International Journal of Cardiology 218 (2016) 206–211

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Imaging right ventricular function to predict outcome in pulmonary arterial hypertension

Melanie J. Brewis [a,*], Alessandro Bellofiore [b], Rebecca R. Vanderpool [c], Naomi C. Chesler [d], Martin K. Johnson [a], Robert Naeije [e], Andrew J. Peacock [a]

[a] Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Glasgow, UK
[b] Department of Biomedical, Chemical and Materials Engineering, San Jose State University, CA, USA
[c] Vascular Medicine Institute, University of Pittsburgh, Pittsburgh, PA, USA
[d] Department of Biomedical Engineering, University of Wisconsin-Madison, WI, USA
[e] Department of Cardiology, Erasme University Hospital, Brussels, Belgium

ARTICLE INFO

Article history:
Received 29 February 2016
Received in revised form 19 April 2016
Accepted 12 May 2016
Available online 13 May 2016

Keywords:
Pulmonary hypertension
Pressure–volume relationship
Prognosis
Right ventricular dysfunction

ABSTRACT

Background: Right ventricular (RV) function is a major determinant of outcome in pulmonary arterial hypertension (PAH). However, uncertainty persists about the optimal method of evaluation.
Methods: We measured RV end-systolic and end-diastolic volumes (ESV and EDV) using cardiac magnetic resonance imaging and RV pressures during right heart catheterization in 140 incident PAH patients and 22 controls. A maximum RV pressure (Pmax) was calculated from the nonlinear extrapolations of early and late systolic portions of the RV pressure curve. The gold standard measure of RV function adaptation to afterload, or RV–arterial coupling (Ees/Ea) was estimated by the stroke volume (SV)/ESV ratio (volume method) or as Pmax/mean pulmonary artery pressure (mPAP) minus 1 (pressure method) ($n = 84$). RV function was also assessed by ejection fraction (EF), right atrial pressure (RAP) and SV.
Results: Higher Ea and RAP, and lower compliance, SV and EF predicted outcome at univariate analysis. Ees/Ea estimated by the pressure method did not predict outcome but Ees/Ea estimated by the volume method (SV/ESV) did. At multivariate analysis, only SV/ESV and EF were independent predictors of outcome. Survival was poorer in patients with a fall in EF or SV/ESV during follow-up ($n = 44$, $p = 0.008$).
Conclusion: RV function to predict outcome in PAH is best evaluated by imaging derived SV/ESV or EF. In this study, there was no added value of invasive measurements or simplified pressure-derived estimates of RV–arterial coupling.

1. Introduction

It has been realized in recent years that right ventricular (RV) function is a major determinant of functional state, exercise capacity and survival in patients with pulmonary arterial hypertension (PAH) [1]. However, how to measure RV function and what variables might be most clinically relevant at the bedside remains uncertain [1,2].

The gold standard measure of RV systolic functional adaptation to increased loading conditions is end-systolic elastance (Ees) (or end-systolic pressure (ESP) divided by end-systolic volume (ESV)), corrected for arterial elastance (Ea) (or stroke volume (SV) divided by ESP). The Ees/Ea ratio defines RV–arterial coupling, or the matching of contractility to afterload. Ees is a measure of RV contractility and unlike other measures of RV function is load independent. Ea is a measure of the afterload faced by the RV and incorporates resistance, compliance and impedance of the pulmonary circulation. The optimal balance between RV work and oxygen consumption occurs at an Ees/Ea ratio of 1.5–2 [1,2].

The reference method for the determination of Ees requires instantaneous and simultaneous measurements of RV pressure and volume and generation of a family of pressure–volume loops at decreasing venous return [3]. This is not practical at the bedside. However Ees can also be estimated from a single P–V loop [4]. This method relies on the calculation of a maximum RV pressure (Pmax) from the extrapolation of early and late systolic portions of a RV pressure curve and the continuous recording of RV pressure and relative change in volume to define ESP and ESV. From these, Ees and Ea are easily calculated. The estimation of RV–arterial coupling by an Ees/Ea ratio can further be simplified for pressure and expressed as a SV/ESV ratio [5], i.e. the volume method. Alternatively the ratio can be simplified for volumes and expressed as Pmax divided by mean pulmonary artery pressure (mPAP), taken as a

* Corresponding author at: Scottish Pulmonary Vascular Unit, Level 1, Golden Jubilee National Hospital, Agamemnon Street, Glasgow G81 4DY, UK.
E-mail address: mbrewis@nhs.net (M.J. Brewis).

http://dx.doi.org/10.1016/j.ijcard.2016.05.015
0167-5273/

surrogate for ESP, minus 1 [6], i.e. the pressure method. A RV pressure curve is easily obtained during a right heart catheterization. RV volumes are ideally determined by magnetic resonance imaging (CMR).

From RV volumes it is naturally also easy to calculate a SV and an ejection fraction (EF) as SV/EDV. Cardiac CMR studies have shown that decreased SV and RV EF are predictive of poor outcome [7], and that a deterioration in RV EF during PAH therapy predicts a poor survival irrespective of improvements in pulmonary vascular resistance (PVR) [8]. However, EF is preload-dependent while Ees/Ea is theoretically not. Therefore, estimates of Ees should be superior in determining clinical state and outcome. Accordingly, a recent study on a limited number of patients referred for investigation of PH showed Ees/Ea estimated by SV/ESV to be an independent predictor of outcome while EF was not [9].

We therefore investigated the prognostic utility of RV–arterial coupling determined by both the volume and the pressure methods, compared to more usual determinations of EF and right heart catheterization-derived RAP and SV in a large cohort of patients with PAH, and in addition examined changes over time of these measurements with targeted therapies and their impact on survival.

2. Methods

We identified 140 treatment naïve incident cases of PAH diagnosed between January 2004 and April 2014 at the Scottish Pulmonary Vascular Unit, Glasgow. Patients were included after multidisciplinary evaluation based on right heart catheterization, echocardiography, pulmonary function testing and CT scan of thorax. All patients underwent invasive measurements and cardiac CMR within 72 h and received pulmonary vasodilator therapy in accordance with guidelines [10]. In 84/140 patients, RV pressures traces were available and were manually re-digitised using GetData Graph Digitizer 2.26. A subgroup of 44 patients underwent serial CMR after a minimum of 3 months of PAH therapy. 22 control patients without pulmonary hypertension (defined as a mPAP <25 mm Hg) who had right heart catheterization and CMR to investigate breathlessness were included to provide reference values for RV–arterial coupling by the two methods.

2.1. Cardiac CMR

CMR imaging was performed in the supine position on a 1.5-T magnetic resonance imaging scanner (Sonata Magnetom, Siemens, Erlangen, Germany) and images were analysed using the Argus analysis software (Houston, Texas). RV and LV volumes were determined by manual tracing endocardial borders of short axis stack obtained during breath-hold as previously described [11]. CMR variables were indexed for body surface area and adjusted for age.

2.2. Calculation of RV–arterial coupling

In those patients for whom RV pressure trace was available for analysis, Ees was calculated using the single beat method [4]. An average RV pressure trace was generated for each patient across a respiratory cycle, typically 4–6 beats. Pmax, the maximum theoretical pressure the ventricle could generate if isovolumetric contraction occurred, was calculated using a manual sine-wave extrapolation of the early systolic and diastolic portions of the RV pressure curve. ESP was approximated by mPAP [6]. Ees was calculated as the slope of end-systolic pressure volume line, Ees = (Pmax − mPAP) / (RVEDV − RVESV). Arterial elastance (Ea) was estimated by mPAP / (RVEDV − RVESV). RV–arterial coupling (Ees/Ea) was simplified for volumes as Pmax / mPAP − 1 (hereafter referred to as the pressure method, Ees/Ea − P), or simplified for pressures as SV/ESV (hereafter referred to as the volume method, SV/ESV) [9]. Stroke volume was calculated as cardiac output measured by thermodilution during the right heart catheterization divided by heart rate or as EDV minus ESV, and indexed for body surface area (SVI).

2.3. Statistical analysis

Statistical analysis was performed using SPSS 22 (SPSS Inc., Chicago, IL) and Graphpad Prism Version 5.00 (Graphpad Software, California, USA). Continuous variables were tested for normality using D'Agostino and Pearson omnibus normality test. Normally distributed variables are shown as mean ± standard deviation and non-normally distributed variables as median (IQR). Categorical variables are described by percentage (number) unless otherwise stated. Correlation coefficients were calculated by the Spearman method.

Survival was from date of diagnostic right heart catheter and endpoint was date of either death, lung transplantation or censoring. In those who underwent serial CMR to assess change in RV function, survival was from the date of the second study. Patients were censored if they were lost to follow-up or alive at last day of study (4th August 2014). All cause mortality was used for survival analysis. Survival predictors were determined using a bivariate Cox proportional hazards regression analysis with age. Variables with a p value ≤ 0.2 were considered for multivariate analysis. Survival of patients with decreased SV/ESV in comparison to those with stable or increased SV/ESV were compared by log-rank test. A p value < 0.05 was considered statistically significant throughout.

3. Results

3.1. Population characteristics

Of the 140 PAH patients included in the study, 61 deaths occurred in the follow-up period (median survival 2086 days). Table 1 describes the characteristics of the whole population and the 84 PAH patients with RV pressure trace analysis in comparison to 22 control patients with mPAP <25 mm Hg. PAH patients had a mPAP range of 28–101 mm Hg and demonstrated impaired RVEF, low SVI and increased RV volumes and mass.

There were no significant differences between SVI calculated as cardiac index/heart rate or as EDV − ESV (30 ± 10 vs 28 ± 10 mL/m^2 in PAH patients and 43 ± 20 vs 45 ± 15 mL/m^2 in controls, p = 0.428).

Table 2 shows calculated values of Ees, Ea, Ees/Ea − P and SV/ESV for PAH patients and controls. Ees and Ea were increased in PAH patients, and Ees correlated with levels of mPAP, and inversely with pulmonary vascular compliance (r = 0.574 and r = −0.619, both p < 0.001). Both Ees/Ea − P and SV/ESV were lower in PAH patients, and inversely correlated with mPAP, r = −0.345 and −0.607 respectively, both p < 0.001.

Between IPAH and CTDPH patients, there was no difference in Ees/Ea − P (1.25 ± 0.7 vs 1.30 ± 0.5, p = 0.759) or SV/ESV (0.48 (0.29–0.80) vs 0.50 (0.29–0.87), p = 0.637). 14 of the 26 CTDPH patients had systemic sclerosis associated PAH (Ssc-PAH). Ees/Ea − P and SV/ESV in comparison to IPAH patients was similar, 1.39 ± 0.5 (p = 0.52) and 0.60 (0.30–0.89) (p = 0.44) respectively.

Both Ees/Ea − P and SV/ESV were moderate predictors of 6MWD in the whole cohort, r = 0.261, p = 0.004 and r = 0.271, p = 0.003 respectively, after adjustment for age. RVEF and SV were both superior predictors of 6MWD r = 0.325 and r = 0.509 respectively, both p < 0.001. NTproBNP moderately correlated with Ees/Ea − P but strongly with SV/ESV, r = −0.325, p = 0.002 and r = −0.777, p < 0.001 respectively.

3.2. Baseline survival analysis

In the cohort of 84 PAH patients whom had both Ees/Ea − P and SV/ESV measures of RV–arterial coupling, 40 deaths occurred in the follow-up period. Median survival was 1167 days with a maximum of 2369 days. Higher Ea and RAP and lower compliance, SVI, RVEF and SV/ESV were predictive of poorer outcome on bivariate Cox proportional hazards regression with age (shown in Table 3). In a multivariate model with age, SVI, RAP and PVR, SV/ESV but not Ees/Ea − P