Scisense PV Technical Note

Pulmonary Artery Hypertension Leading to Right Ventricle (RV) Remodelling and RV-PV Loop Measurements

PULMONARY HYPERTENSION AND RIGHT VENTRICLE REMODELING

The pulmonary circulation has shorter arteries and veins, more distensible (high compliant and low resistant) large arteries, and a larger number of peripheral arteries as compared to the systemic circulation. This leads to RV afterload being significantly lower than LV afterload and matching ventricular-vascular coupling. Pulmonary hypertension (PH) is diagnosed when mean pressure in the pulmonary artery increases over a threshold. Pulmonary artery hypertension (PAH) is a subtype of PH classification defined as a mean pulmonary artery pressure (PAP) greater than 25 mmHg with peak pressure greater than 33 mmHg at rest or mean PAP greater than 30 mmHg during exercise (1, 19). Other clinically distinct PH causes include: PH owing to the left heart disease, PH owing to lung disease or hypoxia, and chronic thromboembolic PH (CTEPH).

PAH is important subtype of PH as it originates when pulmonary arteries muscularize while its vascular media hypertrophies, leading to a progressive narrowing of the arterial lumen. It is a syndrome in which obstruction of pulmonary arteries increases pulmonary vascular resistance (PVR) leading to right ventricular (RV) hypertrophy (20). Its etiology is not completely understood at this time, as multiple factors are involved. Vascular pathology changes induced by PH are characterized by intimal thickening and fibrosis, medial hypertrophy, muscularization of previously non-muscularized arteries, adventitial proliferation and increased extracellular matrix (ECM) deposition (8). PAH is responsible for proximal pulmonary artery stiffening (changes of PA pulsatility, compliance, capacitance, distensibility, elastic modulus, and pressure-independent stiffness index beta) (2) and RV dysfunction (18). RV has to accommodate (the compensatory changes) an increased afterload due to the PA pressure elevation or it will fail.

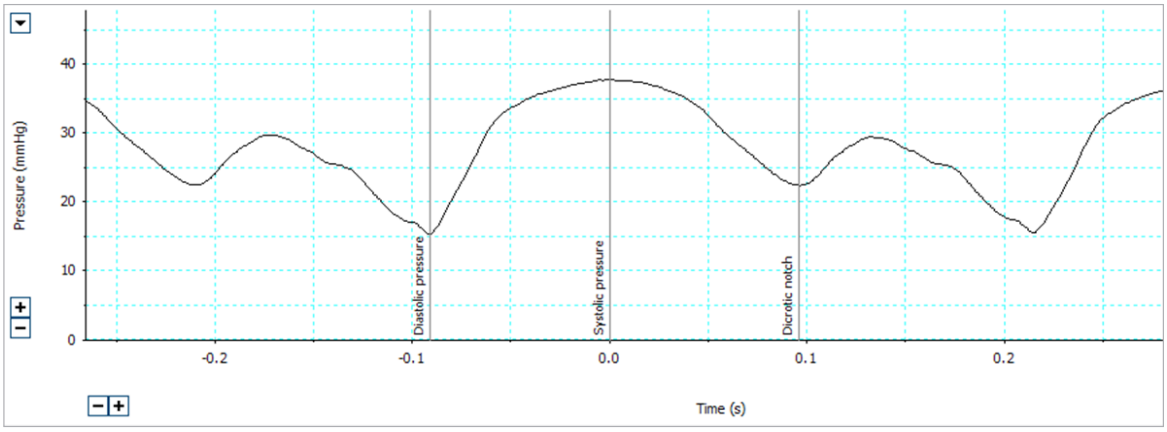

Fig. 1: Pressure trace in pig pulmonary artery during hypertension. Peak pressure is over 35 mmHg at rest.

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Pulmonary Artery Hypertension & RV PV Loops Cont.

PULMONARY HYPERTENSION AND RIGHT VENTRICLE REMODELING CONT.

Experimental models of pulmonary hypertension include direct damage of pulmonary endothelial cells (EC) by monocrotalin, alpha-napthyltiourea, microspheres, Angiopoetin-1, or Bleomycin, and subsequent EC and vascular smooth muscle cells proliferation in the area (19). In this context, RV autoregulation changes promote a temporary increase in RV contractility. During this condition, elevated wall stresses develop in the RV lateral free wall (4) and outflow tract (5). Increased wall stresses from increased mean pressure in the PA and increased pulmonary vascular resistance (PVR) further stimulate RV hypertrophy (5) and RV free wall fibrosis (6).

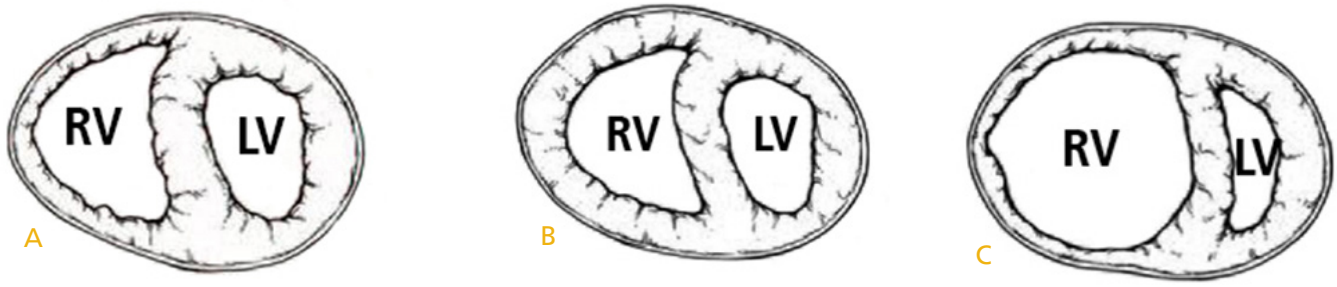

Fig. 2: A) Intact Rigth Ventricle B) PAH compensatory changes are responsible for RV free wall hyperthrophy which temporarily protects RV cardiac output and stroke volume. Heart rate might temporarily increase. RV afterload increases without significant volume changes (Fig. 3A). As PAH progresses changes in RV chamber volume occur (Fig. 3B) C) Right Ventricle dilates and fails, decrease in stroke work, stroke volume, cardiac output, and ejection fraction (Fig. 3C). Figures from Champion HC, et. al. Comprehensive Invasive and Noninvasive Approach to the Right Ventricle–Pulmonary Circulation Unit: state of the art and clinical and research implications. Circulation. 2009 Sep 15;120(11):992-1007

ASSESSMENT OF RIGHT VENTRICLE POST PAH USING RV PV LOOPS

Based on experimental data obtained from mouse RV pressure-volume study of PAH injury, models of the ventricular mechanics showed increasing RV afterload while effectively putting strain on the RV. The models show that vascular resistance, arterial elastance and arterial narrowing all play important roles in final RV remodeling (21).

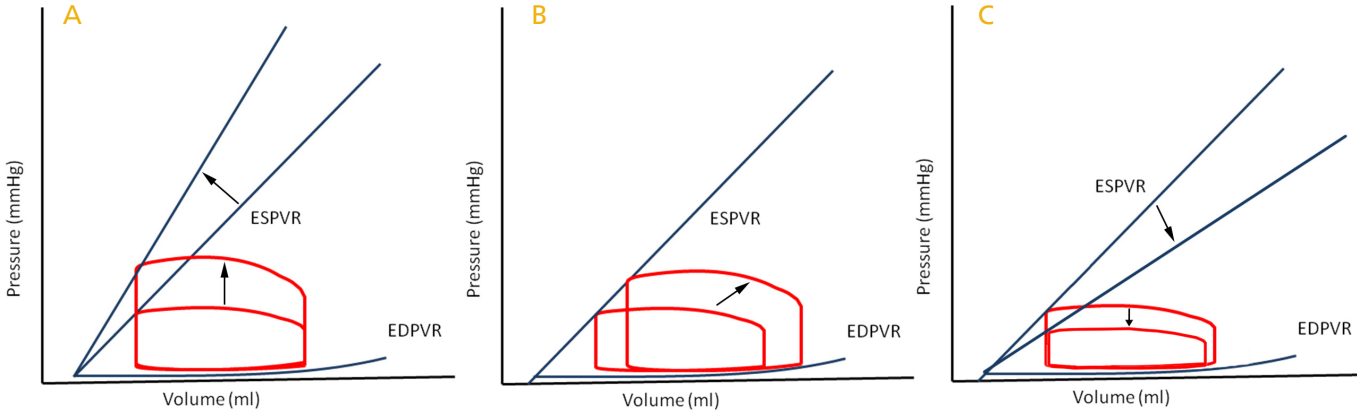

Fig. 3: Representative drawing of RV PV loops post PAH. A) Represents situation of PAH where temporary increase of pressure in the PA (increase of after-load) can be detected in the RV PV loop without volume changes. B) Represents compensatory changes of RV (increase of after-load) where both pressure and volumes changes during PAH. C) Represents failing RV as chamber dilates which is marked by decrease of stroke work, cardiac output and ejection fraction and other key parameters.

Pulmonary Artery Hypertension & RV PV Loops Cont.

ASSESSMENT OF RIGHT VENTRICLE POST PAH USING RV PV LOOPS CONT.

In the mouse, the onset of PAH is characterized by significant RV ESP increase. During early PAH the right ventricle increases its efficiency during systole to meet an increasing afterload, but as PAH progresses, its work efficiency plateaus (Fig. 3A) (22). During diastole RV EDV increases, suggesting a larger RV compliance, but in fact, as RV EDP increases, it also makes the RV chamber stiffer in diastole and that is most likely a consequence of RV wall stiffening (22). Because increased RV EDV is a strong predictor of mortality in PAH (7) detection of changes using pressure-volume measurements are very important.

Since the mechanism(s) and factors involved in the transition from an adaptive hypertrophy to maladaptive remodelling are currently unknown, a comprehensive study of RV hemodynamics is valuable. More research is underway to assess RV hemodynamics, energy balance, LV-RV dysynchrony and other possible mechanisms leading to this progressive RV failure and multiple studies in recent years used RV PV loops in their pulmonary hypertension research (9-17). For an excellent in-depth review of *in-vivo* measurements and detection of stiffening of the PA influencing the RV hemodynamics in clinical, large animal and small animal setting, please refer to an article by Chesler & Tian (18).

Historically, RV mass measured by non-invasive magnetic resonance imaging has been used as an indication of RV dysfunction due to PAH. This method, however, is not considered a strong predictor of mortality, and for this reason, this finding cannot be fully translated into the clinic (7). This disconnect between mass and mortality is possibly due to an adaptive remodelling, known also as a concentric hypertrophy without dilation happening in the RV post PAH. This leads to more longitudinal monitoring of RV pressure and volume during PAH.

One of the first uses of 5F and 6F Conductance Catheters was described by Dickstein *et. al.* in 1995. This group measured volume in the RV and correlated data to flow derived volumes measured by 16 mm Transonic Flowprobe placed on the pulmonary artery (3). The advances of Admittance technology reduces the geometric dependence of PV measurements and has allowed for right ventricular pressure-volume measurements to be more precise (15, 16).

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Pulmonary Artery Hypertension & RV PV Loops Cont.

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