How prostacyclin therapy improves right ventricular function in pulmonary arterial hypertension

To the Editor:

Within recent years, right ventricular (RV) function has been recognised as a major determinant of outcome in pulmonary arterial hypertension (PAH) [1, 2]. Clinical [3] and *in vitro* experimental [4, 5] data suggest that prostacyclins, the treatment of choice for most severely ill PAH patients [6], might have a positive inotropic effect on RV function, and reduce pulmonary vascular resistance (PVR). Nevertheless, inotropic effects are difficult to demonstrate *in vivo*, as ventricular contractility adjusts to afterload to preserve ventricular-arterial coupling [7]. In fact, the ratio of ventricular end-systolic elastance (Ees), a measure of *in vivo* contractility, to pulmonary arterial elastance (Ea) or the "coupling ratio" (Ees/Ea), was restored by epoprostenol in a model of load-induced acute RV failure; however, this was explained by a reduction in afterload [8].

In the present study, we prospectively measured RV pressures and volumes, before and after the administration of an intravenous infusion of the prostacyclin analogue, treprostinil, in patients with advanced PAH. Inotropic RV function was assessed by measurements of Ees, and afterload was assessed by measurements of Ea. In addition, diastolic function of the RV was assessed by measurements of diastolic stiffness, and diastolic elastance was determined either by the curve-fit parameters (β), or by the slope (Eed) of the diastolic pressure-volume relationship.

33 treatment-naïve incident patients with PAH (27 women and six men, aged 55±12 years) gave informed consent to the study, which was approved by the institutional review board at the University of Arizona. The diagnosis of PAH was established, following updated guidelines [6]. The patients were severely ill, as all 33 patients were in advanced WHO (World Health Organization) functional classes III (19%) or IV (81%).

After inclusion, all patients underwent right heart catheterisation (RHC) for measurements of RV pressure, pulmonary artery pressure (PAP), wedged PAP (PAWP), right atrial pressure (RAP) and cardiac output, cardiac magnetic resonance (CMR) imaging of RV volumes and a standard echocardiography. Blood was sampled for measurement of brain natriuretic peptide (BNP).

Treprostinil was started intravenously at 2 $ng \cdot kg^{-1} \cdot min^{-1}$ and then titrated by 2 $ng \cdot kg^{-1} \cdot min^{-1}$ every 4–6 h, to a dose target of 10–15 $ng \cdot kg^{-1} \cdot min^{-1}$ or to dose-limiting side effects while the patients were hospitalised. This target was achieved after an average of 29 h. Before discharge, all patients had a 6-min walk test (6MWD), CMR, and BNP measurement. In a subset of 25 patients, RHC was done before discharge. All patients were transitioned to a home pump prior to discharge.

After discharge, treprostinil was titrated up by 2 $ng \cdot kg^{-1} \cdot min^{-1}$ every 3–7 days, to a goal of 30–50 $ng \cdot kg^{-1} \cdot min^{-1}$ within 3 months [9]. At 3 months follow-up, patients again underwent RHC, CMR, echocardiography, BNP and a 6MWD.

Owing to clinical constraints, baseline CMR studies were not feasible on all patients. In these patients, baseline RV volumes (end-diastolic and end-systolic) were estimated from the corresponding echocardiographic area, using a single simple linear regression equation (RV volume = 7.63 × echo area − 0.69; $r=0.76$, $p<0.001$) constructed from quasi-simultaneous measurements of echocardiographic areas and CMR volumes. There was good agreement between CMR-measured and echocardiographic estimates of

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Cite this article as: Vanderpool RR, Desai AA, Knapp SM, *et al*. How prostacyclin therapy improves right ventricular function in pulmonary arterial hypertension. *Eur Respir J* 2017; 50: 1700764 [https://doi.org/10.1183/13993003.00764-2017].

ventricular volumes in a subset of 11 patients with baseline (pre-treatment) CMR (r=0.71, p<0.001). Stroke volume (SV) was calculated as end-diastolic volume (EDV) - end-systolic volume (ESV). Global RV function was assessed by the ejection fraction (RVEF) and the ratio of SV to ESV.

Theoretical pressure–volume (PV) loops were acquired by integrating pressure–time tracings during catheterisation with EDV and ESV measurements from CMR images (or echo/CMR-based estimation for baseline), as previously reported [10]. A maximum isovolumic pressure P_{max} was determined from sinusoidal curve fitting of the RV pressure-time waveform during early systole (from end-diastolic to maxima dP/dt) and early diastole (minima dP/dt to beginning of diastole) [11]. The Ees, or contractility, was calculated as (P_{max}–mPAP)/(EDV–ESV), where mPAP represents the mean pulmonary artery pressure. The Ea, or afterload, was calculated asmPAP/SV. The RV–PA coupling was estimated by the Ees/Ea ratio, and simplified for RV volumes as P_{max}/mPAP − 1. Diastolic function was assessed by a nonlinear fit of the end-diastolic pressure–volume relationships, $P=\alpha (e^{V\beta}-1)$, from which we derived the diastolic stiffness, β, and a curve fitting constant, α [12]. Generally, as β increases, diastolic stiffness increases. Diastolic elastance (Eed) or the slope of the end-diastolic pressure-volume relationship alone might be a satisfactory measure of diastolic stiffness [12].

Summary statistics were reported as mean±SD. Changes in metrics over time were assessed by non-parametric Kruskal–Wallis tests and Dunn tests, with Bonferroni correction for multiple comparisons.

PAH was idiopathic in 18 patients and associated in the other patients. The patient population was predominately female (81%). The dose of treprostinil was 13.0±2.2 $ng{\cdot}kg^{-1}{\cdot}min^{-1}$ at discharge and 43.0 ±9.9 $ng{\cdot}kg^{-1}{\cdot}min^{-1}$ at 3 months. Functional class improved to II–IIIa in 72% of subjects at 3 months. Furthermore, both the 6MWD and BNP showed significant improvement. No deaths occurred and no patients were placed on combination therapy during the follow-up period.

As shown in table 1, at baseline, the patients presented with severe pulmonary hypertension and RV failure, increased mPAP and PVR, reduced cardiac index, and enlarged RV with reduced ejection fraction (EF) and SV/ESV. Both Ees and Eed were increased, and the Ees/Ea ratio was maintained at a normal value of 2.

Treprostinil therapy reduced mPAP by an average of 3 mmHg (acutely) and 6 mmHg (over 3 months), with minimal effect on PAWP, a reduction in RAP and an increase in the cardiac index. There was also a reduction in Ees, with an unchanged Ees/Ea, along with reduced ventricular volumes and diastolic stiffness (β and Eed). The RVEF and SV/ESV were both increased to values associated with a better prognosis, and

TABLE 1 Pulmonary haemodynamics and right ventricular function variables in patients with pulmonary arterial hypertension, before and after the institution of intravenous treprostinil therapy

	Baseline	Discharge	3 months	ANOVA
mPAP mmHg	57±11	54±11	49±11*	0.01
PAWP mmHg	9.7±3	8.8±3.8	7.7±3.9*	0.052
RAP mmHg	13±5.7	12±4.9	7.5±4.5*,#	0.0001
CI $L{\cdot}min^{-1}{\cdot}m^{-2}$	2.1±0.6	2.5±0.8*	2.9±0.8*	<0.0001
PVR $mmHg{\cdot}L^{-1}{\cdot}min^{-1}$	13±4.5	12±5.4	8.3±3.6*,#	0.0002
Ees $mmHg{\cdot}mL^{-1}$	3.2±1.9	1.7±0.8*	1.9±0.9*	<0.0001
Ea $mmHg{\cdot}mL^{-1}$	1.6±0.9	1±0.5*	1±0.5*	0.0002
Ees/Ea	2.0±0.7	1.7±0.7	2.1±0.7	0.09
V_0 mL	141±43	104±54*	102±54*	0.02
RVEF %	21±8.3	30±8.7*	32±10*	<0.0001
SV/ESV	0.3±0.1	0.5±0.2*	0.5±0.2*	<0.0001
Beta mL^{-1}	0.08±0.04	0.05±0.02*	0.05±0.02*	<0.0001
Eed $mmHg{\cdot}mL^{-1}$	1.7±1.1	1.0±0.5*	0.7±0.5*	<0.0001
6-min walk distance m		269±109	327±155*	
BNP $pg{\cdot}mL^{-1}$	623±449	280±235*	187±183*	<0.0001

Data are presented as mean±SD. The ANOVA column shows the significance of the F-ratios of the analysis of variance *: p<0.05 *versus* baseline; #: p<0.05 high *versus* low dose of treprostinil. mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; RAP: right atrial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; Ees: end-systolic elastance; Ea: arterial elastance; V_0: pressure volume intercept; RVEF: right ventricle ejection fraction; SV: stroke volume; ESV: end-systolic volume; Eed: end-diastolic elastance; BNP: brain natriuretic peptide.

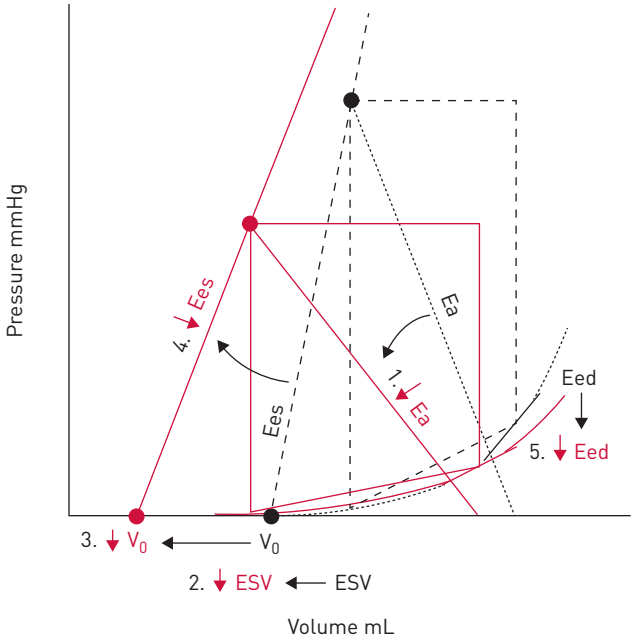

FIGURE 1 Theoretically derived right ventricular (RV) pressure–volume (PV) loops demonstrating mean treatment-related changes. PV loops at a) baseline (black, dashed) and b) 3 months (red, solid) depict mean patterns in treatment response by coupling parameters. After 3 months of treatment, afterload (1) was reduced (arterial elastance, Ea). In terms of volume, there was a significant reduction in end-systolic volume (ESV) (2) along with a zero pressure volume intercept (V_0) (3). In terms of RV function, end-systolic elastance (Ees) (4) and end-diastolic elastance (Eed) (5) were both reduced. As a consequence, RV ejection fraction, ratio of stroke volume to ESV and diastolic function improved, although there was no significant change in coupling ratio (Ees/Ea).

moved RV function towards the flat region of the RVEF to SV/ESV relationship [13]. Right ventricular unstressed volume, V_0, was reduced. There was a moderate to strong correlation between Ees and diastolic stiffness (range r=0.61–0.86, p<0.001) at baseline, the acute stage and at 3 months. As illustrated in figure 1, the observed changes in RV function and volumes could be explained by the reduction in RV afterload; however, an additional effect of treprostinil on diastolic function has not been excluded.

To our knowledge, this is the first prospective study of the effects of targeted therapy on RV-arterial coupling in patients with PAH. The present results confirm that even advanced PAH is associated with increased RV inotropic function to match the increase in afterload, which preserves ventriculo-arterial coupling [7]. In spite of the apparent adaptive increase in RV contractility, which has also been observed in experimental pulmonary hypertension [14], RV volumes and V_0 were increased, the EF and SV/ESV were reduced, and diastolic function was severely altered.

Unlike the left ventricle, where treatment-related improvements in SV and EF often occur owing to an increase in the coupling ratio, treprostinil acutely improves SV predominantly by a reduction in ESV, without any change in the Ees/Ea. Improvements in afterload were accompanied by a reduction in contractility (Ees) and diastolic stiffness. These changes collectively are associated with reduced unloaded volume, V_0, possibly due to restoration of Frank–Starling reserve or a decline in the afterload (figure 1) [15].

This study has several limitations. A simplified pressure method was applied to estimate Ees and Ees/Ea, which might have spuriously increased both Ees and Ea, without affecting the Ees/Ea ratio [10], and baseline ESV and EDV were recalculated from echocardiographic areas in some patients. Nevertheless, the data strongly suggests that in PAH, prostacyclins reduce RV afterload without an intrinsic inotropic effect. Alternatively, the prostacyclin-associated increase in SV and RVEF could be associated with improved RV diastolic function and decreased V_0.

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Received: Feb 24 2017 | Accepted after revision: May 29 2017

Support statement: The initial phase of this study (patients 1–15) was supported in part by United Therapeutics Corp., which did not participate in the design of the study, acquisition of data, analysis, interpretation of the results, or writing of the manuscript. The secondary phase of this study (patients 16–33) was supported in part by the U01 grant HL125208-01 from the National Heart Lung and Blood Institute (PVDOMICS) (F.P. Rischard, A.A. Desai, J.X.-J. Yuan and J.G.N. Garcia). Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

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