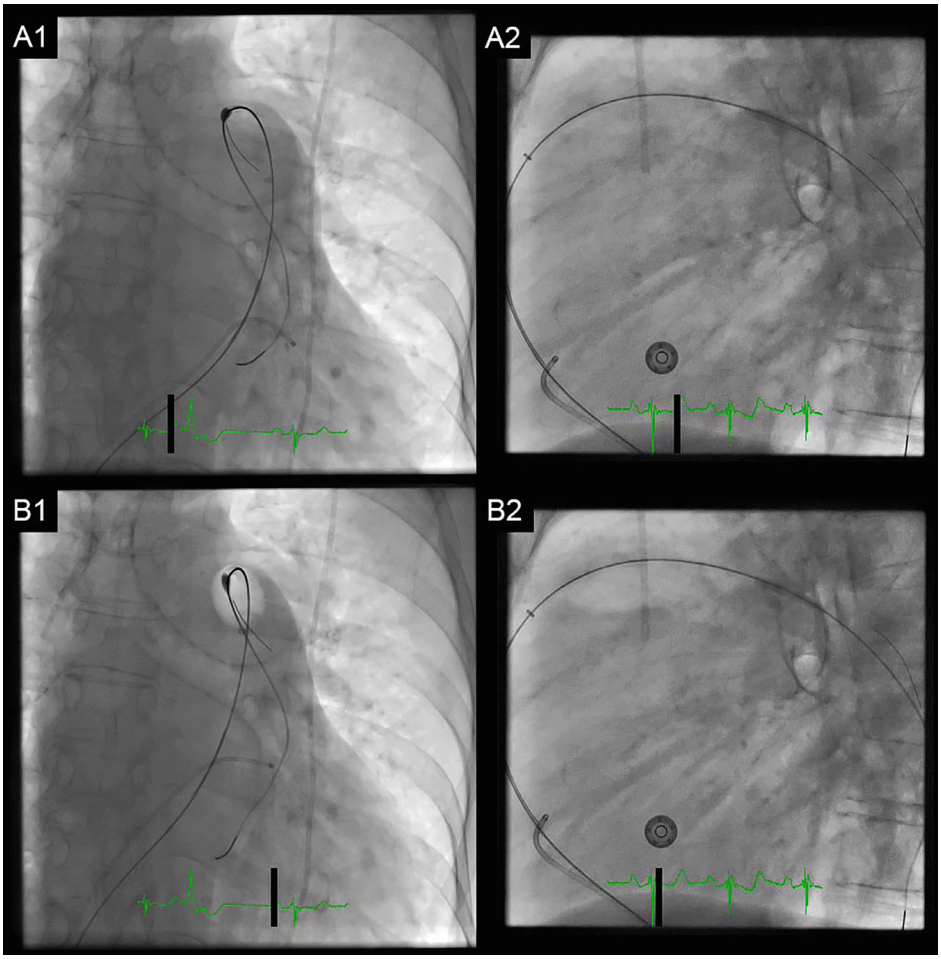


Figure 1 Aria pulmonary endovascular device during systole and diastole. Anterior-posterior (1) and lateral projections (2) of the device with deflated balloon during systole (*A1* and *A2*) and with inflated balloon during diastole (*B1* and *B2*).

groups, while the paired-sample *t*-test was used to compare differences within groups. Data with skewed distribution were described as medians (25th and 75th percentiles). One-way analysis of variance (ANOVA) with correction for multiple pairwise comparisons using the Bonferroni method was applied to assess differences across several groups. The 10 PAH patients, who had been included in the previous first-in-human pilot study, served as controls.[18] Data were analysed with R (version 4.1.0 for Mac, R Core Team, Vienna, Austria). All *p*-values result from two-sided tests, with significance inferred at $p < 0.05$.

Results

Patients

Demographic and baseline clinical and haemodynamic characteristics are shown in *Table 1*. Mean age was 74 ± 5 years, 72 ± 7 years, and 52 ± 17 years in PH-LHD, PH-CLD, and PAH, respectively. All eight PH-LHD patients had heart failure with preserved ejection fraction and combined post- and pre-capillary PH with PVR >2 WU.[4] In the PH-CLD group, PH was associated with chronic obstructive pulmonary disease in six patients, emphysema in three patients, and idiopathic pulmonary fibrosis in one patient; PH was severe in all 10 patients with PVR >5 WU.[4] PAH was idiopathic in six patients, drug- and toxin-induced in two patients and associated with congenital heart disease in two patients (one corrected ventricular septal defect and one uncorrected atrial septal defect).

Primary endpoint: Device safety

All 18 patients with PH-LHD and PH-CLD underwent successful insertion of the Aria pulmonary endovascular device following right heart catheterization. Total procedural time was 107 ± 14 min. Based on CEC-adjudicated data, there were no observed investigational device-related serious adverse events (SAEs) through 30 days post-procedure. Likewise, no unanticipated serious adverse device effects occurred during this study. Of the 18 subjects, there were three adverse events that occurred in two subjects. One subject experienced two adverse events, one of which was considered an SAE. At 19 days after the index

Table 1 Baseline characteristics

Clinical/haemodynamic variables	PH-LHD ($n = 8$)	PH-CLD ($n = 10$)	PAH ($n = 10$)
Clinical variables			
Age, years	74 ± 5	72 ± 7	52 ± 17
Female sex, *n* (%)	4 (50.0)	6 (60.0)	4 (40.0)
Body mass index, kg/m^2	34.0 ± 4.4	26.1 ± 5.8	25.2 ± 5.2
NT-proBNP, pg/dl	5518 ± 8315	1940 ± 1883	2301 ± 2624
Pulmonary hypertension aetiology, *n* (%)			
Idiopathic PAH	0 (0)	0 (0)	6 (60.0)
Drug- and toxin-induced PAH	0 (0)	0 (0)	2 (20.0)
Associated PAH—congenital heart disease	0 (0)	0 (0)	2 (20.0)[a]
Heart failure with preserved ejection fraction	8 (100.0)	0 (0)	0 (0)
Chronic obstructive pulmonary disease	0 (0)	6 (60.0)	0 (0)
Emphysema	0 (0)	3 (30.0)	0 (0)
Idiopathic pulmonary fibrosis	0 (0)	1 (10.0)	0 (0)
Haemodynamic variable			
Heart rate, bpm	81.6 ± 24.2	75.2 ± 13.0	75.3 ± 5.6
Cardiac output, L/min	6.3 ± 1.9	4.8 ± 1.9	7.1 ± 1.7
Cardiac index, L/min/m^2	3.1 ± 0.8	2.6 ± 1.1	3.8 ± 1.1
Mean right atrial pressure, mmHg	14.7 ± 6.8	8.3 ± 5.2	8.3 ± 5.1
Systolic pulmonary arterial pressure, mmHg	74.0 ± 16.9	72.4 ± 12.6	77.9 ± 16.8
Diastolic pulmonary arterial pressure, mmHg	36.3 ± 9.1	28.9 ± 5.3	30.8 ± 11.3
Mean pulmonary arterial pressure, mmHg	46.4 ± 15.4	44.7 ± 5.7	48.8 ± 11.9
Pulmonary arterial wedge pressure, mmHg	22.3 ± 6.7	10.8 ± 3.4	9.8 ± 3.4
Diastolic pressure gradient, mmHg	14.0 ± 11.6	18.0 ± 5.1	21.0 ± 10.3
Pulmonary vascular resistance, WU	4.0 ± 2.4	8.0 ± 3.0	6.0 ± 2.6
Pulmonary arterial compliance, ml/mmHg	2.4 ± 1.1	1.6 ± 1.0	2.4 ± 1.3
Effective arterial elastance, mmHg/ml	2.0 ± 1.1	1.4 ± 0.5	0.5 ± 0.3

NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH-CLD, pulmonary hypertension associated with chronic lung disease; PH-LHD, pulmonary hypertension associated with left heart disease; WU, wood units.
[a]One corrected ventricular septal defect and one uncorrected atrial septal defect.

procedure, this subject (PH-CLD) experienced an episode of atrial flutter, which led to the SAE of transient cardiac decompensation. This subject had a past medical history of atrial flutter. The subject was hospitalized and received amiodarone for treatment of the events. The events were successfully resolved, and the subject discharged 3 days later, without residua.

Another subject (PH-LHD) with past medical history of coronary artery disease underwent successful percutaneous coronary intervention. This was not considered an SAE, since it occurred as a planned intervention for pre-existing coronary artery disease. Furthermore, the percutaneous coronary intervention was performed 2 days before the Aria pulmonary endovascular device procedure. This event is clearly unrelated to the device or procedure based on the temporal relationship but is reported as an adverse event since it occurred in a study subject. In the previous acute study of the Aria device involving PAH patients, no adverse events occurred.[18]

Exploratory endpoints: Haemodynamic effects

Table 2 and *Figure 2* provide a summary of selected haemodynamic parameters with device off and device on. Haemodynamics at baseline were not significantly different from device off ($p > 0.05$).

With device off, cardiac index (CI), mPAP, total pulmonary resistance and C_{PA} were similar in PH-LHD, PH-CLD and PAH patients (all ANOVA $p > 0.05$). With device on, PH-CLD patients exhibited a significant acute decrease in PAPP and acute increase in CI, SV and C_{PA}. In PH-LHD, an acute decrease in PAPP paired with an acute increase in C_{PA} could be observed, while CI and SV remained unchanged. Changes in PH-LHD and PH-CLD upon device activation were comparable to those previously observed in PAH (all ANOVA $p > 0.05$). Left ventricular end-diastolic pressure remained unchanged with device on.

Impact on C_{PA} was uniformly directionally the same in all patients (*Figure 2A*). C_{PA} increased by 22.5 ± 13.7% in PH-LHD ($p = 0.003$), by 24.8 ± 17.4% in PH-CLD ($p = 0.002$), and by 19.8 ± 10.9% in PAH ($p = 0.003$). Relative improvement in C_{PA} upon device activation was comparable between all groups (ANOVA $p = 0.742$; *Figure 2A*). Oxygen saturation did not change significantly between device off and device on in all three groups.

Impact on arterial elastance, right ventricular end-systolic elastance and right ventricular-to-pulmonary vascular coupling

The effects of the Aria pulmonary endovascular device on effective arterial elastance (E_a), end-systolic elastance (E_{es}) and E_{es}/E_a are shown in *Table 3*. With device off, E_{es} and E_a were comparable in PH-LHD (0.43 ± 0.22 mmHg/mL and 0.66 ± 0.26 mmHg/ml),

Table 2 Acute haemodynamic effects of the Aria pulmonary endovascular device

	PH-LHD ($n=8$)				PH-CLD ($n=10$)				PAH ($n=10$)			
Haemodynamic variable	**Device off**	**Device on**	**% change**	***p*-value**	**Device off**	**Device on**	**% change**	***p*-value**	**Device off**	**Device on**	**% change**	***p*-value**
HR, bpm	76.7 ± 16.5	75.3 ± 16.1	−1.7 ± 3.8	0.241	78.3 ± 12.2	77.9 ± 11.8	−0.5 ± 3.5	0.675	76.5 ± 8.5	75.1 ± 6.5	−1.5 ± 3.1	0.136
SaO_2, %	92.2 ± 4.3	91.9 ± 3.1	−0.2 ± 3.3	0.813	82.4 ± 9.8	81.9 ± 10.4	−0.8 ± 1.7	0.250	91.7 ± 4.0	92.0 ± 4.0	0.4 ± 2.3	0.590
CI, L/min/m^2	2.8 ± 1.0	2.9 ± 1.0	5.2 ± 8.3	0.133	2.7 ± 0.8	2.9 ± 0.9	9.4 ± 6.8	**0.003**	3.7 ± 0.9	4.0 ± 1.1	8.8 ± 7.5	**0.010**
SV, ml	80.8 ± 40.9	85.3 ± 40.3	7.1 ± 11.5	0.127	65.1 ± 22.5	71.4 ± 25.0	9.7 ± 8.3	**0.005**	91.5 ± 28.4	101.6 ± 35.2	10.5 ± 7.1	**0.010**
sPAP, mmHg	68.3 ± 14.9	65.7 ± 12.9	−3.3 ± 6.8	0.279	68.9 ± 12.2	67 ± 11.9	−2.8 ± 2.7	**0.017**	77.8 ± 18.2	76.2 ± 18.2	−2.1 ± 5.1	0.199
dPAP, mmHg	29.6 ± 4.1	32.3 ± 5.3	9.1 ± 10.8	0.059	29.3 ± 5.3	31.2 ± 7.1	5.9 ± 8.4	0.061	30.2 ± 8.5	32.1 ± 9.0	6.6 ± 9.3	0.051
mPAP, mmHg	45.6 ± 7.8	46.3 ± 7.7	1.7 ± 6.9	0.595	44.6 ± 6.3	45.2 ± 6.9	1.2 ± 4.5	0.463	48.1 ± 12.7	49.0 ± 12.6	2.4 ± 7.2	0.385
PAPP, mmHg	40.9 ± 13.7	35.3 ± 10.5	−12.3 ± 7.4	**0.007**	40.0 ± 11.0	35.8 ± 11.8	−11.4 ± 6.2	**<0.001**	47.6 ± 12.1	44.1 ± 11.6	−7.4 ± 5.4	**0.002**
LVEDP, mmHg	18.7 ± 2.5	16.9 ± 4.5	−9.4 ± 19.8	0.220	11.3 ± 4.3	10.2 ± 3.9	−6.4 ± 28.0	0.514	–	–	–	–
TPR, WU	8.5 ± 2.2	8.4 ± 2.4	−2.3 ± 8.1	0.476	9.5 ± 2.7	9.1 ± 3.1	−4.5 ± 8.5	0.155	7.7 ± 3.9	7.3 ± 3.7	−5.4 ± 10.8	0.128
PVR, WU	4.9 ± 2.2	5.2 ± 2.2	14.7 ± 31.4	0.145	7.2 ± 2.8	7.2 ± 2.7	0.5 ± 9.3	0.997	–	–	–	–
C_{PA}, ml/mmHg	2.0 ± 0.8	2.5 ± 0.9	22.5 ± 13.7	**0.003**	1.6 ± 0.4	2.1 ± 0.6	24.8 ± 17.4	**0.002**	2.1 ± 1.0	2.5 ± 1.2	19.8 ± 10.9	**0.003**

Note: Bold printed *p*-values indicate statistical significance inferred at $p < 0.05$.
Data are given as mean ± standard deviation; *p*-values are results of paired samples *t*-test comparing 'device off' and 'device on'.
CI, cardiac index; C_{PA}, pulmonary arterial compliance; dPAP, diastolic pulmonary arterial pressure; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary arterial pressure; PAPP, pulmonary arterial pulse pressure; PAH, pulmonary arterial hypertension; PH-CLD, pulmonary hypertension associated with chronic lung disease; PH-LHD, pulmonary hypertension associated with left heart disease; PVR, pulmonary vascular resistance; SaO_2, oxygen saturation; sPAP, systolic pulmonary arterial pressure; SV, stroke volume; TPR, total pulmonary resistance; WU, Wood units.

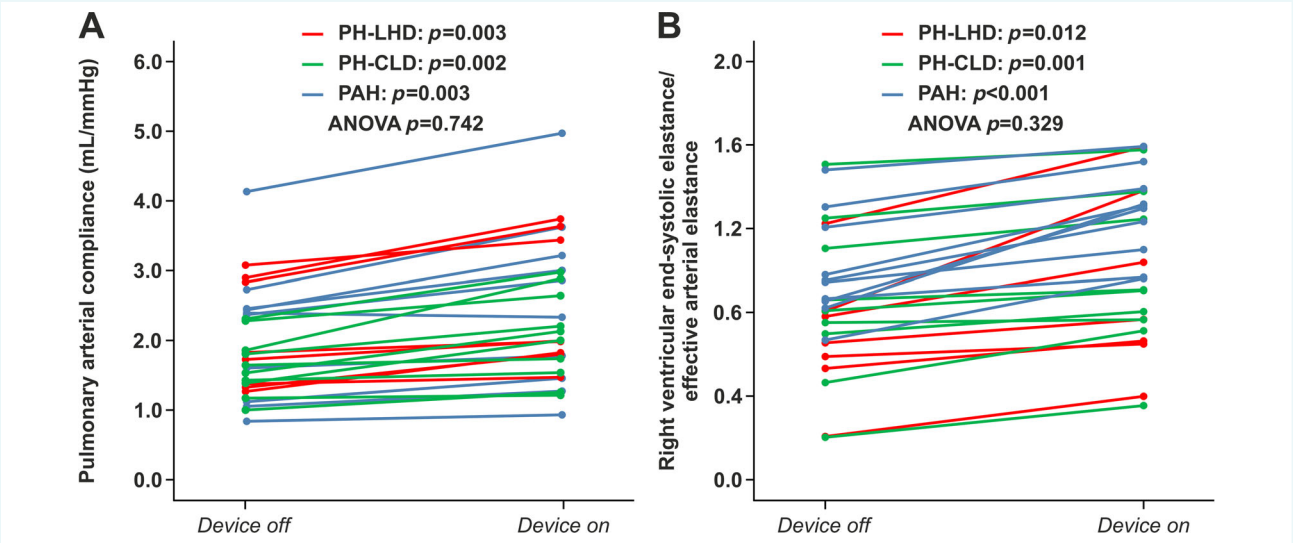


Figure 2 Effect of the Aria pulmonary endovascular device on pulmonary arterial compliance and right ventricular-to-pulmonary vascular coupling. Line graphs illustrating individual changes in pulmonary arterial compliance (*A*) and ratio of right ventricular end-systolic elastance to effective arterial elastance (*B*). PAH, pulmonary arterial hypertension; PH-CLD, pulmonary hypertension associated with chronic lung disease; PH-LHD, pulmonary hypertension associated with left heart disease.

Table 3 Effects of the Aria pulmonary endovascular device on right ventricular-to-pulmonary vascular coupling

	PH-LHD ($n=8$)				PH-CLD ($n=10$)				PAH ($n=10$)			
Haemodynamic variable	**Device off**	**Device on**	**% change**	***p*-value**	**Device off**	**Device on**	**% change**	***p*-value**	**Device off**	**Device on**	**% change**	***p*-value**
E_{es}, mmHg/ml	0.43 ± 0.22	0.54 ± 0.24	29.5 ± 19.7	**0.004**	0.60 ± 0.24	0.66 ± 0.24	14.2 ± 24.1	0.143	0.56 ± 0.22	0.67 ± 0.32	19.1 ± 17.5	**0.004**
E_a, mmHg/ml	0.66 ± 0.26	0.62 ± 0.25	−5.9 ± 12.7	0.324	0.77 ± 0.28	0.73 ± 0.28	−5.6 ± 6.3	**0.047**	0.60 ± 0.32	0.56 ± 0.30	−6.8 ± 11.2	0.068
E_{es}/E_a	0.69 ± 0.31	0.93 ± 0.43	39.9 ± 30.5	**0.012**	0.85 ± 0.40	0.96 ± 0.38	21.1 ± 25.2	**0.001**	1.01 ± 0.25	1.27 ± 0.21	28.7 ± 18.3	**<0.001**

Note: Bold printed *p*-values indicate statistical significance inferred at $p < 0.05$.
Data are given as mean ± standard deviation; *p* values are results of paired samples *t*-test comparing 'device off' and 'device on'.
E_a, effective arterial elastance; E_{es}, end-systolic elastance; PAH, pulmonary arterial hypertension; PH-CLD, pulmonary hypertension associated with chronic lung disease; PH-LHD, pulmonary hypertension associated with left heart disease.

PH-CLD (0.60 ± 0.24 mmHg/ml and 0.77 ± 0.28 mmHg/ml) and PAH (0.56 ± 0.22 mmHg/ml and 0.60 ± 0.32 mmHg/ml, all ANOVA $p > 0.05$). RV-PV coupling as assessed by the ratio of E_{es}/E_a was lowest in PH-LHD (0.69 ± 0.31), followed by PH-CLD (0.85 ± 0.40), and highest in PAH (1.01 ± 0.25).

In PH-LHD with the device on, E_{es} and E_{es}/E_a increased by $29.5 \pm 19.7\%$ ($p = 0.004$) and $+39.9 \pm 30.5$ ($p = 0.012$), respectively, while E_a remained unchanged. Comparable changes could be observed in PAH. In contrast, PH-CLD patients showed a significant decrease in E_a ($-5.6 \pm 6.3\%$, $p = 0.047$) and an increase in E_{es}/E_a ($+21.1 \pm 25.2\%$, $p = 0.001$), while E_{es} remained unchanged. The impact on E_{es}/E_a was uniformly directionally the same in all patients (*Figure 2B*). Improvement in E_{es}/E_a upon device activation was comparable between all groups (ANOVA $p = 0.329$; *Figure 2B*).

Discussion

In this study, we evaluated safety and feasibility, and haemodynamic effects of the Aria pulmonary endovascular device to restore the physiologic Windkessel function of healthy pulmonary arteries in patients with PH-LHD and PH-CLD. In addition, haemodynamic performance data were compared with those from our previous first-in-human study in PAH. We found that (i) temporary device implantation was feasible and safe, and (ii) device activation was associated with an acute increase in C_{PA} and E_{es}/E_a in PH-LHD and PH-CLD; and (iii) effects on RV afterload and RV-PV coupling were comparable to those previously reported in PAH.[18] The value of our results is the demonstration of a universal effect of the Aria pulmonary endovascular device of C_{PA} enhancement in all studied subsets of PH (*Graphical Abstract*).

The compliance characteristics of the normal pulmonary circulation allow for the conversion of pulsatile CO to continuous blood flow. Loss of C_{PA}, resulting from increased fibrosis and deposition of ground substance, in association with abnormal shear stress, altered PAPP, increased pulsatile load, and RV-PV uncoupling are features of PH. Augmentation of C_{PA}, a critical determinant of RV afterload and RV-PV coupling, resulted in increased CI and reduced PAPP. By single beat analysis of RV pressure curves, we found that RV end-systolic elastance (E_{es}), as a measure of RV contractility, increased after balloon activation leading to an improvement in RV-PV coupling (increase in E_{es}/E_a) in patients with PH-LHD, similar to that previously reported in PAH.[18] In contrast, the increase in E_{es}/E_a in PH-CLD was primarily mediated by a drop in E_a, while E_{es} remained almost unchanged. We speculate that the ability of RV function to respond in PH-CLD may be more compromised than in the other subsets, presumably due to hypoxia.[19]

Currently available pharmacologic PH-targeted treatments are mainly designed to counteract vasoconstriction and their success has been judged by measurement of vascular resistance. Vasodilator drugs, and the variables utilized to assess their effectiveness, fail to address the pulsatile component of RV afterload. This dynamic or pulsatile component is thought to account for a significant portion of the afterload seen by the right ventricle and is dependent upon the compliance or viscoelastic properties of the pulmonary circulation as a whole. In addition, the timing and magnitude of the reflectance waves, generated by the frequent branching over short distances seen in the pulmonary circulation, are in part determined by the compliance characteristics of the pulmonary arteries. Experimental data suggest that, through the effects of an increased PAPP on the endothelium, loss of C_{PA} stimulates increases in resistance[20–23] and adverse vascular remodelling in the small pulmonary arteries,[23–25] and consequently unloading may reverse occlusive vascular lesions.[26] Low C_{PA} may account for up to 50% of RV afterload.[27–30] The resistance-compliance curve of the pulmonary circulation shows early loss of C_{PA} in PH that is not addressed by current therapy which primarily decreases PVR.[1,31,32] C_{PA} correlates with exercise capacity, quality of life and CO.[33–36] Not surprisingly, low C_{PA} (high stiffness) is highly correlated with mortality.[6–15] In non-compliant arteries the main reflected waves travel rapidly backward toward the pulmonary valve and may arrive early enough to 'sum' into the afterload experienced by the right ventricle. The measurement of reflectance waves generated over very short distances is difficult even in animal models of PH. However, modifications in C_{PA} and PAPP resulting from the balloon may favourably delay the return and magnitude of reflectance waves and alter their influence on RV afterload.

There was a marked acute effect of the device on PAPP. Arterial circulations are able to 'sense' and respond to the force and compliance signals in their environment via cell surface integrins as well as matrix YAP and TAZ proteins. Recent work[37] has elucidated a critical pathway for biomechanical signal transduction altering nuclear gene activation and transcription. This work suggests pulse pressure interacting with cell surface integrins has a direct input into cell nuclei. Furthermore, integrin response-elements appear to be capable of graded reactions to the magnitude of the pulse pressure. The theoretical implications of this process suggest a high PAPP may stimulate adverse pulmonary arterial remodelling. Similarly, reductive modification of PAPP as seen with the Aria pulmonary endovascular device might favourably alter gene activation and transcription to reduce or even reverse arterial remodelling.

Because activation of the device results in increased CO, when designing this study, we sought to determine whether increased flow could impact left ventricular filling pressure in PH-LHD and aortic saturation in PH-CLD. During the procedure, with the Aria device in place, use of a Swan–Ganz catheter was not possible, therefore a left ventricular catheter was utilized to measure left ventricular end-diastolic pressure. Activation of the device did not result in a rise in left ventricular end-diastolic pressure. Additionally, in PH-CLD, activation of the device did not significantly lower aortic oxygen saturation by worsening ventilation–perfusion mismatch, as can be observed with administration of systemic vasodilator therapy.

No device-related adverse effects from the temporary placement of the device were noted. Specifically, there was no evidence of clot on the balloons at the time of withdrawal. No pulmonary arterial damage or induction of arrhythmias during the procedure was observed.

The data obtained during this first-in-human use were uniformly directionally similar in all patients; however, the magnitude of the effect varied from patient to patient. This variation in magnitude

might be expected in a population of patients where the duration of the disease, length and type of treatment varied.

Clinical application of the Aria pulmonary endovascular device will be both in the acute setting as a bridge to other effective treatment, for example, lung transplantation or effective parenteral medical treatment; and in the chronic setting to support a failing right ventricle in PH.

Limitations

The findings of this study are of course limited by the small number of patients. In the interest of patient safety, device activations were short and therefore the longer-term impact of device activation, especially with exertion, could not be assessed. Also, in contradistinction to the clinical epidemiology of the disease, our PAH group contained an excess of male patients. This was because the test device was only of one size and, therefore, we were unable to match balloon size to patient size with this prototype design. However, two relatively small females (body surface areas of 1.54 m^2 and 1.59 m^2) were also part of the study and were safely treated. In future studies, more balloon sizes will become available. Whether the observed acute haemodynamic changes ensure long-term haemodynamic benefits is unknown.

Conclusion

Temporary implantation of the Aria pulmonary endovascular device was feasible and did not result in safety concerns. Device activation resulted in acute improvement of C_{PA} and RV-PV coupling. The magnitude of improvement in C_{PA} and E_{es}/E_a was comparable to that previously reported for PAH. The Aria pulmonary endovascular device improves RV afterload and RV-PV coupling in PH irrespective of the underlying aetiology. Thus, a permanent device could be useful for many patients with PH, especially in patients with PH-LHD and PH-CLD, who have limited approved therapeutic options in case of RV failure. The permanent device is currently under investigation, and includes an implantable reservoir connected to the balloon-carrying catheter that is attached to the left pulmonary artery via a stent. Passive cycling of the balloon is expected to improve RV function and protect the pulmonary capillary bed. Further studies are needed to assess long-term efficacy and safety of the device as a chronic implant.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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