Current perspectives

Modern hemodynamic evaluation of the pulmonary circulation. Application to pulmonary arterial hypertension and embolic pulmonary hypertension

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The hemodynamic evaluation of the pulmonary circulation normally includes the measurements of mean pulmonary artery pressure and a calculation of pulmonary vascular resistance (PVR). The definition of PVR can be improved by the measurements of pulmonary vascular pressures at several levels of flow to derive a pressure-flow line, and the site of PVR can be identified by the analysis of pulmonary artery pressure decay curves after balloon occlusion. An analysis of the morphology of pulmonary artery pressure and flow waves informs about right ventricular (RV) hydraulic load. As pulmonary hypertension is clinically a right heart failure syndrome, it is important to measure the coupling of RV to pulmonary arterial function. This can be done using a single beat method with sampling and synchronization of instantaneous pulmonary artery flow and RV pressure to calculate a ratio of end-systolic to arterial elastances. The optimal value of this ratio is depressed in minimally symptomatic pulmonary arterial hypertension patients, indicating pending right heart failure.

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Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a syndrome of dyspnea, fatigue, chest pain and syncope caused by a progressive increase in pulmonary vascular resistance (PVR) and right ventricular (RV) failure without identifiable causal cardiac or pulmonary disease[1]. The condition is either purely idiopathic (formerly called primary pulmonary hypertension), or occurs in association with a variety of diseases or circumstances, which include human immunodeficiency syndrome, intake of fenfluramines, connective tissue disease, portal hypertension, and congenital cardiac shunts. Patients with PAH present with broadly similar clinical presentation, histopathology and response to prostacyclin or endothelin receptor blocker therapies.

PAH is a disease of small resistive pulmonary arterioles. Progressive remodeling of the pulmonary arteriolar wall causes an increase in PVR, which becomes symptomatic mainly because of the inability of afterloaded right ventricle to adapt flow output to peripheral oxygen demand. Accordingly, a right heart catheterization with measurements of pulmonary vascular pressures and blood flow quantify both the disease process (PVR) and its main functional consequence, which is cardiac output limitation. It is therefore understandable that standard hemodynamic measurements in patients with PAH are correlated with clinical state, functional class, exercise capacity, and prognosis[2-6]. However, these correlations are loose, and often fail to reach significance on mean pulmonary artery pressure (Ppa)[2-6].

The reasons why pulmonary hemodynamic measurements do not appear to be tightly correlated with the clinical state of patients with PAH are 2-fold. First, in most reported studies, the measurements are performed at rest only, with minimal stress on the right ventricle, and minimal symptomatology. Second, mean Ppa and flow (Q) determinations may be insufficient to measure RV afterload.

A single point measurement of mean pulmonary vascular pressures, Ppa and occluded Ppa (Ppao) and Q, and derived PVR calculation may be misleading because the inherent assumptions of linearity and zero crossing of the (Ppa-Ppao)/Q relationship are not met[7]. It can indeed be shown that multipoint (Ppa-Ppao)/Q coordinates are described by a linear approximation, but

actually present with a positive extrapolated pressure intercept, which is at least partly explained by a slight curvilinearity, with decreased slope of Ppa vs Q relationships at high Q. Single point PVR determinations at variable flow therefore may underestimate or overestimate changes in the functional state of the pulmonary circulation. These errors or approximations can be limited by the definition of PVR by a multipoint pressure/flow line[7]. Recent studies showed that improvement in exercise capacity with prostacyclin therapy in PAH patients may not be associated with significant changes in pulmonary hemodynamics at rest, while PVR defined by a multipoint (Ppa-Ppao)/Q plot shows a significant decrease[8]. Cardiac output can be increased by exercise[8] or by an infusion of low-dose dobutamine[9]. The advantage of exercise is an enhanced stress on the pulmonary circulation because of decreased mixed venous oxygenation and activation of the sympathetic nervous system. The advantage of dobutamine is that Ppa increases as a purely passive consequence of increased flow[10], allowing for an optimal evaluation of pulmonary vascular function.

The site of PVR can be determined by the analysis of a Ppa decay curve. The pressure at the intersection between the fast and slow components of the curve allows for the calculation of an upstream arterial resistance (PVRa) and a downstream "venous" resistance which includes the smallest arterioles, capillaries and veins[7]. As expected, PVRa is increased in chronic thromboembolic pulmonary hypertension (CTEPH) and decreased in pulmonary veno-occlusive disease, but there is overlap[11]. However, the method appears to be useful for the identification of distal small vessel involvement in CTEPH[12]. In these patients, a decreased PVRa has been shown to be associated with the potentially lethal complication of persistent postoperative pulmonary hypertension[12].

RV afterload results from a dynamic interplay between resistance, elastance and wave reflection. Resistance, even if optimally defined by a multipoint (Ppa-Ppao)/Q plot gives an only incomplete description of all the forces that oppose RV flow output[7]. An acceptable measurement of RV afterload is given by pulmonary arterial input impedance (PVZ), which is the ratio of pulsatile Ppa to pulsatile Q[7]. The calculation of PVZ requires a spectral analysis of Ppa and Q waves and a mathematical elaboration to derive a PVZ spectrum, which is expressed as a ratio of Ppa and Q moduli and a phase angle, both as a function of frequency. The method has been applied to patients with PAH[13,14], but is complicated, and requires expensive high-fidelity technology, which is unavailable in many catheterization laboratories. The clinical relevance of PVZ determinations is unknown.

RV afterload can be indirectly evaluated by pulmonary pressure and flow waveform analysis. Increased pulmonary arterial elastance and wave reflection decreases the acceleration time and causes late or midsystolic deceleration of pulmonary arterial flow waves, and increased pulse pressure and late systolic peaking of Ppa waves[7]. Shortened acceleration times of pulmonary arterial flow has been associated with decreased survival in a small series of PAH patients[15]. Increased pulse pressure has been reported to help in the differential diagnosis between PAH and CTEPH, whether pressures are directly measured during a right heart catheterization[16], or recalculated from tricuspid and pulmonary regurgitant waves and the simplified form of the Bernoulli equation[17]. Refined indices of wave reflection such as the time to inflection point of the upstroke of RV pressure or the peak (pressure minus inflection point pressure) referred to mean Ppa (called the "augmentation index") may also be useful[18]. However, discrepant results have been reported[19] and therefore the diagnostic value of pulmonary pressure waveform analysis remains uncertain.

Instead of trying to quantify RV afterload by pulmonary pressure wave analysis, it might be more appropriate to directly quantify RV function and coupling to the pulmonary circulation. Sagawa et al.[20] showed that this can be done graphically using a ventricular pressure-volume diagram. The diagram allows for the determination of maximal ventricular elastance (Emax), which is the best possible load-independent measurement of contractility, and of arterial elastance Ea as a measurement of afterload as it is "seen" by the ventricle, and the calculation of an Emax/Ea ratio as a measurement of the coupling of ventricular to arterial function. Complex mathematical modeling shows that the optimal matching of systolic ventricular and arterial elastances occurs at an Emax/Ea ratio around 1.5. Isolated increase in Ea, or decrease in Emax, decrease the Emax/Ea ratio, indicating uncoupling of the ventricle from its arterial system. Everything else being the same, a decrease in the Emax/Ea ratio is necessarily accompanied by a decrease in stroke volume. On the other hand, an isolated increase in preload is associated with an increase in stroke volume with unaltered ventriculo-arterial coupling.

However, the complex geometry of the right ventricle makes functional evaluations with measurement of instantaneous volume changes technically difficult, and the determination of Emax may be unreliable because of the particular shape of the RV pressure-volume loop and non-coincidence of end-ejection and end-systole. This problem can be overcome by measuring pressure-volume loops at several levels of preload[21], but bedside manipulations of venous return are too invasive to be ethically acceptable. In addition, when applied to intact beings, changes in venous return are associated with reflex sympathetic nervous system activation, which affects the ventricular function that is measured. These concerns have been addressed by a most recently reported single beat method allowing for a direct quantification of the coupling of the RV to the pulmonary circulation[22]. The approach had been initially proposed for the left

ventricle by Sunagawa et al.[23]. In its principle, the method avoids absolute volume measurements and related technical complexities, to calculate Emax and Ea from instantaneous RV pressure and flow output measurements. As shown in figure 1, maximal pressure (Pmax) is estimated from a non-linear extrapolation of the early and late systolic isovolumic portions of the RV pressure curve. This estimated Pmax has been shown to be tightly correlated with Pmax directly measured during a non-ejecting beat[22]. A straight line drawn from Pmax to the RV pressure vs relative change in volume curve allows for the determination of Emax. A straight line drawn from the Emax point to the end-diastolic relative volume point allows for the determination of Ea.

The Emax/Ea ratio determined by this single beat method is around 1.5, which is similar to values reported for left ventricular-aortic coupling, and compatible with an optimal ratio of mechanical work to oxygen consumption[20]. The Emax/Ea ratio is decreased by propranolol and increased by dobutamine, and maintained in the presence of increased Ea due to hypoxic pulmonary vasoconstriction[22]. In fact, Emax increases adaptedly to increased Ea in hypoxia, even in the presence of adrenergic blockade, which is compatible with the notion of homeometric adaptation of RV contractility[20]. On the other hand, the approach allows for the demonstration that clinically relevant doses of dobutamine do not affect pulmonary arterial hydraulic load[24]. The single beat approach has also already been used to show the superiority of dobutamine over norepinephrine to restore right ventriculo-arterial coupling in acute right heart failure produced by a brisk increase in Ppa[24], and the profound decoupling effects of inhaled anesthetics in the same setting[25], this being due to the devastating effects of both negative inotropy and pulmonary vasoconstriction. Also, the optimal values for the Emax/Ea ratio were found not different in dogs, goats and in pigs[26], and shown to be well maintained in piglets with PAH induced by 3-month systemic to pulmonary shunting, without or with endothelin receptor blocker therapy[27,28]. The method also showed that, contrary to current belief[29], intravenous prostacyclin has no intrinsic positive inotropic effects on the right ventricle[27].

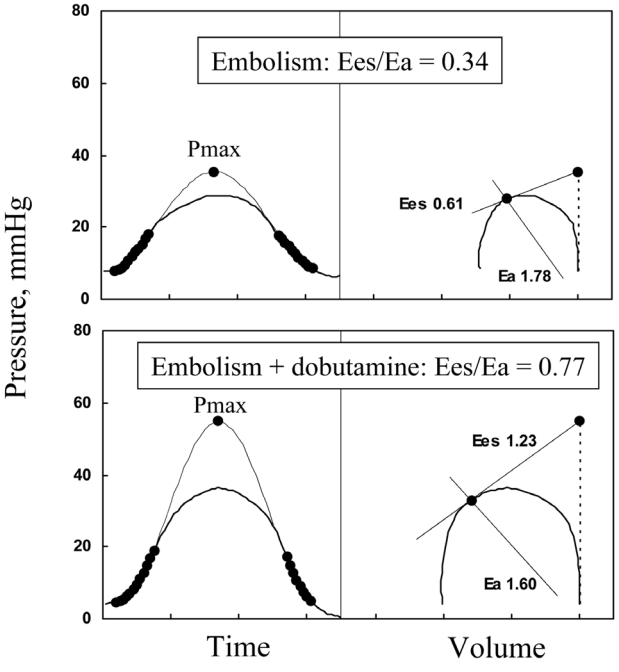

Figure 1. *Right ventricular pressure and volume after transient pulmonary arterial banding (embolism) before* (upper panels) *and during an infusion of dobutamine 10 μg/kg/min* (lower panels). *Transient pulmonary arterial banding caused a profound right ventricular-arterial uncoupling, with a decrease of the ratio of end-systolic (Ees) to arterial elastances (Ea) from 1.56 (not shown) to 0.34, which was restored to 0.77 by dobutamine. The maximal pressure (Pmax) of an isovolumic beat was predicted from isovolumic portions of the right ventricular pressure curve* (left panels). *The predicted isovolumic beat pressure was reported on the right ventricular pressure-volume graph* (dashed line, right panel). *Ventricular Ees line was derived from end-systolic points of isovolumic and ejecting beats. Effective Ea was derived from end-systolic and end-diastolic points.*

Practically, all that is needed to determine single beat Emax/Ea ratios is measurements of instantaneous pulmonary blood flow and RV pressure. This is feasible by echocardiography (Fig. 2). Doppler pulmonary flow measurements synchronized to invasively measured Ppa have been reported to allow for realistic pulmonary arterial impedance calculations[14]. RV pressure can be recalculated from the envelope of tricuspid regurgitant jets and point-by-point application of the simplified form of the Bernoulli equation[30]. However, the entirely non-invasive Doppler echocardiographic determination of Emax/Ea ratios in patients has not yet been validated. Most recently, Kuehne et al.[31] used magnetic resonance imaging together with RV pressure measurements to generate pressure-volume loops and Emax and Ea determinations. As compared to controls, RV Emax was increased from 5.2 ± 0.9 to 9.2 ± 1.2 mmHg/ml/100 g ($p < 0.05$), but RV Emax/Ea was decreased from 1.9 ± 0.4 to 1.1 ± 0.3 ($p < 0.05$), indicating an increased RV contractility in response to increased afterload that was however insufficiently coupled to its hydraulic load, with inefficient mechanical work production[31]. It will be interesting to correlate these findings with newly developed tissue Doppler indices of RV contractility.

Embolic pulmonary hypertension

The PVR equation is an extrapolation to the pulmonary circulation of Poiseuille's law, which predicts resistance to be the laminar flow of a Newtonian fluid in a straight capillary tube to be inversely related to the fourth power of its internal radius. This, together with high pulmonary vascular distensibility and recruitment of the pulmonary circulation, explains that the relationship between amount of embolic obstruction and mean Ppa is hyperbolic, with minimal increase in pressure until about 50% of obstruction, and increasingly rapid increase of pressure at higher levels of obstruction[32]. It

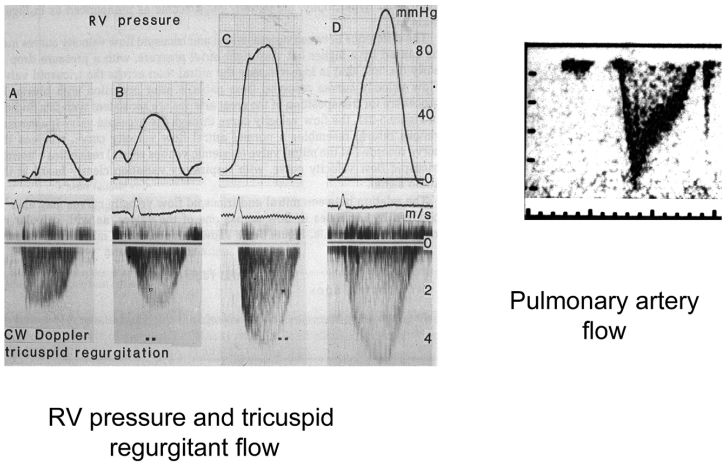

Figure 2. *Doppler tricuspid regurgitant jet and pulmonary artery flow in a patient with severe pulmonary hypertension. The right ventricular (RV) pressure curve can be resynthesized from the envelope of the tricuspid regurgitant jet by point-by-point application of the simplified form of the Bernoulli equation. Both show late systolic peaking. The pulmonary flow wave shows a shortened acceleration time and late systolic deceleration.*

can be shown experimentally that a unilateral pulmonary artery balloon obstruction doubles flow in the contralateral lung with an increase in mean Ppa to only 20-25 mmHg, the upper limit of normal, and an insignificant change in PVR[33]. Mélot et al.[34] modeled the pulmonary circulation of dogs with pulmonary embolism at variable levels of angiographically measured obstruction, and expressed the results as mean Ppa as a function of flow and percent obstruction. As shown in figure 3, mean Ppa at a normal cardiac output of 3 l/min exceeds 20 mmHg at an obstruction of 50%, to reach 40 mmHg at an obstruction of 80%. In this study, the adequacy of the prediction of mean Ppa based on percent obstruction, flow and a realistic viscoelastic model strongly indicates that embolic pulmonary hypertension has no significant functional component[35].

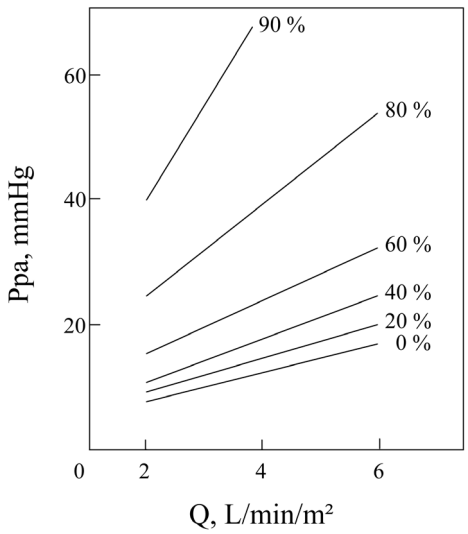

Figure 3. *Mean pulmonary artery pressure (Ppa) as a function of flow (Q) as different levels of embolic obstruction. At the standardized Q of 3 l/min, mean Ppa reaches 20 mmHg, the upper limit of normal, at an obstruction of 50%, and 40 mmHg at an obstruction of 80%.*

Pulmonary arterial obstruction in acute pulmonary embolism is proximal in more than 90% of the cases[36]. CTEPH is most often exclusively proximal as well[37]. Proximal obstruction increases wave reflection[38], and is therefore expected to be associated with an increased RV afterload at a given level of PVR. As mentioned above, these patients present with late systolic peaking of RV pressure, and late or midsystolic deceleration of pulmonary arterial flow, both being easily detected at Doppler echocardiography. Although there has been no report yet on RV-arterial coupling in acute embolic pulmonary hypertension or in CTEPH, these patients likely present with insufficient adaptation of RV systolic function to pulmonary arterial elastance, justifying inotropic therapy. For this purpose, dobutamine is the ideal choice because of short half-life allowing for fine tuning of effects, and increased RV contractility with no changes in pulmonary arterial impedance[10,24].

Conclusions

PAH symptomatology is essentially caused by RV dysfunction. The evaluation of PAH by the steady flow hemodynamic approach and a calculation of PVR is essential to the accurate measurement of resistive vessel obstruction, but does not inform of RV adaptation to associated increase in afterload. Modern hemodynamics includes an evaluation of RV function and how it is adaptedly coupled to the pulmonary circulation. This can be done using non-invasive methods.

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