Early View

Review

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THE PHYSIOLOGIC BASIS OF PULMONARY ARTERIAL HYPERTENSION

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Abstract

Pulmonary arterial hypertension (PAH) is a rare dyspnea-fatigue syndrome caused by a progressive increase in pulmonary vascular resistance (PVR) and eventual right ventricular (RV) failure. In spite of extensive pulmonary vascular remodeling, lung function in PAH is generally well preserved, with hyperventilation and increased physiologic dead space, but minimal changes in lung mechanics and only mild to moderate hypoxemia and hypocapnia. Hypoxemia is mainly caused by a low mixed venous PO_2 from a decreased cardiac output. Hypocapnia is mainly caused by an increased chemosensitivity. Exercise limitation in PAH is cardiovascular rather than ventilatory or muscular. The extent of pulmonary vascular disease in PAH is defined by multipoint pulmonary vascular pressure-flow relationships with a correction for hematocrit. Pulsatile pulmonary vascular pressure-flow relationships in PAH allow for the assessment of RV hydraulic load. This analysis is possible either in the frequency-domain or in the time-domain. The RV in PAH adapts to increased afterload by an increased contractility to preserve its coupling to the pulmonary circulation. When this homeometric mechanism is exhausted, the RV dilates to preserve flow output by an additional heterometric mechanism. Right heart failure is then diagnosed by imaging of increased right heart dimensions and clinical systemic congestion signs and symptoms. The coupling of the RV to the pulmonary circulation is assessed by the ratio of end-systolic to arterial elastances, but these measurements are difficult. Simplified estimates of RV-PA coupling can be obtained by magnetic resonance or echocardiographic imaging of ejection fraction.

Introduction

Pulmonary arterial hypertension (PAH) is a rare dyspnea-fatigue syndrome due to a progressive increase in pulmonary vascular resistance (PVR) and eventual right ventricular (RV) failure. The diagnosis of PAH relies on the exclusion of cardiac, pulmonary or thrombo-embolic causes of increased pulmonary artery pressure (PAP) followed by a right heart catheterization showing a mean PAP (mPAP) higher than 20 mmHg, a wedged PAP (PAWP) lower than or equal to 15 mmHg and a PVR equal to or higher than 3 Wood units (1). PAH is idiopathic (IPAH) in approximately half of the cases (1). In spite of therapeutic advances during the last decades, PAH remains incurable (2).

The histopathology of PAH is characterized by arteriolar intimal proliferation, evolving to aspects of concentric or eccentric laminar sclerosis, medial hypertrophy and adventitial proliferation, with variable inflammatory reactions and occasional aspects of fibrinoid necrosis (3,4). Advanced PAH may be associated with so-called plexiform lesions consisting of a proliferation of channels with an accumulation of endothelial and inflammatory cells in the vicinity of occluded arterioles. These aspects are illustrated in Fig 1. Plexiform lesions are scattered, with a preference for supernumerary arteries, branches that arise perpendicularly from large muscular or even elastic pulmonary artery, do not bear relationship to increased PVR, and cannot actually be found in approximately two-thirds of the patients (4). Microthrombotic lesions may also occur, in up to one third of PAH patients, also without clear relationship to increased PVR (4). Medial hypertrophy is correlated to acute prostacyclin-induced decrease in PVR (5).

While the pulmonary circulation is extensively remodeled in PAH, symptoms and outcome in these patients are largely determined by altered RV structure and function (6,7). The concept of PAH as a two-sided pulmonary/cardiac entity is summarized in the upper and lower rows of the central illustration (Fig 1).

The physiologic basis of both aspects of PAH will be here reviewed with focus on the idiopathic form of the condition to avoid the confounding effects of comorbidities.

Lung mechanics, ventilation and gas exchange

Lung function tests in PAH show a mild restriction in volumes and no or only a mild decrease in lung diffusing capacity for carbon monoxide (DL_{CO}) documented in registries of rigorously confirmed cases of IPAH (8). A more important decreases in DL_{CO} is reported in more contemporary PAH registries which include older patients with associated conditions, smoking, clinically silent cardiovascular or respiratory conditions and less stringent hemodynamic definition (9,10). There may be an increase in small airways resistance in advanced PAH as a cause of dynamic hyper-inflation and exercise-induced dyspnea (11,12). Decreased respiratory muscle strength has also been reported (13). However, these alterations in lung mechanics and respiratory muscle function do not appear to limit aerobic exercise capacity (14,15).

Arterial blood gas analysis in PAH is characterized by normal or decreased arterial partial pressures of oxygen and carbon dioxide (PaO_2 and $PaCO_2$) (8,9,16). As illustrated in Fig 2, either PaO_2 or $PaCO_2$ are below normal in about half of the patients, but severe hypocapnia is more common than severe hypoxemia (16). Hypocapnia, but not hypoxemia is an independent

predictor of decreased survival in IPAH (17). Arterial blood gases, spirometry and DL_{CO} are similarly disturbed in IPAH and in chronic thrombo-embolic PH (CTEPH), so that these measurements cannot be used to distinguish between the two conditions (18).

The physiology of abnormal blood gases in PAH was explored using the multiple inert gas elimination technique in the 1980s (19-21). Alveolar ventilation (V_A)/perfusion (Q) matching was found to be preserved, with no additional modes of ventilation or perfusion to higher or lower than normal V_A/Q . Physiologic dead space as calculated by the Bohr-Enghoff equation was increased. Hypoxemia at rest and during exercise was explained by a decreased mixed venous PO_2 due to a low cardiac output, combined with a mild inhomogeneity of perfusion distribution((19-21). Administration of the calcium channel blocker nifedipine in 2 of the patients increased perfusion to lower than normal V_A/Q , but this alteration in gas exchange was not associated with a decrease in PaO_2 because of increased cardiac output and mixed venous PO_2 (20). Occasional severe arterial hypoxemia was explained by the addition of a right to left cardiac shunt through a patent with a foramen ovale (20). There was no diffusion limitation of alveolar-to-arterial PO_2 gradients (19-21). Arterial hypoxemia in PAH is a form of "hemodynamic hypoxemia", that is arterial hypoxemia mainly caused by mixed venous hypoxemia with a low cardiac output (16).

Distributions of V_A/Q in a healthy subject and in a patient with IPAH are illustrated in Fig 2. The V_A/Q distributions in the IPAH patient were recalculated after correcting for increased ventilation and decreased cardiac output, as is possible using the mathematical model of the method (22). It can be seen that mean V_A/Q shifted back to normal with tightening of both V_A and Q modes, but shunt ($V_A/Q = 0$) increased. The latter finding is explained by both increased Q and decreased V_A (16).

Patients with PAH hyperventilate, at rest, during exercise and even during sleep, in relation to increased physiologic dead space and chemosensitivity (16). Increased chemosensitivity in PAH has been demonstrated by measurements of increased ventilatory responses to both hypoxemia and hypercapnia (23). Physiologic dead space as calculated by the Bohr-Enghoff equation is sensitive to increased ventilation (24). The respective contributions of increased chemosensitivity and dead space to hyperventilation in PAH can be sorted out by plotting ventilatory equivalents for CO₂ (ventilation, V_E vs CO₂ output, V_{CO_2}) as a function of either end-tidal or PaCO₂ (25) (Fig 2). An upward shift of V_E/V_{CO_2} vs PaCO₂ curves with an increase of the arterial to end-tidal PCO₂ gradient to above the upper limit of normal of 5 mmHg suggests an increased physiologic dead space (16). Only slightly higher than normal PCO₂ gradients are typically found in PAH (26). Thus hyperventilation in PAH is predominantly due to increased chemosensitivity

The mechanisms of increased chemosensitivity in PAH remain incompletely understood (27). Ventilation at rest and during exercise in PAH is unrelated to PaO₂, PaCO₂ or pH (28) but tightly correlated to RV diastolic stiffness (26). This observation is consistent with increased sympathetic nervous system activity demonstrated by microneurographic studies in PAH patients (29,30). Both increased sympathetic activation and increased V_E/V_{CO_2} are of poor prognosis in PAH (30,31).

Clinical relevance. Pulmonary gas exchange in PAH is surprisingly well preserved. Hyperventilation and altered blood gases in these patients are essentially explained by a combination of decreased cardiac output, increased physiologic dead space and increased chemosensitivity.

Pulmonary circulation: steady-flow hemodynamics

Pulmonary vascular resistance

The definition of pulmonary vascular disease rests on a determination of PVR (1). However, PVR decreases with increased cardiac output because of flow- and pressure-induced vascular recruitment and/or distension (32,33). Therefore, the resistive properties of the pulmonary circulation in PAH or PH on left heart failure are better defined by multi-point pressure-flow relationships. This approach has been used to unravel the effects of prostacyclin therapy in PAH (34). In that study, parenteral epoprostenol decreased the slope mPAP-cardiac output relationships while resting PVR remained unchanged ((Fig3).

As illustrated in Figs 1 and 3, the slope of the linear adjustment of mPAP-cardiac output relationships in PAH is less than predicted by the PVR equation (34,35). This is explained by an increased pulmonary vascular closing pressure (32,33). The slope of mPAP-cardiac output in PH on heart failure during exercise is steeper than predicted by the PVR equation (36). As previously discussed (35) this is to be explained by exercise-induced pulmonary vasoconstriction and increased PAWP.

In healthy individuals with fully recruited lung vessels, the decrease in PVR with increasing cardiac output is explained by resistive vessel distension, known from in vitro experiments to be a 2% change in diameter per mmHg of transmural pressure (37). Accordingly, the PVR equation can be improved by the incorporation of a resistive vessel

distensibility coefficient α (in %/mmHg) with R_0 calculated as the ratio between mPAP and cardiac output (Q) (38)

$$PVR = [(1 - \alpha \cdot PAWP)^5 + 5 \alpha R_0 \cdot Q]^{1/5} - \alpha \cdot PAWP - 1] / \alpha Q$$

This equation allows to calculate α from a set of pulmonary vascular pressure and flow measurements (37). The derived distensibility factor α is normally of 1.5-2 %/mmHg, is lower in men compared to pre-menopausal women, and decreases with aging and chronic but not acute hypoxic exposure (37,39,40). It is reduced in early or latent pulmonary vascular disease (41,42) and in heart failure with preserved ejection fraction (42,43). In PAH, mPAP-cardiac output relationships conform to a linear or quasi linear model, and thus flow-induced decrease in PVR is mainly to be accounted for by a recruitment of closed resistive vessels (35). As illustrated in Fig 4, in normal fully recruited lungs, pulmonary vascular distension by only 1-2 %/mmHg markedly limits the increase in PAP at increased cardiac output during exercise (40,41).

Blood is not a Newtonian fluid, so that PVR increases linearly as a function of blood viscosity, which in turn is exponentially related to hematocrit. As illustrated in Fig 5, the impact of hematocrit on PVR increases at high hematocrit, PVR and PAWP (44). Measurements of PVR in anemic or polycythemic patients may markedly under- or over-estimate pulmonary vascular obstruction.

Distensibility models of the pulmonary circulation allow to recalculate the amount of pulmonary vascular obstruction from a given pair of mPAP and cardiac output measurements (45). This is illustrated in Fig 6. At a cardiac output of 5 L/min, a mPAP of 25 mmHg (former

definition of PH) corresponds to 50 % obstruction - or resection of one lung - while a mPAP of 20 mmHg (new definition of PH) correspond to 20-25 % obstruction.

Clinical relevance. A refined definition of PVR by multipoint pulmonary vascular pressure-flow relationships may be useful to diagnose early pulmonary vascular disease and helps to understand the effects of interventions in clinically established PAH. Corrections for hematocrit are needed for anemic or polycythemic patients. Current definitions of PH at normal cardiac output correspond to pulmonary vascular remodeling with 25-50 % of vascular obstruction

Partitioning of PVR

The pressure decay curve after PA balloon occlusion to measure PAWP presents with a fast portion, corresponding to an upstream arterial resistance, and a slow portion corresponding to a downstream resistance which incorporates arterioles, capillaries and veinules (46). This is illustrated in Fig 1. Upstream PVR increases in purely proximal CTEPH. Downstream PVR increases in PAH and pulmonary veno-occlusive disease (PVOD) (46).

The partitioning of PVR by arterial occlusion may identify patients with proximal CTEPH who are most likely to benefit from surgical or interventional des-obstruction (47-49). The analysis is not helpful to differentiate PAH and PVOD because of overlaps in pulmonary vascular remodeling (4,50).

Clinical relevance: Single balloon occlusion pressure decay curves during a right heart catheterization may reveal differences in the partitioning of PVR between proximal pulmonary arterial obstruction (proximal CTEPH) and distal arteriolar, capillary and or venular obstruction (PAH, PVOD).

Pulmonary circulation: pulsatile-flow hemodynamics

Pulmonary vascular impedance

Hydraulic work - or "dynamic afterload" of the RV is determined by an interaction between resistance, compliance and wave reflection (51). These determinants of the opposition to PA flow can be quantified by a spectral analysis of PA pressure and flow waves (7,52,53). The result is graphically represented as a pulmonary vascular impedance (PVZ) spectrum or PAP/flow (Q) and phase angle as a function of frequency (Figs 1 and 7). Zero Hz impedance (mPAP/Q) is mainly determined by the small vessel resistance as well as by left atrial pressure. As frequency increases, impedance is affected by more proximal arterial resistance. A negative low frequency phase angle shows that flow leads pressure. At high frequencies the PAP/Q ratio is decreased and oscillates around a constant value called characteristic impedance (Z_c). It is possible to calculate Z_c in the time-domain as the early systolic slope of PAP/Q (54). Z_c is a ratio of inertance to compliance, and thus measures proximal PA stiffness.

Pulmonary vascular impedance determinations have been reported until now in a limited number of pediatric and adult patients with IPAH (55-58). The general pattern has been that of an upwards shift of PVZ spectra, with the first minima and maxima of PAP-flow moduli

shifted to higher frequencies, increased Z_c and more negative low-frequency phase angle. Increased Z_c was interestingly associated with RV-arterial uncoupling (57) and worse clinical outcome than predicted by PVR alone in pediatric PH patients (58).

Clinical relevance. The measurement of PVZ in PAH allows for an assessment of RV afterload but is limited by the complexity of frequency-domain analysis. The clinical relevance of determinants of PVZ other than Z_0 and Z_c remains an area of investigation.

Time-domain pulsatile hemodynamics

Severe pulmonary hypertension is characterized by increased PA pulse pressure (PP, or systolic PAP, sPAP minus diastolic PAP, dPAP), late systolic peaking of pressure and a short plateau in the upstroke of the pressure wave (53). These aspects are determined by decreased PA compliance (or stroke volume, SV divided by PP) and delayed addition of the first reflected pressure wave (59). Wave reflection can be quantified by the so-called augmentation index, or sPAP minus plateau pressure divided by PP initially proposed by Murgo for the systemic circulation (60). Pulmonary artery PP has been reported to be increased in proximal PA obstruction, such as in CTEPH compared distal small vessel obstruction such as in PAH (61). However, the discrimination between these two conditions based on PP or a Murgo index was not possible on an individual basis (62).

Pulmonary hypertension is also characterized by a late or mid-systolic deceleration of flow also called "notching" (63,64) caused by earlier return of the first reflected flow wave (59). Quantification of notching by measuring a "time to notching" from the onset of the flow wave to the moment of maximum mid-systolic deceleration has been proposed as an index of

increased wave reflection, and thus of predominantly proximal CTEPH (65). However, this approach has not gained acceptance probably because of overlap with high pressure PAH and common coexistence of distal small vessel disease in CTEPH (66). The presence of PA flow notching is associated with a high likelihood of increased PVR (67).

Clinical relevance. There is interest in PA pressure and flow wave morphology analysis for the diagnostic work-up of PH. High pulse pressure, late systolic peaking of pressure and mid-systolic deceleration of flow are indices of advanced pulmonary vascular disease and/or proximal PA obstruction. Proximal PA stiffening increases Z_c , which can be assessed in the time- as well as in the frequency domain, and may be relevant to RV afterload.

The time constant of the pulmonary circulation

Pulmonary arterial compliance is mostly (> 80 %) distributed to the peripheral part of the arterial tree (68), in contrast to systemic arterial compliance which is mostly (>80 %) proximal, in the thoracic aorta (69). While in the systemic circulation resistance and compliance are unrelated, the product of PA compliance and PVR, also called RC-time remains constant with a hyperbolic relationship that is maintained over a wide range of severities, etiologies and treatments of pulmonary hypertension (68-73). This property has two consequences. The first is that PA compliance becomes a more important determinant of RV afterload than PVR when PAP and PVR are only modestly elevated (73). The second is that the oscillatory component (W_{osc}) of total hydraulic load (W_{TOT}) of the pulmonary circulation is a constant fraction of approximately 23 % (74) Accordingly, W_{TOT} can be calculated from steady-flow hydraulic load (W_{ST}) or product of mPAP by SV:

$$W_{TOT} = 1.3 \times W_{ST}$$

The RC-time decreases in relation to PA proximal obstruction like in experimental PA banding or in CTEPH (75,76) or increased PAWP in patients with heart failure (77). In these circumstances, PA compliance decreases out of proportion to increased PVR (Fig 7), and therefore contributes proportionally more to RV afterload.

The RC-time is a small number exposed to amplification of errors on measurements of both PA compliance and PVR, so that it may vary considerably (78). However, extreme reported changes in RC-time do not greatly affect the oscillatory component of total work (79).

It has been proposed that the stability of RC-time of the pulmonary circulation explains why sPAP, dPAP and mPAP are tightly correlated in normal subjects and in patients with PH of all possible etiologies and severities (80). It has been repeatedly demonstrated that the sPAP/mPAP and mPAP/dPAP ratios are remarkably stable and actually match the golden ratio (81). Mean PAP can be predicted from sPAP by the formula (82):

$$\text{mPAP} = 0.6 \times \text{sPAP} + 2 \text{ mmHg}$$

The constant proportionality between sPAP and mPAP is useful in clinical practice as sPAP is easily determined noninvasively from the maximum velocity of tricuspid regurgitation measured by Doppler echocardiography (83).

Clinical relevance. The tight hyperbolic relationship between PA compliance and PVR explains the relatively more important contribution of PA compliance to afterload in mild to

moderate PAH, the stability of the prediction of mPAP from noninvasively estimated sPAP, and absent or limited impact of wave reflection on RV afterload load.

Right ventricular function

Ventriculo-arterial coupling

In spite of obvious embryological and structural differences, the mechanical properties of the RV and the LV are similar (84). The so-called "laws of the heart" equally apply to both (85). The immediate ventricular adaptation to increased afterload is by increased dimensions following Starling's law of the heart. However, this "heterometric" response is in a few minutes replaced by a "homeometric" increased contractility following Anrep's law of the heart allowing for a preserved flow output without dilatation and increased filling pressures. Long-term homeometric adaptation is strengthened by ventricular hypertrophy. When the homeometric adaptation becomes exhausted, a heterometric adaptation is turned on again to preserve cardiac output, but at the price of ventricular dilatation and upstream congestion (6,7,85,86).

These notions with analysis of LV function by pressure-volume (PV) relationships were introduced by Suga et al in the 1970's (87). They have been revived along with increased interest into RV function as a main determinant of symptoms and outcome in PAH (6,7,53,86).

The gold standard of the measurement of contractility in an intact ventricle is maximum or end-systolic elastance (Ees), or the ratio between end-systolic pressure (ESP) and end-systolic volume (ESV). A lumped afterload parameter can be defined by a ratio between ESP and SV.

$$E_{es} = ESP/ESV$$

$$E_a = ESP/SV$$

Accordingly, the coupling of RV contractility to afterload can be assessed by the Ees/Ea ratio (6,7,53,85,86). Mathematical modeling and experimental studies have established that the Ees/Ea ratio allowing for the ejection of a SV at minimal energy expenditure is optimally between 1.5 and 2.0 (85).

The left ventricular PV loop has a square shape with easily identifiable Ees at its upper left corner (87). The normal RV PV loop has a rounded triangular shape with early systolic peaking of pressure, with Ees more difficult to discern (Fig 5) (88). Accurate definition of the RV Ees/Ea ratio requires a family of PV loops at several levels of preload decreased by a manipulation of systemic venous return (88), or a single beat PV loop with analysis of the RV pressure curve (89). The single beat approach relies on an estimation of maximal pressure (Pmax) from a nonlinear extrapolation of the early and late isovolumic portions of the RV pressure curve. Maximal RV pressure corresponds to the pressure generated by a non-ejecting beat at end-diastolic volume (EDV) (Fig 8)

The coupling of RV function to the pulmonary circulation by Ees and Ea measurements was first reported in 6 PAH patients in 2004 (90). The study showed that Ees was approximately tripled compared to controls, but with a decreased Ees/Ea ratio indicating pending RV failure. These results have been confirmed in small cohorts of patients with either PAH or CTEPH (91-94). In these studies, Ees/Ea was measured either by the single beat method (90,92,93) or on a family of PV loops at decreasing venous return (91,94). End-systolic elastance was constantly increased (90-94). The Ees/Ea ratio was either maintained or decreased at rest (90-94) but constantly decreased during exercise (93,94). Decreased Ees/Ea on exercise was accompanied by an increase in EDV, corresponding to exercise-induced RV failure (94).

Measurements of the Ees/Ea ratio by single or multiple beat approaches produce on average the same results, but with individual variability (95). The coupling of RV function to the hypertensive pulmonary circulation has reserve: RV dimensions increase when the Ees/Ea ratio is down to a critical value of 0.7-0.8, thus approximately half-normal (96) (Fig 8). At similar severity of PH, the Ees/Ea is better preserved in female compared to male PAH patients (97). The Ees/Ea ratio independently predicts outcome in PAH (95).

As illustrated in Fig 8, the shape of RV PV loops changes with progression of pulmonary hypertension, from a triangular shape with early systolic peaking of pressure in subjects without PH, to trapezoid and triangular shapes with late systolic peaking of pressure and mid systolic dip of pressure ("notching") (98,99). These morphological changes in RV PV loops have been shown to be of prognostic relevance (99).

Clinical relevance. Right ventricular function adaptation to increased afterload in PAH relies on increased contractility to match increased arterial elastance. RV-arterial coupling in PAH is decreased during exercise and either preserved or decreased at rest. RV-arterial uncoupling eventually results in RV dilatation, increased RV filling pressures and clinically manifest right heart failure. RV-arterial coupling is of prognostic relevance.

Simplified measurements of RV-arterial coupling at the bedside

Since the Ees/Ea ratio has pressure as a common term, it can be simplified to a ratio of volumes (100,101):

$$E_{es}/E_a = ESP/ESV / ESP/SV$$

$$E_{es}/E_a = SV/ESV$$

The cut-off value for the SV/EDV ratio below which RV dimensions increase above the upper limits of normal while preserving SV is theoretically 0.54 (102). Since SV is equal to EDV - ESV, and thus

$$SV/ESV = EF / (1 - EF)$$

this corresponds to a RV EF of 35 % (102)

Because the Ees/Ea ratio has built-in common volume terms, it can also be simplified to a ratio of pressures (101,103):

$$E_{es}/E_a = (P_{max}-PES)/SV / PES/SV$$

$$E_{es}/E_a = P_{max}/PES - 1$$

Based on the above developed equations, RVEF can be derived from an RV pressure curve (104):

$$EF = 1 - PES/P_{max}$$

Simplified measurements of RV-PA coupling have limitations (105). The volume method assumes E_{es} as a straight line crossing the origin, which is unrealistic since ventricular end-systolic elastance curves are slightly curvilinear with a positive extrapolation to the volume axis defining an unstressed volume (V_0) (106). The pressure method requires to calculate P_{max} , for which several methods have been reported and may not be equivalent (89, 93, 101,104). It has been proposed to replace ESP by easier to measure mPAP during a right heart catheterization (103). However, mPAP under-estimates ESP in proportion to increased PAP (107) following the equation:

$$ESP = 1.65 \times mPAP - 7.79 \text{ mmHg}$$

The pressure-dependent discrepancy between mPAP and ESP is related to the changes in the shape of PV loops (98,99) as shown in Fig 8.

The best validated simple imaging assessment of RV-PA coupling in PAH is RVEF. Several studies have demonstrated that RVEF is an independent predictor of outcome in PAH, with a cut-off value of 35-40 % down from normal values around of 60-70 % (108-110). A large-scale study has shown that RVEF < 37 %, between 37 % and 54 % and > 54 % are significantly associated with high, intermediate and low risk of decreased survival in PAH (111). A meta-analysis has estimated that any decrease in 1 % of RVEF increases by 5 % the risk of clinical deterioration at 2 years and by 2 % the risk of death at 5 years (numbers rounded up) (112). The fractional area change (FAC) or the ratio of the difference between end-diastolic and end-systolic areas to end-diastolic area of the RV assessed by 2D echocardiography as a surrogate of RVEF has been shown to be predictive of outcome as well, also with a rigorously determined cut-off value of ~35 % (113).

Reversing RV dimensions and increasing EF or FAC by targeted therapies restores PAH life expectancy to normal (114). Reverse remodeling with improved EF or FAC is best achieved by a decrease in PVR by > 40 to 50 % (114-117). Such a decrease in PVR requires the combination of at least two therapies targeting different pathways and may be more consistently achieved with parenteral prostacyclins (114-117).

Clinical relevance. Severe RV-arterial uncoupling in PAH is associated with RV dilatation, systemic congestion and shortened life expectancy. Right heart failure defined by increased RV dimensions occurs when EF or SV/ESV decrease to below 35 % and 54 % respectively, with variability due to preserved or decreased stroke volume. Reverse remodeling of the RV improves the outcome of PAH, and is achieved with combined therapies to decrease PVR by at least 40 to 50 %.

Diastolic function

Coupling of RV function to afterload has an inevitable diastolic component (6,85,86,96,101,118,119). As illustrated in Fig 8, diastolic function is described by a diastolic elastance curve, which can be determined by a family of pressure-volume loops at variable loading or by the fitting of end-systolic and end-diastolic P-V relationships on a single PV loop (86). The fitting consists in a non-linear exponential curve through the origin and end-systolic and end-diastolic P-V coordinates with the formula $P = \alpha (e^{V\beta} - 1)$, where α is a curve fitting constant and β a diastolic stiffness constant (86).

There are data but from yet a limited number of patients suggesting that the diastolic stiffness constant β independently predicts of outcome in PAH (118,119). This will require confirmation. The biology of diastolic adaptation to afterload in PAH is being explored (118). Diastolic stiffness simply quantified by a simple end-diastolic P-V coordinate retains the prediction capability of more complex β calculation (119). Both systolic and diastolic stiffness increase in PAH and decrease along with decreased RV volumes when PVR decreases sufficiently by the effect of targeted therapies (120).

Clinical relevance. RV diastolic and systolic elastances are both increased in PAH. The biology of diastolic dysfunction and its prognostic relevance in PAH are being explored.

Ventricular interactions

Right ventricular function has also to be understood in the context of its direct and indirect interactions with LV function (84,121). A negative diastolic ventricular interaction (ie altered diastolic function of one ventricle by changed diastolic function of the other) occurs in PAH because of ventricular competition for space. This alters LV filling and may eventually be associated with a depression of LV systolic function, atrophic remodeling of the LV and impairment of cardiac output (121). A negative systolic ventricular interaction may add to the effects of diastolic interaction as a consequence of decreased LV contractility (121). It has been shown experimentally that aortic constriction to enhance LV contraction by homeometric adaptation, markedly improves RV function in animals with PA banding (122). In intact experimental animal hearts, 20-40 % of RV systolic pressure results from LV contraction and 4 to 10 % of LV systolic pressure results from RV contraction (123).

Systolic ventricular interaction is essentially explained by a direct mechanical entrainment effect as both ventricles have the septum in common and are furthermore encircled by common fibres (84,121). An added factor is decreased coronary perfusion pressure in case of systemic hypotension, which may render the RV relatively ischemic with ensuing uncoupling from the pulmonary circulation, but with increased sensitivity to LV contraction (124). Increased RV filling pressures and excessive decrease in blood pressure combine to cause RV ischemia and decreased contractility (125).

Ventricular interactions play an important role in acute right heart failure, like in pulmonary embolism, or right heart failure in end-stage PAH. Correcting negative diastolic and systolic ventricular interactions is an essential part of treatment in these patients as they are hospitalized in critical care settings (126).

An additional cause of negative ventricular interaction disclosed by imaging studies is regional and inter-ventricular asynchrony with post-systolic contraction or “shortening”, which has been shown to develop in parallel to increased pulmonary artery pressures and contributes to altered RV systolic function and LV under-filling (127). Right ventricular regional asynchrony (loss of inter-ventricular synchrony of contraction) and dyssynchrony (loss of regional intra-ventricular synchrony of contraction) can now be identified and quantified by speckle tracking echocardiography (128,129). Dyssynchrony of RV contraction may already be present in early stage or borderline PH (129). Dyssynchrony of RV contraction in advanced PAH is associated with worse functional state and decreased survival (128).

Clinical relevance. Negative diastolic and systolic interactions are major determinants of RV-arterial coupling in right heart failure. Loss of intra- and inter-ventricular synchrony of contraction contribute to altered RV-arterial coupling and are associated with a shortened survival rate.

Stressing the right ventricle

Stressing the RV to measure its “contractile reserve” may disclose borderline or latent functional uncoupling from the pulmonary circulation (95).

Exercise-induced increase in systolic RV pressure estimated from the maximum velocity of tricuspid regurgitation by Doppler echocardiography has been shown to be a strong predictor of survival in patients with PAH or CTEPH (130). However, a single estimate of pressure does not adequately describe RV-PA coupling (94). Another approach is to assess exercise-induced increase in cardiac output (131). Since the Ees/Ea ratio and EF are related, and are either maintained or increased during exercise (93,94,132), exercise stress EF should be a valid challenge to detect early or pending RV failure. This approach was historically implemented using radionuclide angiography to identify RV dysfunction in COPD (133). However, MRI measurements of RV volumes during exercise are technically challenging and not generally available.

The possibility to replace the stress of exercise by low-dose dobutamine and measure the RV contractile response by a tricuspid annular plane systolic excursion (TAPSE) or tricuspid annulus S wave, is being considered (134). There is experimental work showing that dobutamine-induced increase in these indices of RV systolic function reflects the resting state of RV-arterial coupling (135).

A measure of VO_2max can be considered as an indirect RV stress test as the main determinant of aerobic capacity in PAH is maximum cardiac output as determined by RV-PA coupling (134). However, VO_2max in PAH like in heart failure is also influenced by extra-cardiac factors including neuro-humoral changes and matching of muscle convectional and diffusional O_2 transport mechanisms (15).

Clinical relevance. Dynamic testing of the RV to assess its contractile reserve might disclose latent or borderline uncoupling of the RV from the pulmonary circulation. The optimal method to stress the RV has not yet been determined.

Perspective

Since RV function is the major determinant of symptoms and outcome in PAH, simple non-invasive methods for its evaluation are being developed. One of those is the ratio of TAPSE (to estimate Ees) to sPAP (to estimate afterload) which are easily measured during a standard Doppler echocardiography (136). The TAPSE/sPAP ratio has been validated against invasive measurements of the Ees/Ea ratio (137,138) and shown to be of prognostic relevance in heart failure (136,137) and in PAH (139).

However, the physiologic basis of PAH goes beyond RV dysfunction. Management of PAH patients requires a thorough understanding of the basic physiology of lung mechanics, pulmonary gas exchange, pulmonary vascular function, and the coupling of the right heart to the pulmonary circulation. This knowledge is essential not only for the correct evaluation of therapeutic interventions, but also for the assessment of the clinical relevance of the rapidly growing understanding of the cellular and molecular biology of this disease.

Legends of the figures

Fig 1. Central illustration showing progressive remodeling of the pulmonary circulation (upper row) and of the right heart (lower row) with in between typical measurements of pulmonary ventilation and gas exchange, steady-flow and pulsatile-flow

hemodynamics and right ventricular (RV) function in pulmonary arterial hypertension (PAH). Vascular remodeling was defined by microscopic views from normal (left) to medial hypertrophy, thickening of the 3 layers of vascular wall and plexiform lesions (upper right). Cardiac remodeling was defined by 2-dimensional 4-chamber echocardiographic views of right atrial and ventricular dilatation and septal shift ventricular dilation respectively. Arrows indicate hypothetical disease progression with increasingly dilating RV and right atrial dimensions. In between are measurements in typical patients with severe idiopathic PAH: (a) quasi-normal distribution of ventilation/perfusion relationships, arterial partial pressure of oxygen (PaO_2) and dead space (V_D/V_T) but with increased alveolar ventilation, (b) increased ventilation (V_E) as a function of carbon dioxide output (VCO_2) during exercise, (c) Poon adjusted mean pulmonary artery pressure (Ppa) as a function of cardiac output (Q) increased by either exercise or dobutamine showing a decreased slope and increased extrapolated pressure intercept ($n=7$ patients) (d) pulmonary artery pressure decay curve after single arterial occlusion showing increased inflection point (e) RV pressure curve with increased pulse pressure, late systolic peaking and increased augmentation index, (f) Doppler RV outflow tract flow with shortened acceleration time and mid-systolic deceleration, (g) pulmonary artery impedance spectrum, or pressure/flow and phase as a function of frequency, showing an upward shift with increased 0 Hz and high-frequency impedances and low frequency negative phase angle, with increased characteristic impedance (Z_c) in either frequency- or time-domain (h) RV pressure-volume loops with increased end-systolic elastance (E_{es}) in the presence of increased arterial elastance (E_a), but decreased E_{es}/E_a and increased dimensions as compared to control measurements. Histologic views and echocardiographic images are courtesies from Drs A Peacock and M D'Alto. Panel(c) is from ref 34, with permission.

Fig 2. A. Distribution of arterial blood gases in 243 patients with idiopathic pulmonary arterial hypertension (PAH) Most values are decreased, with 51 % of $\text{PaO}_2 < 70$ mmHg, and 45 % of $\text{PaCO}_2 < 33$ mmHg taken as lower limits of normal (shaded columns).

B. Alveolar ventilation (V_A)/perfusion (Q) distributions in a patient with PAH before and after a normalization procedure correcting for increased V_A and decreased Q , and in a middle-aged control (from left to right). In the IPAH patient, V_A/Q distributions are shifted to higher V_A/Q , but V_A and Q modes remain matched. Both the PAH patient and the healthy control have a small amount of perfusion to low V_A/Q . The IPAH patient has also a small amount of shunt ($V_A/Q=0$) which was increased with correction for high V_A and low Q .

C. Ventilation (V_E) as a function of carbon dioxide (CO_2) output adjusted for inter-individual variability in 12 PAH patients and in 10 controls. V_E was increased at rest and more so at exercise.

D. Plotting V_E/V_{CO_2} as a function of arterial PCO_2 (PaCO_2) at the anaerobic threshold during exercise (AT) uncovers increased physiologic dead space (V_D/V_T) and chemo-sensitivity as causes of increased ventilation in PAH and chronic obstructive pulmonary disease (COPD), only increased chemosensitivity in in this group of heart failure patients. The arterial to end-tidal PO_2 gradient increased above 5 mmHg (the upper limit of normal) in PAH and in COPD. From refs 16 and 25, with permissions.

Fig 3. Mean pulmonary artery pressure (mPAP) as a function of cardiac output increased by exercise in 7 patients before and after 6 weeks of prostacyclin therapy, which was associated with an improvement in the 6-minute walk distance by an average of 80 m. Prostacyclin did not affect resting pulmonary vascular resistance (PVR) but decreased exercise PVR and the slope of mPAP as a function of cardiac output (after ref 36)

Fig 4. Modeled mean pulmonary arterial pressure (mPAP)-cardiac output relationships during dynamic exercise with progressively increased distensibility coefficients α from 0 to 10 % of vessel diameter per mmHg trans-mural pressure. Normal values for α are between 1 and 2 %/mmHg. Pulmonary vascular distension markedly decreases mPAP at high levels of cardiac output. (from ref 40 with permission).

Fig 5. Pulmonary vascular resistance (PVR) as a function of hematocrit (HCT). Iso-PVR curves allow for a prediction of PVR "normalized" for a hematocrit at 45 % in anemic or polycythemic patients, at normal or increased pulmonary artery wedge pressures (PAWP) vs cardiac output (CO) relationships. Measured PVR in anemic or polycythemic patients at increased or decreased HCT by blood transfusion or hemodilution are shown by arrows in upper window, with mean responses (thick arrows) showing conformance to predicted changes (From ref 44, with permission).

Fig 6. Model predictions of % pulmonary vascular obstruction by linearized adjustments of mean pulmonary artery pressure (PAP) as a function of cardiac output. A mPAP of 25 mmHg or 20 mmHg at a cardiac output of 5 L/min correspond to 50 % and 25 % obstruction respectively. After ref 45, with permission.

Fig 7. A. Pulmonary vascular impedance spectrum expressed as pulmonary artery pressure-flow ratio ("modulus") as a function of frequency. Discussion of relevant points: see indications on figure and comments in the text B. Pulmonary artery pressure (PAP) curve in severe PH showing an increased augmentation index, or gradient between systolic PAP (sPAP) and inflection of the upstroke pressure (Pi) divided by PA pulse pressure (PAPP). C. Doppler pulmonary artery flow waves in a normal subject (left panel) and in patients with

severe PH (right and lower panels). PH was associated with a decreased acceleration time (AT) corrected for ejection time (ET) and mid-systolic deceleration of flow (notching) or late systolic deceleration of flow. TN: time to notching, NET: time from notching to end-ejection.

D. Hyperbolic relationship between PA compliance (PAC) and pulmonary vascular resistance (PVR) in patients with either a high or a normal pulmonary artery wedge pressure (PAWP). A high PAWP shifts the relationship to the left with decreased RC-time. From refs 53, 64 and 77 with permissions.

Fig 8. A. Multiple- and single-beat methods for calculating right ventricular (RV)-arterial coupling. In both methods, arterial elastance (E_a) is calculated from the ratio of end-systolic pressure (ESP) to stroke volume (SV). End-systolic elastance (E_{es}) as an approximation of maximum elastance is estimated by the ratio of ESP to end systolic volume (ESV). In the multiple-beat method, E_{es} is defined by a tangent to a family of loops determined at decreasing venous return. In the single-beat method, a maximum pressure (P_{max}) is estimated from the non-linear extrapolation of the early systolic and diastolic portions of the RV pressure curve, and E_{es} defined by a straight line drawn from P_{max} tangent to RV pressure to relative change in volume relationship. Diastolic stiffness β is calculated by fitting the non-linear exponential, $P = \alpha (e^{\beta V} - 1)$, to pressure and volume measured at the beginning and end of diastole (BDP: beginning diastolic pressure, EDP: end-diastolic pressure, ED end-diastolic volume; ESV: end-systolic volume). B. Evolution from normal to progressively more severe PAH (T1 to T3) of RV E_{es}/E_a , ejection fraction (EF) end-diastolic elastance (E_{ed}) and RV EDV corrected for body surface area (BSA). The RV dilates with EDV above limits of normal when E_{es}/E_a and EF approximate 0.8 and 0.35 respectively. Increased E_{ed} mirrors decreased E_{es}/E_a . C. RV PV loops from patients without PH (a, upper left) to severe PH (d, lower right) showing progressive change in shape with shift to late

systolic peaking of pressure and "notching", while ESP becomes higher than pressure at the onset of ejection (BSP). After refs 86, 96, and 99 with permission.

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Fig 1. Central illustration showing progressive remodeling of the pulmonary circulation (upper row) and of the right heart (lower row) with in between typical measurements of pulmonary ventilation and gas exchange, steady-flow and pulsatile-flow hemodynamics and right ventricular (RV) function in pulmonary arterial hypertension (PAH). Vascular remodeling was defined by microscopic views from normal (left) to medial hypertrophy, thickening of the 3 layers of vascular wall and plexiform lesions (upper right). Cardiac remodeling was defined by 2-dimensional 4-chamber echocardiographic views of right atrial and ventricular dilatation and septal shift ventricular dilatation respectively. Arrows indicate hypothetical disease progression with increasingly dilating RV and right atrial dimensions. In between are measurements in typical patients with severe idiopathic PAH: (a) quasi-normal distribution of ventilation/perfusion relationships, arterial partial pressure of oxygen (PaO₂) and dead space (VD/VT) but with increased alveolar ventilation, (b) increased ventilation (VE) as a function of carbon dioxide output (VCO₂) during exercise, (c) Poon adjusted mean pulmonary artery pressure (Ppa) as a function of cardiac output (Q) increased by either exercise or dobutamine showing a decreased slope and increased extrapolated pressure intercept (n=7 patients) (d) pulmonary artery pressure decay curve after single arterial occlusion showing increased inflection point (e) RV pressure curve with increased pulse pressure, late systolic peaking and increased augmentation index, (f) Doppler RV outflow tract flow with shortened acceleration time and mid-systolic deceleration, (g) pulmonary artery impedance spectrum, or pressure/flow and phase as a function of frequency, showing an

upward shift with increased 0 Hz and high-frequency impedances and low frequency negative phase angle, with increased characteristic impedance (Z_c) in either frequency- or time-domain (h) RV pressure-volume loops with increased end-systolic elastance (E_{es}) in the presence of increased arterial elastance (E_a), but decreased E_{es}/E_a and increased dimensions as compared to control measurements . Histologic views and echocardiographic images are courtesies from Drs A Peacock and M D'Alto. Panel(c) is from ref 34, with permission.

Fig 2. A. Distribution of arterial blood gases in 243 patients with idiopathic pulmonary arterial hypertension (PAH) Most values are decreased, with 51 % of PaO₂ < 70 mmHg, and 45 % of PaCO₂ < 33 mmHg taken as lower limits of normal (shaded columns).

B. Alveolar ventilation (VA)/perfusion (Q) distributions in a patient with PAH before and after a normalization procedure correcting for increased VA and decreased Q, and in a middle-aged control (from left to right). In the IPAH patient, VA/Q distributions are shifted to higher VA/Q, but VA and Q modes remain matched. Both the IPAH patient and the healthy control have a small amount of perfusion to low VA/Q. The IPAH patient has also a small amount of shunt (VA/Q=0) which was increased with correction for high VA and low Q.

C. Ventilation (VE) as a function of carbon dioxide (CO₂) output adjusted for inter-individual variability in 12 PAH patients and in 10 controls. VE was increased at rest and more so at exercise.

D. Plotting VE/VCO₂ as a function of arterial PCO₂ (PaCO₂) at the anaerobic threshold during exercise (AT) uncovers increased physiologic dead space (VD/VT) and chemo-sensitivity as causes of increased ventilation in PAH and chronic obstructive pulmonary disease (COPD), only increased chemosensitivity in this group of heart failure patients. The arterial to end-tidal PO₂ gradient increased above 5 mmHg (the upper limit of normal) in PAH and in COPD. From refs 16 and 25, with permissions.

Fig 3. Mean pulmonary artery pressure (mPAP) as a function of cardiac output increased by exercise in 7 patients before and after 6 weeks of prostacyclin therapy, which was associated with an improvement in the 6-minute walk distance by an average of 80 m. Prostacyclin did not affect resting pulmonary vascular resistance (PVR) but decreased exercise PVR and the slope of mPAP as a function of cardiac output (after ref 36)

Fig 4. Modeled mean pulmonary arterial pressure (mPAP)-cardiac output relationships during dynamic exercise with progressively increased distensibility coefficients α from 0 to 10 % of vessel diameter per mmHg trans-mural pressure. Normal values for α are between 1 and 2 %/mmHg. Pulmonary vascular distension markedly decreases mPAP at high levels of cardiac output. (from ref 40 with permission).

Fig 5. Pulmonary vascular resistance (PVR) as a function of hematocrit (HCT). Iso-PVR curves allow for a prediction of PVR "normalized" for a hematocrit at 45 % in anemic or polycythemic patients, at normal or increased pulmonary artery wedge pressures (PAWP) vs cardiac output (CO) relationships. Measured PVR in anemic or polycythemic patients at increased or decreased HCT by blood transfusion or hemodilution are shown by arrows in upper window, with mean responses (thick arrows) showing conformance to predicted changes (From ref 44, with permission).

Fig 6. Model predictions of % pulmonary vascular obstruction by linearized adjustments of mean pulmonary artery pressure (PAP) as a function of cardiac output. A mPAP of 25 mmHg or 20 mmHg at a cardiac output of 5 L/min correspond to 50 % and 25 % obstruction respectively. After ref 45, with permission.

Fig 7. A. Pulmonary vascular impedance spectrum expressed as pulmonary artery pressure-flow ratio ("modulus") as a function of frequency. Discussion of relevant points: see indications on figure and comments in the text B. Pulmonary artery pressure (PAP) curve in severe PH showing an increased augmentation index, or gradient between systolic PAP (sPAP) and inflection of the upstroke pressure (Pi) divided by PA pulse pressure (PAPP). C. Doppler pulmonary artery flow waves in a normal subject (left panel) and in patients with severe PH (right and lower panels). PH was associated with a decreased acceleration time (AT) corrected for ejection time (ET) and mid-systolic deceleration of flow (notching) or late systolic deceleration of flow. TN: time to notching, NET: time from notching to end-ejection. D. Hyperbolic relationship between PA compliance (PAC) and pulmonary vascular resistance (PVR) in patients with either a high or a normal pulmonary artery wedge pressure (PAWP). A high PAWP shifts the relationship to the left with decreased RC-time. From refs 53, 64 and 77 with permissions.

Fig 8. A. Multiple- and single-beat methods for calculating right ventricular (RV)-arterial coupling In both methods, arterial elastance (E_a) is calculated from the ratio of end-systolic pressure (ESP) to stroke volume (SV). End-systolic elastance (E_{es}) as an approximation of maximum elastance is estimated by the ratio of ESP to end systolic volume (ESV). In the multiple-beat method, E_{es} is defined by a tangent to a family of loops determined at decreasing venous return. In the single-beat method, a maximum pressure (P_{max}) is estimated from the non-linear extrapolation of the early systolic and diastolic portions of the RV pressure curve, and E_{es} defined by a straight line drawn from P_{max} tangent to RV pressure to relative change in volume relationship. Diastolic stiffness β is calculated by fitting the non-linear exponential, $P = \alpha(e^{\beta V} - 1)$, to pressure and volume measured at the beginning and end of diastole (BDP: beginning diastolic pressure, EDP: end-diastolic pressure, ED end-diastolic volume; ESV: end-systolic volume). B. Evolution from normal to progressively more severe PAH (T1 to T3) of RV E_{es}/E_a , ejection fraction (EF) end-diastolic elastance (E_{ed}) and RV EDV corrected for body surface area (BSA). The RV dilates with EDV above limits of normal when E_{es}/E_a and EF approximate 0.8 and 0.35 respectively. Increased E_{ed} mirrors decreased E_{es}/E_a . C. RV PV loops from patients without PH (a, upper left) to severe PH (d, lower right) showing progressive change

in shape with shift to late systolic peaking of pressure and "notching", while ESP becomes higher than pressure at the onset of ejection (BSP). After refs 86, 96, and 99 with permission.