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A novel noninvasive method for estimating right ventricular systolic pressure in rodents with pulmonary artery banding

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Pulmonary arterial hypertension (PAH) is a devastating disease characterized by remodeling of small pulmonary arteries, which causes increases in right ventricular (RV) afterload, RV hypertrophy, failure and death [1]. Pre-clinical disease models characterized by PAH-associated RV remodeling are currently utilized in proof-of-concept, dose-finding and efficacy studies to characterize novel RV-focused therapy. In these models it remains challenging to dissect afterload-dependent and -independent effects of potential therapeutics. Therefore, an animal model that exclusively affects the RV independently from changes in the pulmonary vasculature was established. This pulmonary artery banding (PAB) model allows one studies to assess direct treatment effects on the RV myocardium and to define mechanisms that underlie the transition from RV hypertrophy towards RV failure [2, 3]. PAB is a surgical technique historically used to limit pulmonary blood flow and treat pulmonary over-circulation caused by large left-to-right shunts in children with congenital heart defects. PAB in rodents creates a partial stenosis of the pulmonary artery (PA), leading to a constant elevation of afterload and resistance in the RV, similar to the effects of pulmonary valve stenosis in humans.

To define the pressure overload in rodents, RV systolic pressure (RVSP) derived from heart catheterization has emerged as "gold standard"; however, this procedure is terminal and thereby precludes longitudinal data acquisition. Therefore, reliable and clinically relevant non-invasively--derived indices may provide a valuable tool to monitor disease progression in pre-clinical studies. Echocardiography may provide a platform to assess such indices, as it's noninvasive and used to characterize cardiac function in a longitudinal fashion [4].

In PAH patients', echocardiography enables estimation of PA systolic pressure by measuring the tricuspid regurgitation jet (TRJ) pressure gradient (TRPG) calculated from Doppler-derived TRJ velocity using a simplified Bernoulli equation: TRPG = 4 × (TRJ)^2 + right atrial (RA) pressure, estimated from vena cava respiratory variation. This method has demonstrated significant correlation between non-invasive Doppler and invasive catheter measurements as an accurate prediction of PAP [5]. While TRJ is challenging to detect in rodents, peak pressure gradient (PPG) measurements across the PA constriction site are routinely assessed in animals subjected to PAB. Using these measurements, herein provided is a novel method to estimate RVSP by echocardiography in PAB mice. Specifically, PPG was combined with E/E' data to noninvasively determine RVSP. It has been shown that E/E' ratio positively correlates with RA pressure [6, 7]. Although several formulas have been proposed to measure systolic or mean PAP in patients with pulmonary hypertension [8],

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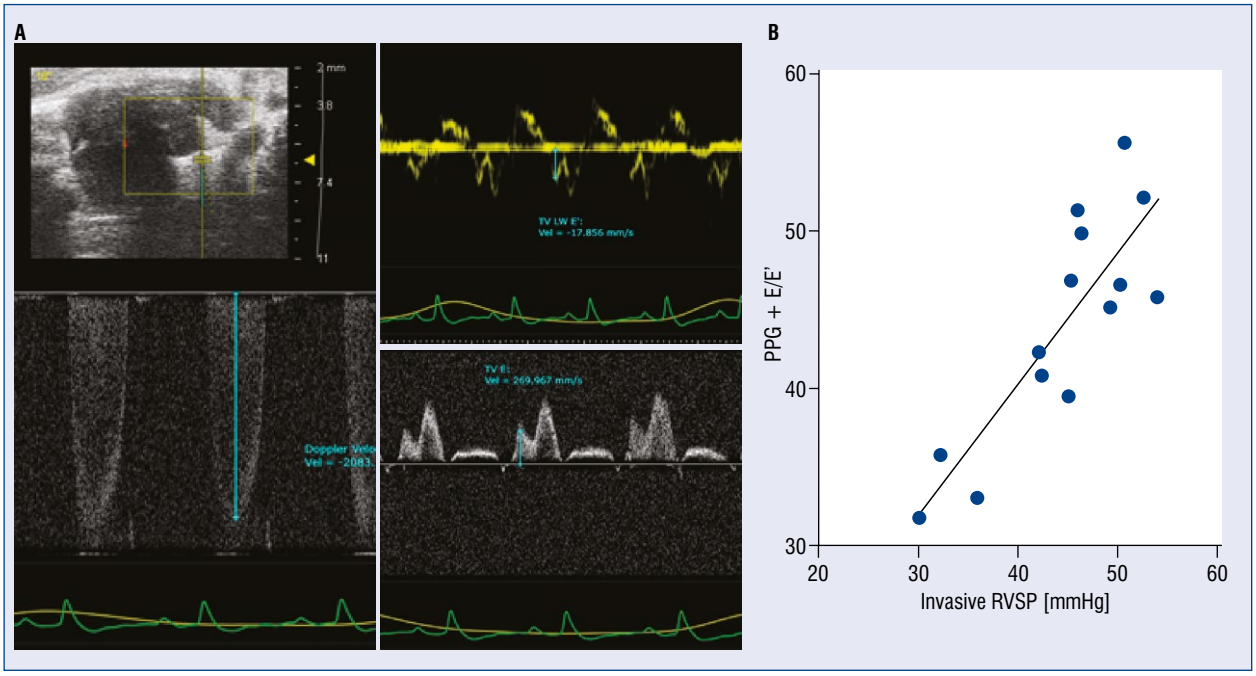

Figure 1. A. Representative images demonstrating measurement of the pressure gradient via pulmonary artery constriction by pulsed wave Doppler, E' and E peak velocity measured by tissue Doppler imaging and subsequent pulsed wave Doppler; **B.** Correlation between invasive right ventricular systolic pressure (RVSP) measurement and echo-Doppler-derived RVSP as a peak pressure gradient (PPG) across a pulmonary artery constriction plus E' to E ratio.

there is a lack of reports describing the measurement of RVSP using pressure gradient (PG) and E/E' ratio.

All experiments were performed according to institutional guidelines complying with national and international regulations and approved by local animal welfare authorities (RP Gießen). Male C57BL/6J mice aged 8–10 weeks (Charles River, Germany) were subjected to sham or PAB (n = 8–14 per group) surgery as described [3]. Three weeks post-surgery, echocardiography was performed using a Vevo2100 (Visualsonics, Canada) followed by invasive hemodynamic RVSP measurements. The PPG velocity was assessed by pulsed-wave Doppler and calculated using Bernoulli's equation: $PPG = 4 \times PG^2$. Tricuspid inflow was recorded from the apical 4-chamber view by pulsed-wave Doppler to measure early (E) diastolic peak velocity. Tissue Doppler imaging was used to measure early (E') diastolic velocity at the lateral corner of the tricuspid annulus (Fig. 1A). Noninvasive RVSP was determined as $RVSP = 4(PG)^2 + E/E'$. Data were examined using Spearman correlation statistical analyses in Prism 8 software (GraphPad Software, La Jolla, CA).

It was previously described that PAB mice developed RV systolic and diastolic dysfunction [3]. In this study, RV catheterization showed increased RVSP to 44.5 ± 7.4 mmHg in PAB mice compared to sham animals 24.2 ± 3.5 mmHg ($p = 0.0001$). Echocardiography demonstrated that the E/E' ratio increased in PAB mice to 26.3 ± 5.7 compared to 18.8 ± 4.3 in sham mice ($p = 0.004$). The PPG measured by echocardiography was 17.8 ± 6.3 mmHg in PAB mice. Interestingly, echo-derived PPG correlated with invasively measured RVSP (0.59, $p = 0.02$), while E/E' ratio did not (0.30, $p = 0.28$). In the next step, RVSP calculations were derived from the echocardiography and was compared with invasive RV catheterization. In the present study, it was demonstrated that echocardiographic-derived RVSP closely correlates with invasively derived RVSP ($r = 0.7978$, $p = 0.001$, Fig. 1B) in a mouse model of PAB.

In the current study, a formula was introduced specifically designed to measure RVSP in the PAB model. This enabled the monitoring of RVSP in PAB mice at different stages of disease progression, providing a unique opportunity to investigate and monitor the effects of treatment on the RV. Therefore, the present study provides a valuable contribution to the current understanding of RV pathophysiology in PAB. Herein, a proposed

formula for measuring RVSP could be a promising approach in clinical practice, especially in patients with congenital pulmonary valve stenosis and/or after palliative PAB surgery. This noninvasive method would enable clinicians to monitor disease progression in these patient populations, which could have significant clinical implications. Therefore, further research in this direction is warranted.

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