Invasive hemodynamic assessment of pulmonary hypertension

PAGNAMENTA, Alberto

Abstract

The diagnosis of pulmonary hypertension requires an invasive confirmation of an elevated mean pulmonary artery pressure during a right heart catheterization. The present thesis reviews the invasive hemodynamic approaches to assess the functional state of the pulmonary circulation and its impact on right ventricular function in pulmonary vascular diseases. Pulmonary vascular resistance is better characterized by multi-point pressure/flow measurements. The occlusion analysis of the pulmonary artery pressure decay curve permits to locate the site of increased resistance. Pulmonary vascular resistance permits to assess the steady component of the pulmonary circulation, whereas the pulsatile component can be better appreciated by pulmonary vascular impedance. Determination of ventriculo-arterial coupling permits to assess the impact of an elevated afterload on right ventricular function, which ultimately determines symptoms and prognosis of patients with pulmonary hypertension.

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"Invasive hemodynamic assessment of pulmonary hypertension"

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Alberto PAGNAMENTA

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List of Abbreviations and Acronyms

CO: cardiac output
DPG: diastolic pressure gradient
Ea: arterial elastance
Ees: ventricular elastance
LAP: left atrial pressure
LHD: left heart disease
LHF: left heart failure
LV: left ventricle
LVEDP: left ventricular end-diastolic pressure
PAC: pulmonary artery catheter
PAH: pulmonary arterial hypertension
PAOP: pulmonary arterial occluded pressure
PAPd: diastolic pulmonary arterial pressure
PAPm: mean pulmonary arterial pressure
PAPs: systolic pulmonary arterial pressure
PAWP: pulmonary arterial wedged pressure
PCP: effective pulmonary capillary pressure
PH: pulmonary hypertension
PVR: pulmonary vascular resistance
PVZ: pulmonary vascular impedance
Q: pulmonary blood flow
RAP: right atrial pressure
RC-time: resistance compliance time
RHC: right heart catheterization
RHF: right heart failure
RV: right ventricle
TPG: transpulmonary pressure gradient
ABSTRACT

Pulmonary hypertension is a frequently encountered condition in daily clinical practice. Nowadays pulmonary hypertension is classified into five well-defined distinct categories. Each category contains multiple clinical conditions according to their similar pathophysiological characteristics and similar treatment options. The diagnosis of pulmonary hypertension requires an invasive confirmation of an elevated mean pulmonary artery pressure during a right heart catheterization. The diagnostic approach to pulmonary hypertension is actually supported by a proposed algorithm, which permits to identify the underlying cause.

The present thesis reviews the invasive hemodynamic approaches to assess the functional state of the pulmonary circulation and its impact on right ventricular function in pulmonary vascular diseases. Pulmonary vascular resistance is better characterized by multi-point pressure/flow measurements instead of a single-point determination. Pulmonary vascular resistance provides information in particular on the peripheral arterial function and consequently it could be useful for early disease identification as well as for the evaluation of treatment response. The occlusion analysis of the pulmonary artery pressure decay curve after balloon’s inflation at the tip of pulmonary artery catheter permits to locate the site of increased resistance and it could be helpful in differentiating proximal vasculopathy form distal vascular involvement especially in chronic thrombo-embolic pulmonary hypertension. Pulmonary vascular resistance permits to assess the steady component of the pulmonary circulation, whereas the pulsatile component can be better appreciated by pulmonary vascular impedance. Alternatively and easier to obtain resistance-compliance relationship could be used. Determination of ventriculo-arterial coupling permits to assess the impact of an elevated afterload on right ventricular function, which ultimately determines symptoms and prognosis of patients with pulmonary hypertension. The clinical usefulness of combining different invasive hemodynamic approaches is still uncertain and remains to be determined.
1. **INTRODUCTION**

1.1 General remarks

The exact prevalence of pulmonary hypertension (PH) in the general population remains unknown, however PH probably accounts for the third most common cardiovascular condition after coronary artery disease and systemic hypertension. Schistosomiasis-associated pulmonary arterial hypertension is potentially the leading cause of PH worldwide [1]. The most common cause of PH in Western countries is realistically left heart failure (LHF) including both LHF with reduced and with preserved ejection fraction [2, 3]. Depending on the selected cohort of patients and the definition of PH used (invasive versus estimation by echocardiography with different cutoff values), up to 80% of patients with LHF may have PH [4, 5], which if present negatively affects patient’s outcome [4, 6]. Chronic lung diseases are considered the second most frequent etiology of PH [7]. The severity of chronic obstructive pulmonary disease (COPD) determines the likelihood of developing PH, which if present exerts a negative impact on survival [8]. Conversely, PH severity is only poorly correlated with lung function impairment in patients with idiopathic pulmonary fibrosis (IPF) [9]. On the other hand the syndrome of combined pulmonary fibrosis and emphysema (CPFE) represents a separate entity especially predisposed to develop PH (estimates range between 30% and 50%) [10]. At the 5th World Symposium on PH (WSPH) held in 2013 it was suggested for PH due to lung diseases to abandon the term “out of proportion” PH, which indicated that the severity of PH was higher than expected on the basis of lung parenchymal impairment [7]. For COPD, IPF and CPFE the following PH definitions have been proposed: COPD/IPF/CPFE without PH (mean pulmonary artery pressure (PAPm) < 25 mm Hg), with PH (PAPm ≥ 25 mm Hg) and with severe PH (PAPm ≥ 35 or PAPm ≥ 25 mm Hg with low cardiac index: < 2.0 l/min/m²) [7]. The cumulative incidence of chronic thromboembolic pulmonary hypertension (CTEPH) has been estimated to lie between 0.1% to 9.1% after a symptomatic event of pulmonary embolism (PE), but a significant number of subjects develops CTEPH without an acute PE [11]. Recent data from the UK suggested that CTEPH represents one of the most frequent causes of precapillary PH [12]. National registries are helpful in providing accurate epidemiologic data on pulmonary arterial hypertension (PAH) [13]. PAH remains a rare disease with an estimated prevalence of about 5-15 cases per one million adults and over the last decades a changed PAH phenotype was observed (age, sex, co-morbidities and survival) [14, 15]. Paradoxically the less frequent forms of PH, PAH are the ones that have been more extensively investigated, whereas fewer data are available on the other etiologies of PH. There are currently no specific and approved treatment options for PH due to left heart diseases or chronic lung diseases in
addition to the optimal management of the underlying cause [2, 7]. Several clinical trials with PAH-approved therapies were undertaken in patients with PH-LHF with disappointing results [2]. Phosphodiesterase 5 inhibitors seem to be encouraging compounds in the management of PH-LHF, but large-scale, multicenter clinical trials in well-defined populations are needed. At the 5th WSPH specific recommendations regarding the conduction of randomized controlled trials (RCTs) in patients with PH-LHD have been proposed (e.g. patient’s selection, invasive confirmation of PH, endpoints’ selection) [2]. Long-term RCTs focusing only on patients with severe PH due to lung diseases are necessary but are still pending [7]. In selected patients CTEPH is a potentially curable disease by pulmonary endarterectomy (PEA) with a very low peri-interventional mortality in experienced centres [16]. Riociguat, an oral soluble guanylate cyclase stimulator significantly improved primary and secondary endpoints in patients with inoperable CTEPH or persistent PH after PEA in a recently published multicenter RCT [17]. Nowadays medical treatment of PAH is targeted on the three well-known pathways involved in the development of PAH: the endothelin, the nitric oxide and the prostacyclin pathways [18]. Despite recent and important advances in the management of PAH [18] this pathology remains a devastating disease with an unacceptable high mortality [15, 19].

1.2 Definition and diagnosis of pulmonary hypertension

PH is defined by an invasive resting PAPm ≥ 25 mm Hg obtained during a right heart catheterization (RHC) [3]. Normal resting PAPm is approximately 14 ± 3 mm Hg (mean ± SD) with an upper limit of 20 mm Hg [20]. Given the unclear prognostic and treatment implications the term “borderline PH” for subjects with a resting PAPm between 21 and 24 mm Hg has been abandoned [21]. However these subjects should be carefully followed, especially those with connective tissue disease (CTD), family members of patients with idiopathic pulmonary arterial hypertension (IPAH) and heritable PAH given the possible future development of manifest PAH [21]. Before the 4th WSPH in 2008, PH was also defined by a PAPm > 30 mm Hg at exercise [22]. This additional criterion was thereafter eliminated and no more introduced [21, 23] because exercise has not been clearly specified and standardized, and exercise PAPm varies with age rendering impossible to find a clear cut-off value for exercise-induced PH [20]. However, recently this is being re-evaluated and the following agreement on diagnosis of exercise-induced PH emerges: PAPm > 30 mmHg at exercise with a cardiac output (CO) < 10 L/min, or a PAPm-CO relationship > 3 mmHg/L/min, or a total PVR (PAPm/CO) at maximum exercise > 3 Wood units (WU) [24]. Pulmonary vascular resistance (PVR) is not part of the general definition of PH, but at the 5th WSPH the working group members proposed
to include PVR in the hemodynamic definition of PAH as followed: PAH is defined by \( PAPm \geq 25 \) mm Hg, pulmonary arterial occluded pressure (PAOP) \( \leq 15 \) mm Hg and PVR \( > 3 \) WU [21]. A fluid challenge during RHC may be an attractive strategy to unmask patients with heart failure and preserved ejection fraction (HFpEF) but normal PAOP at baseline. Unfortunately the intrinsic diagnostic characteristics of this manoeuvre (positive and negative likelihood ratios) have not been rigorously evaluated. Recently Robbins et al. found in a retrospective cohort of patients primarily classified of having PAH (n = 207) that rapid intra-venous fluid challenge (500 ml of 0.9% NaCl over 5-10 minutes) increased PAOP \( > 15 \) mm Hg in 46 patients (22.2%) unmasking occult pulmonary venous hypertension. Unfortunately concomitant assessment of left ventricular end-diastolic pressure (LVEDP) was performed only in a minority of patients [25]. This interesting finding with direct consequences for PH classification and for patients selection in clinical PAH trials, requires additional validation. The working group members at 5th WSPH made further proposals for the proper use of RHC especially regarding the standardization of PAOP measurements: e.g. values determination at end-expiration, zero levelling of pressure transducer at the midthoracic line in supine position and accuracy of PAOP determination in differentiating pre- from post-capillary PH (see later for details) [21]. Unfortunately even nowadays the diagnosis of PH is often delayed because the presenting symptoms and signs are typically nonspecific [26]. Clinical suspicion of PH should be considered in any patient with exertional dyspnea, fatigue and impaired exercise tolerance of unexplained etiology, syncope and/or signs of right ventricular (RV) dysfunction. Transthoracic echocardiography represents the first and most important noninvasive screening tool to estimate the likelihood of PH, but for definitive diagnosis RHC remains compulsory. An extensive diagnostic workup is required in order to identify the underlying cause. PAH is diagnosed after exclusion of other causes of PH and in 2009 the European guidelines proposed a diagnostic algorithm [27], which was slightly modified and simplified and thereafter adopted at the 5th WSPH [21] as shown in Figure 1.
Figure 1. Diagnostic approach to Pulmonary Hypertension.

BGA = blood gas analysis; CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; HR-CT = high resolution CT; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PAPm = mean pulmonary artery pressure; PCH = pulmonary capillary hemangiomatosis; PEA = pulmonary endarterectomy; PFT = pulmonary function testing; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; RHC = right heart catheterization.
heart catheter; RV = right ventricle; V/Q: ventilation/perfusion; x-ray = chest radiograph. Form Hoeper MM, et al\textsuperscript{21} with permission.

1.3 Clinical classification of pulmonary hypertension

The original WHO clinical classification of PH proposed in 1973 was simple based on only two categories: primary PH (PPH) and secondary PH \textsuperscript{28}. Twenty-five years later at the second WSPH held in Evian, France in 1998 a remarkable modification of the first classification was adopted. Five well-defined major categories of PH were created based on similar underlying pathophysiologic mechanisms: 1) PAH; 2) PH due to left heart diseases; 3) PH due to chronic lung diseases and/or hypoxia; 4) chronic thromboembolic pulmonary hypertension (CTEPH); and 5) PH by unclear multifactorial mechanisms \textsuperscript{29}. This new classification permitted thereafter to conduct in clear-defined patient populations well-designed RCTs, which have led to the approval of eight different drugs for the treatment of PAH. At the 3\textsuperscript{rd} WSPH held in Venice, Italy in 2003 the previously adopted clinical classification of PH was slightly modified with the following major changes: the term PPH was abandoned; familial PAH was adopted in the presence of a family history of PAH; associated PAH in the presence of identifiable cause, such a CTD or portal hypertension and so on; veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) were moved from two categories into a single PAH subcategory \textsuperscript{30}. During the 4\textsuperscript{th} WSPH held in Dana Point, California in 2008 the general disposition of the Evian-Venice classification was maintained, but some changes were carried out to accurate reflect new information published in the last years. Major modifications concerned PAH group (Group 1). Familial PAH was abandoned in favour of heritable PAH with subcategories according to germline mutations. The categorization of drug- and toxin-induced PAH and the corresponding probability of developing PAH have been implemented. Schistosomiasis and chronic haemolytic anemia appeared as separated entities. PVOD and PCH appeared in a separate group but very close to Group 1 in accordance with similarities in pathologic characteristics and clinical presentation \textsuperscript{31}. The last updated clinical classification of PH proposed during the 5\textsuperscript{th} WSPH held in Nice, France in 2013 maintained the general architecture of previous classifications. Following modifications were adopted: persistent PH of the newborn was withdrawn from Group 1 given the relevant differences with other PAH subgroups; chronic haemolytic anemia-associated PH moved form PAH-Group to Group 5; congenital/acquired left heart inflow or outflow obstructive lesions and congenital cardiomyopathies have been added to PH due to left heart disease Group, creating a common classification for both paediatric and adult patients; segmental PH was added to Group 5. \textsuperscript{32} The updated 5\textsuperscript{th} WSPH Nice 2013 classification of PH is presented below.
1. Pulmonary arterial hypertension (PAH)
   1.1 Idiopathic PAH
   1.2 Heritable PAH
      1.2.1 BMPR2
      1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
      1.2.3 Unknown
   1.3 Drug and toxin induced
   1.4 Associated with:
      1.4.1 Connective tissue disease
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart diseases
      1.4.5 Schistosomiasis

1’ Pulmonary veno-occlusive diseases and/or pulmonary capillary hemangiomatosis
1’’ Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   2.1 Left ventricular systolic dysfunction
   2.2 Left ventricular diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen-storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
1.3 References

4. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012; 126; 975-990
11. Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. Circulation 2014; 130: 508-518


2. PULMONARY VASCULAR PRESSURE-FLOW RELATIONSHIP

2.1. Limits of single-point pressure-flow measurement of pulmonary vascular resistance

The pressure drop through the pulmonary circulation determines pulmonary blood flow (Q). The inflow pressure of the pulmonary circulation is the mean pulmonary artery pressure (PAPm) and the outflow pressure is the left atrial pressure (LAP). Pulmonary vascular pressure and flow are typically measured in daily clinical practice with a fluid-filled thermodilution pulmonary artery catheter (PAC) [1, 2]. The PAC does not allow to directly measure LAP, but this latter can be derived from a “wedged” or an occluded pulmonary artery pressure (PAWP or PAOP) after balloon’s inflation at the tip of PAC. The estimation of LAP by PAOP measurement was previously believed to be accurate [3]. This was confirmed in a recently large-scale clinical study (n = 11’523) with sequential measurements of PAOP and LAP estimated by left ventricular end-diastolic pressure (LVEDP) during left heart catheterization (LHC), which found an excellent accuracy but a lack of precision [4]. Moreover, among 4’320 patients with PH, roughly half of those with PAOP ≤ 15 mmHg had LVEDP > 15 mmHg. This finding could suggest that PAOP frequently underestimates LAP, but invasive diagnostic criteria for left heart failure with preserved ejection fraction require a PAOP > 12 mm Hg or a LVEDP > 16 mm Hg [5]. However, routine left heart catheterization (LHC) is currently not recommended as a part of PH evaluation in order to differentiate between pre- and post-capillary PH [6]. In patients with echocardiographic signs of left ventricular (LV) dysfunction (systolic and/or diastolic) or at risk for coronary heart disease or heart failure with preserved ejection fraction LHC should be carefully considered [6]. LeVarge et al. reported that 29% of patients (n = 93) with phenotype of pre-capillary PH without clinical or echocardiographic evidence of LV dysfunction had an end-expiratory PAOP > 15 mmHg, especially obese and patients with obstructive pulmonary disease, likely as a consequence of a spontaneous positive end-expiratory intrathoracic pressure [7]. In those situations the clinical utility of averaging PAOP through the respiratory cycle remains to be determined. The frequency response of fluid-filled PAC has been generally assumed to be insufficient for accurate instantaneous pressure measurements. To assess accuracy and precision of fluid-filled PAC in pressure determination we compared in an intact animal model under different conditions fluid-filled PAC pressure data with PAP measurements obtained with the gold standard method (high-fidelity micromanometer-tipped catheter) [8]. Using correlation and Bland-Altman agreement analyses [9] PAPm and pulse pressure (PP = PAPs-PAPd) were significantly correlated ($r^2$ = 0.98, and 0.85 respectively, both $p < 0.001$) with little bias between the methods (bias: -0.59; 95%-limits of agreement: 2.83 for PAPm and bias: 0.4; 95%-limits of agreement: 8.2 for PP). These
results suggest that realistic pulmonary vascular pressures can be derived from bedside fluid-filled catheter. Mean Q is measured with a fluid-filled PAC by the thermodilution technique, which requires several cardiac cycles using the Stewart-Hamilton equation [2]. Only in certain situations such as severe tricuspid regurgitation, low output syndrome or intracardiac shunts this technique could provide imprecise estimations of cardiac output (CO) as compared the with the direct Fick method [2]. In order to cope with the intrinsic random errors of fluid-filled PAC pressure and flow determinations it is now clearly recommended to take several measurements and averaging them [10]. In accordance with the Ohm’s electrical law pulmonary vascular resistance (PVR) can be reasonably calculated as the ratio of pressure to Q as followed

\[ PVR = \frac{(PAPm - LAP)}{Q} \]

This equation assumes a linear relationship between pressure and flow and an extrapolated pressure intercepts at zero Q crossing the origin. When these assumptions are satisfied PVR remains constant at increasing Q (Figure 1). This happens in West’s lung zone III by healthy well-oxygenated lungs. However, in several respiratory and heart diseases as well as in hypoxic pulmonary vasoconstriction the outflow pressure of the pulmonary circulation is not LAP and PVR (the slope of pressure/flow relationship) is increased. In these situations the effective downstream pressure is a closing pressure higher than LAP and therefore LAP becomes an irrelevant pressure to Q. This has been nicely demonstrated in an experimental intact animal model of acute lung injury, where an increased closing pressure became the effective outflow pressure of the pulmonary circulation only after inducing an oleic acid acute lung injury [11]. In accordance with the Starling resistor model of the pulmonary circulation a single-point pressure-flow measurement of PVR is unable to discriminate between active tone dependent and passive flow dependent pulmonary pressure changes and PVR calculation can therefore be misleading to assess the functional state of the pulmonary circulation as shown in Figure 1.
**Figure 1.** Starling resistor model to explain the concept of closing pressure within a circulatory system. Flow (Q) is determined by the gradient between mean pulmonary artery pressure (Ppa) and an outflow pressure which is either closing pressure (Pc) or left atrial pressure (Pla). When Pla > Pc, the (Ppa-Pla)/Q relationship crosses the origin (A curve) and PVR is constant. When Pc > Pla, the (Ppa-Pla)/Q relationship has a positive pressure intercept (B and C curves) and PVR decreases curvilinearly with increasing Q. The B and C curves are curvilinear at low flow representing recruitment. Possible misleading PVR calculations: PVR, the slope of (Ppa-Pla)/Q remain unchanged in the presence of a vasoconstriction (from 1 to 2) or decreased (from 1 to 3) with no change in the functional state of the pulmonary circulation (unchanged pressure/flow line). Adapted from Naeije R\(^{11}\) with permission.

2.2 Advantages of multi-point pressure-flow curves

In order to overcome the inherent limitation of a single point pressure/flow determination pulmonary vascular pressures should be measured at different levels of Q permitting to generate
multi-point pressure-flow curves [12]. These curves can be linearly approximated over a limited physiologic range of Q. The slope of these pressure/flow coordinates defines the incremental PVR and the intercept at zero Q defines the effective outflow pressure of the pulmonary circulation. In experimental intact animal models the manipulation of systemic venous return modulates Q permitting to generate multipoint pressure/flow curves. This can be achieved by a rapid inflation of a vena cava inferior balloon to reduce flow. These less than 10 sec changes in Q prevent sympathetic nervous system activation-induced pulmonary vasoconstriction [13]. This technique cannot be used in clinical practice for obvious ethical concern. CO can be increased by exercise, but exercise per se can induce a pulmonary vasoconstriction and an increase in LAP leading to an increased slope of pressure-flow plots [14]. Dobutamine is a chronoinotropic substance, which can be used as valuable alternative to exercise to increase CO. We investigated in an intact animal model the pulmonary vascular tone response at increasing doses of dobutamine before and after inducing a microembolic lung injury [15]. We maintained CO constant by manipulating venous return to avoid the potentially confusing effects of Q-induced vascular responses. Dobutamine at doses up to 10 mcg·kg⁻¹·min⁻¹ has no intrinsic vasomotor properties of the pulmonary circulation and therefore it can be properly used as a generator of multi-point pressure/flow plots. The clinical usefulness of multi-point PAP/Q curves has been previously shown in patients with pulmonary arterial hypertension (PAH) under PAH-targeted therapy [16, 17]. In seven patients with PAH and a negative acute nitric oxide vasodilator test resting pulmonary hemodynamics remained unchanged after 6 weeks of continuous intravenous prostacyclin treatment despite an increased exercise capacity as assessed by the 6-min-walk-distance (6-MWD: from 398 ± 59 to 478 ± 72 m; p < 0.05). In contrast the slope of pressure/flow plots (incremental PVR) during exercise significantly decreased from baseline (from 18.2 to 13.1 mm Hg/L/min/m²; p < 0.01), suggesting a predominately vasodilator effect of the drug [16]. Provencher et al. found in 42 idiopathic PAH (IPAP) patients that improvement in exercise capacity (6 MWD from 399 ± 88 to 442 ± 86 m; p < 0.001) several months (5 ± 2 months) after PAH-targeted therapy (epoprostenol, bosentan or both) was independently associated only with changes in exercise isoflow-PAPm (from 73 ± 15 to 66 ± 18 mm Hg; p = 0.006 and regression coefficient ± SE: -2.551 ± 0.373; p < 0.001) and not with resting pulmonary hemodynamics on multivariable analysis [17]. The extrapolated isoflow-PAPm is a simple and useful index in pressure/flow analysis. The findings of these two studies indicate that exercise pulmonary hemodynamics is more sensitive than resting hemodynamics in capturing treatment responses in IPAH patients. Recently Lau et al. assessed noninvasively the functional state of the pulmonary circulation using dobutamine stress echocardiography in 16 patients with PAH and 22 control
subjects. PAPm was estimated from the peak tricuspidal regurgitation jet as \([\text{PAPm} = 0.6 \cdot \text{PAPs} + 2]\) and Q was assessed from the velocity time integral of the LV outflow tract, together with heart rate and LV outflow tract diameter. PAH patients showed a significantly elevated PAPm-Q slope \((5.1 \pm 2.5 \text{ mm Hg/L/min versus } 1.1 \pm 0.7 \text{ mm Hg/L/min}; p < 0.001)\) and a markedly reduced pulmonary vascular distensibility coefficient \((0.003 \pm 0.001 \text{ versus } 0.02 \pm 0.01 \text{ mm Hg}; p < 0.001)\) (calculated from the curvilinear adjustment of mPAP-Q plots) as compared with matched healthy control subjects during dobutamine administration. Furthermore New York Heart Association functional class (FC) was significantly associated with dobutamine-induced PAPm-Q slope \((3.7 \pm 1.2 \text{ mm Hg/L/min for FC I-II versus } 6.5 \pm 2.5 \text{ mm Hg/L/min for FC III-IV}; p = 0.014)\), whereas resting total PVR was not affected by FC status [18]. Stress testing of the pulmonary circulation with generation of pressure/flow coordinates can potentially be useful for early PAH identification in at-risk populations with normal resting pulmonary hemodynamics (e.g. patients with connective tissue disease, family members of patients with IPAH or heritable PAH), for prognosis and monitoring of treatment effects in PAH. These preliminary promising results require further validation.

2.3 Transpulmonary pressure gradient versus diastolic pressure gradient for the diagnosis of “out of proportion” post-capillary pulmonary hypertension.

PH is defined by a resting PAPm \(\geq 25 \text{ mm Hg}\) measured during right heart catheterization (RHC) [5]. A threshold value of PAOP of 15 mm Hg is used to differentiate between pre- and post-capillary PH. The hemodynamic definition of post-capillary PH requires a combination of PAPm \(\geq 25 \text{ mm Hg}\) and PAOP \(> 15 \text{ mm Hg}\). Post-capillary PH occurs as a consequence of left heart diseases (LHD) [19]. Post-capillary PH was further sub-classified as passive and reactive (or “out of proportion”) depending on the transpulmonary pressure gradient (TPG). The difference between PAPm and PAOP defines the TPG. A threshold value of TPG of 12 mm Hg has been recommended for the differentiation between passive and reactive post-capillary PH in order to identify intrinsic pulmonary vascular disease in PH-LHD [19]. Reactive post-capillary PH (PAOP \(> 15 \text{ mm Hg}\) and TPG \(> 12 \text{ mm Hg}\)) refers to a PAPm higher than expected from a passive backward transmission of an elevated LAP, as a consequence of superimposed vasoconstriction and/or vascular remodelling of the pulmonary circulation. The clinical utility of TPG in differentiating passive from reactive postcapillary PH has been recently questioned [20]. CO, LAP, pulmonary vessels distensibility and recruitment influence this gradient leading to a possible misclassification of concomitant pulmonary vascular disease in LHD. In contrast PAPd is less sensitive to changes in the above-mentioned
variables and the diastolic pressure gradient (DPG = PAPd - PAOP) appears to be more useful for the diagnosis of reactive post-capillary PH [20]. Furthermore a proposed diagnostic tree based on PAOP, DPG and CO determinations in sequence can be helpful to identify intrinsic pulmonary vascular disease in LHD patients, but a prospective validation of this algorithm is required [20]. In a large non-concurrent cohort study of patients with post-capillary PH (n = 1094) a DPD ≥ 7 mm Hg identified more accurately the presence of pulmonary vascular remodelling (histologically proven in a sample of 38 patients undergoing lung biopsy) than did TPG > 12 mm Hg alone, and DPG ≥ 7 mm Hg has been identified as an independent predictor of poor survival in patients with post-capillary PH [21]. The proposed diagnostic tree based on PAPm, PAOP, TPG and DPG can be helpful in identifying pulmonary vascular disease superimposed on LHD, but a validation of this clinical prediction rule is still pending [21]. At the 5th WSPH held in Nice, France in 2013 it was recommended to abandon the term reactive (or “out of proportion”) post-capillary PH and two types of PH-LHD were proposed on the basis of the DPG-level: “isolated post-capillary PH” (PAOP > 15 mm Hg and DPG < 7 mm Hg) and “combined post-capillary PH and pre-capillary PH” (PAOP > 15 mm Hg and DPG ≥ 7 mm Hg) [22].

2.4. References


7. LeVarge BL, Pomerantsev E, Channick RN. Reliance on end-expiratory wedge pressure leads to misclassification of pulmonary hypertension. Eur Respir J 2014; 44: 425-434


(ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009; 30: 2493-2537


2.5. Personal contribution to pulmonary vascular-pressure relationship:

Pulmonary vascular effects of dobutamine in experimental pulmonary hypertension

Alberto Pagnamenta, MD; Pierre Fesler, MD; Alain Vandinivit, MD; Serge Brimiouelle, MD, PhD; Robert Naeije, MD, PhD

**Objective:** To characterize the dose-related effects of dobutamine on pulmonary vascular tone and associated changes in right ventricular afterload in canine microembolic lung injury.

**Design:** Prospective, interventional study.

**Setting:** University laboratory.

**Subjects:** Ten anesthetized and ventilated dogs.

**Interventions:** Right heart catheterization for the measurement of pulmonary vascular resistance by multipoint mean pulmonary artery pressure (Ppa)/cardiac output (Q) plots, partitioning of pulmonary vascular resistance by the occlusion method, and determination of pulmonary arterial input impedance from spectral analysis of Ppa and Q waves, in ten anesthetized and ventilated dogs, before and after induction of acute microembolic lung injury, and without or with 5, 10, 15, and 20 μg·kg⁻¹·min⁻¹ dobutamine.

**Measurements and Main Results:** Microembolic pulmonary hypertension was associated with a shift of Ppa/Q plots to higher pressures, a slight decrease in the arterial component of pulmonary vascular resistance, a decrease in characteristic impedance, and an increase in the pulsatile component of right ventricular hydraulic load. At baseline, dobutamine had no effect on Ppa/Q plots at 5 and 10 μg·kg⁻¹·min⁻¹ but increased Ppa at 15 and 20 μg·kg⁻¹·min⁻¹. In microembolic pulmonary hypertension, the only effect of dobutamine on Ppa/Q plots was a decrease in Ppa at 20 μg·kg⁻¹·min⁻¹. Dobutamine had no effect on the partitioning of pulmonary vascular resistance or on pulmonary arterial input impedance spectrum.

**Conclusions:** Dobutamine at doses up to 10 μg·kg⁻¹·min⁻¹ has no flow-independent effect on the normal or the acutely hypertensive pulmonary circulation. Higher doses may be constricting or dilating depending on preexisting tone. (Crit Care Med 2003, 31:1140–1146)

**Key Words:** microembolic lung injury, pulmonary vascular resistance, pulmonary vascular impedance, dobutamine, pulmonary circulation, animal experiment

Inotropic support with dobutamine is routinely prescribed in the intensive care setting to patients with low output states secondary to septic shock, acute respiratory distress syndrome, end-stage heart failure, and postoperative cardiovascular instability. All these disease states are complicated by variable degrees of pulmonary hypertension (1–4). At doses usually given in clinical practice (up to 20 μg·kg⁻¹·min⁻¹), dobutamine has been reported to decrease pulmonary vascular resistance (PVR), in experimental (1, 5) and clinical (4, 6) pulmonary hypertension. However, whether dobutamine decreases PVR independently of associated changes in flow remains uncertain. In controlled flow conditions, dobutamine has been reported to affect (7, 8, 9), to decrease (10, 11), or even to increase (7, 10) the gradient between pulmonary artery pressure (Ppa) and occluded pulmonary artery pressure (Ppao) (or left atrial pressure, depending on dose, experimental model, and ambient P02).

A dobutamine-induced change in PVR may be clinically relevant because of an associated change in right ventricular afterload. However, PVR fails to give a complete description of the forces opposing right ventricular ejection, which result from a dynamic interplay between resistance, elastance, and wave reflection (12). Because pulse pressure relative to mean pressure is proportionally much higher in the pulmonary circulation than in the systemic circulation, the pulsatile component of right ventricular work is relatively more important than that of the left ventricle (12). Although dobutamine has been reported to improve the coupling between the left ventricle and the systemic circulation because of decreased characteristic impedance, wave reflection indexes, and low-frequency moduli of impedance (13), no such data are available for the right ventricle and the pulmonary circulation. Dobutamine conceivably could increase pulmonary arterial compliance and/or decrease wave reflections, even at unchanged PVR, and thereby relatively decrease right ventricular hydraulic load. Whether such effects could occur at unchanged flow is unclear.

We therefore thought that it would be of interest to investigate the dose-related pulmonary vascular effects of dobutamine at clinically relevant doses (up to 20 μg·kg⁻¹·min⁻¹), before and after induction of microembolic lung injury, an experimental acute respiratory distress syndrome model characterized by increased shunt and severe pulmonary hypertension (14). To avoid the confusing effects of flow-induced responses, we maintained cardiac output constant by manipulating systemic venous return (7). At each dose of dobutamine, cardiac output was rapidly and transiently decreased to refine the measurement of PVR by a...
pressure-flow relationship devoid of the effects of reflex sympathetic nervous system activation (15). To locate any possible pulmonary vascular effects of dobutamine, PVR was partitioned into an arterial and a venous component by using the occlusion method (16). Finally, right ventricular afterload was quantified from spectral analysis of pulmonary artery pressure and flow waves and pulmonary arterial impedance (PVZ) calculations (16).

METHODS

The experiments were approved by the Committee on the Care and Use of Animals in Research of the Brussels Free University School of Medicine.

Preparation. Ten mongrel dogs (mean weight, 27 kg; range, 14–37 kg) were anesthetized with α-chloralose (80 mg/kg) and morphine (0.1 mg/kg), followed by a continuous infusion of α-chloralose (20 μg/hr) and morphine (0.5 mg·kg⁻¹·hr⁻¹), and were paralyzed with pancuronium bromide (0.2 mg·kg⁻¹·hr⁻¹). The dogs were ventilated (Elma 900 B servo-ventilator, Siemens, Elmata, Solna, Sweden) via auffed endotracheal tube with an FIO₂ of 0.4, a respiratory rate of 10 breaths/min, a tidal volume of 15–25 mL/kg to maintain arterial PcO₂ between 35 and 45 mmHg, and a positive end-expiratory pressure of 5 cm H₂O. Periodic deep inspirations were administered to avoid atelectasis formation. Sodium bicarbonate was given as required to correct metabolic acidosis. Body temperature was maintained at 34–38°C by use of an electric heating blanket. The dogs were lying supine.

A thermocilion balloon-tipped pulmonary artery catheter (Baxter Edwards, Irvine, CA) was inserted via the left external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery for measurements of pulmonary capillary pressure (PC) by the analysis of the Ppa decay curve after balloon occlusion, cardiac output (Q), and central temperature and for mixed venous blood sampling. A polyethylene catheter was inserted in the abdominal aorta through the right femoral artery for measurements of systemic arterial pressure (Psa) and for arterial blood sampling. A balloon catheter (Percor Stat-DL 10.5F, Datascope, Paramus, NJ) was advanced into the inferior vena cava via a right femoral venotomy. Inflation of this balloon produced a titratable decrease in Q by reducing venous return. Thrombus formation along the balloon catheter was prevented by 100 units/kg sodium heparin administered intravenously just before its insertion.

In all the animals, left lateral thoracotomy was performed. A thermocilion balloon-tipped pulmonary artery catheter (131H-7F; Baxter Edwards) was inserted into the left atrium through the atrial appendage to measure left atrial pressure (Pia). A 16- to 24-mm nonconstricting ultrasonic flow probe (T101, Transonic Systems, Ithaca, NY) was positioned around the main pulmonary artery to measure instantaneous Q. The Transonic flowmeter is linear to 60 Hz, with a flat amplitude response to 35 Hz. A 5-Fr high-fidelity manometer-tipped catheter (SPC 350; Millar Instruments, Houston TX) was introduced through the right ventricle into the main pulmonary artery, and its tip was positioned just distal to the flow probe to measure instantaneous Ppa. The frequency response of the micromanometer system is flat beyond 200 Hz. The chest was tightly closed and pleural air was evacuated, with some large inspirations to reexpand the lungs. Absence of pneumothorax was ensured by auscultation and preserved arterial Pao₂.

Measurements. Heart rate was obtained from an electrocardiographic lead monitoring. Psa, Ppa, Ppa, and Pia were measured by using Gould Statham P50 transducers (Gould, Oxnard, CA). The vascular pressures and flow signals were displayed on a monitoring system (Sirecust 404; Siemens, Erlangen, Germany), and recorded on a six-channel Gould recorder (2600S; Gould, Instruments Division, Cleveland, OH). The fluid-filled catheter-derived pressures were zero referenced at midchest and obtained at end expiration. Cardiac output was measured by thermodilution as a mean of at least three successive measurements (Cookset; Baxter Edwards, Santa Ana, CA). The zero Q from the ultrasonic flow probe was adjusted to the end-diastolic value, assumed to be zero. The instantaneous pulmonary pressures and flow signals were digitized at a sampling rate of 200 Hz by using an analog/digital converter (DAS 8-PGA; Keithley-Metabyte, Taunton, MA), stored, and analyzed on a personal computer. PVZ was calculated from the Fourier series expressions for pressure and flow signals as previously described (15, 16). Between three and five end-expiratory heartbeats were analyzed for each data-collection interval. Pressure and flow harmonics with amplitude <1% of pressure and flow pulse amplitude were considered as noise and excluded from impedance calculations. The PVZ modulus was computed as the ratio between pressure and flow moduli and the impedance phase as the difference between flow and pressure phases. The impedance at 0 Hz was taken as the total resistance (Ppa/Q), and characteristic impedance (Zc) was calculated as the average of impedance moduli between 2 and 15 Hz. From the impedance spectra we derived the first harmonic modulus and the first harmonic phase angle. Total hydraulic power (Whot) was calculated as the integral of the pressure-flow product over time. Steady hydraulic power was calculated as the product of mean pressure and mean flow and oscillatory power (Wow) as the difference between total and steady power.

PC was computed in triplicate from the Ppa decay curve after inflation of the balloon at the tip of the pulmonary artery catheter. For this measurement, the dogs were disconnected from the ventilator at end expiration for 10 sec. The Ppa decay curve was analyzed by a dual exponential fitting procedure, which includes a rapidly decreasing exponential (filling of the capillary compartment from the arterial one) and a slowly decreasing one (emptying of the capillary compartment into venous one). The resulting compartmental resistance and compliance values were used to generate a capillary pressure decay curve and estimate Pc at the instant of occlusion (17). The arterial component of PVR was calculated as (Ppa − Pc)/Q and expressed as percentage of PVR calculated as (Ppa − Pao)/Q.

Arterial and mixed venous blood gases were measured by an automated analyzer (ABL 2; Radiometer, Copenhagen, Denmark) immediately after samples were drawn and corrected for temperature. Venous admixture, percentage of total blood flow, was calculated as (capillary oxygen content − arteriovenous oxygen content)/(capillary oxygen − mixed venous oxygen content), where capillary oxygen content is estimated with the alveolar Pao₂, and oxygen saturations are determined from a nomogram (18).

Experimental Protocol. As soon as the animals were in steady-state conditions (stable heart rate, Psa, Ppa, and Q for 20 min), a baseline set of all hemodynamic and blood gas measurements was obtained, instantaneous Ppa and flow signals were sampled for PVZ calculations, and Pc was recorded. A first multipoint (Ppa − Pia)/Q plot was obtained by a rapid inflation of the venous catheter balloon. This rapid (Ppa − Pia)/Q curve was obtained by filling the caval balloon to reduce flow by approximately 50% in <10 sec to prevent effects of sympathetic nervous system activation (15). Thereafter, dobutamine was infused at 5, 10, 15, and 20 μg·kg⁻¹·min⁻¹ to increase Q. After each increase in dose, Q was controlled at its baseline value by stepwise inflations of the inferior vena cava balloon, and, after 20 min of stabilization, a complete set of hemodynamic and blood gases measurements was collected.

The dobutamine infusion was stopped and the cardiovascular state allowed to come back to its baseline state in about 30 min. One to 3 μg of 100-μm glass beads (Sigma Chemical, St. Louis, MO) were then slowly administered into the right atrium in about 20 min as previously described (14). The embolization was carried out until Ppa reached 40 mm Hg and then stopped, allowing Ppa to stabilize in 20–30 min at a value around 30 mm Hg (14). Dobutamine was then infused again at 5, 10, 15, and 20 μg·kg⁻¹·min⁻¹. At each of these doses, Q was maintained constant, and, after 20 min of stabilization, a complete set of hemodynamic and blood gases measurements was collected.
Statistical Analysis. Results are expressed as mean values ± se. The (Ppa – Pia)/Q coordinates obtained by the rapid inflation of the ventricle inferior balloon were best described by a linear approximation, and thus a linear least-squares regression analysis was performed to compute slope and extrapolated pressure intercepts at zero flow (P) for each of them. The hemodynamic and blood gas data were analyzed by a repeated-measures analysis of variance. Orthogonal contrasts were used to detect the presence of trends related to increasing dobutamine doses. We accepted p < .05 as indicating statistical significance (19).

RESULTS

Effects of Microembolic Pulmonary Hypertension. Microembolic pulmonary hypertension was associated with increases in heart rate, Ppa, Pa, PVR, and slope and di of (Ppa – Pia)/Q plots (p < .01) and decreases in Q and Psa (p < .01; Tables 1 and 2). Arterial Pao2 decreased from 187 ± 10 to 104 ± 14 mm Hg (p < .001), and venous admixture increased from 7 ± 2 to 22 ± 2% (p < .001), without significant change in arterial pH. The arterial component of PVR decreased slightly (p < .05; Tables 1 and 2). As shown in Figure 1, microembolic pulmonary hypertension affected pulsatile pulmonary hemodynamics by an increase in impedance at 0 Hz, no change in the first harmonic modulus, and a decrease in Zc (p < .001). The first harmonic phase angle became more negative (p < .01) and the first minimum of the ratio of pressure and flow moduli (fmin) was displaced to higher frequencies (p < .01). Wt increased and Wosc/Wt decreased (p < .01; Tables 3 and 4).

Effects of Dobutamine at Constant Flow. Before as well as after induction of microembolic pulmonary hypertension, dobutamine decreased Pia and Psa (the latter at the highest doses only) and increased heart rate; did not affect Pao2, venous admixture, or arterial pH; and did not affect the gradient between Ppa and Pia or the partition of PVR (Tables 1 and 2). Dobutamine had no effect on any of the indexes of pulsatile pulmonary hemodynamics, except for a shift of (fmin) to higher frequencies at the highest given doses of 15 and 20 μg·kg−1·min−1 and at baseline (Fig. 1). Dobutamine increased Wosc/Wt (Tables 3 and 4).

Effects of Dobutamine on Rapid (Ppa – Pia)/Q Plots. At baseline, dobutamine had no effect on (Ppa – Pia)/Q plots at 5 and 10 μg·kg−1·min−1 but shifted (Ppa – Pia)/Q plots to higher pressures at 15 and 20 μg·kg−1·min−1 (Fig. 2). After microembolic pulmonary hypertension, dobutamine had no effect on (Ppa – Pia)/Q plots excepted for a shift of (Ppa – Pia)/Q plots to lower pressures at the highest dose of 20 μg·kg−1·min−1.

DISCUSSION

In the present study, dobutamine, at doses up to 10 μg·kg−1·min−1 as most generally used in clinical practice, had no flow-independent effects on the normal or acutely hypertensive pulmonary circulation. At higher doses, dobutamine increased PVR (evaluated by rapid multipoint pressure/flow plots) at 15 and 20 μg·kg−1·min−1 at baseline but decreased PVR at 20 μg·kg−1·min−1 after induction of microembolic pulmonary hypertension. Dobutamine had no intrinsic effect.

| Table 1. Steady-flow hemodynamic data in dogs before and after administration of increasing doses of dobutamine |
|---|---|---|---|---|
| Variables | Baseline | Dobu 5 | Dobu 10 | Dobu 15 |
| HR, beats/min−1 | 110 ± 7 | 130 ± 14<sup>a</sup> | 150 ± 17<sup>b</sup> | 180 ± 11<sup>b</sup> | 177 ± 10<sup>b</sup> |
| Q, L/min·m−2 | 4.1 ± 0.3 | 4.1 ± 0.3 | 4.1 ± 0.3 | 4.1 ± 0.3 | 3.9 ± 0.3 |
| Psa, mm Hg | 101 ± 6 | 112 ± 7 | 95 ± 7 | 81 ± 6<sup>a</sup> | 85 ± 6<sup>a</sup> |
| Ppa, mm Hg | 17 ± 1 | 17 ± 1 | 17 ± 1 | 17 ± 1 | 17 ± 1 |
| Pla, mm Hg | 12 ± 1 | 13 ± 1 | 16 ± 1<sup>c</sup> | 16 ± 1<sup>c</sup> | 10 ± 1<sup>c</sup> |
| Pe, mm Hg | 14 ± 1 | 13 ± 1 | 13 ± 1 | 13 ± 1 | 13 ± 1 |
| Ra, % | 62 ± 2 | 62 ± 2 | 62 ± 2 | 62 ± 2 | 62 ± 2 |
| Pi, mm Hg | 2.0 ± 0.7 | 1.4 ± 1.1 | 3.1 ± 2.4 | 2.9 ± 0.8 | 2.5 ± 1.0 |
| Slope, mm Hg | 1.1 ± 0.2 | 1.5 ± 0.2 | 0.8 ± 0.6 | 1.3 ± 0.2 | 1.4 ± 0.2 |

Dobu 5, 10, 15, and 20 dobutamine infusion at 5, 10, 15, and 20 μg·kg−1·min−1; HR, heart rate; Q, cardiac index; Psa, mean systemic arterial pressure; Ppa, mean pulmonary arterial pressure; Pla, left atrial pressure; Pe, pulmonary capillary pressure; Ra, arterial component of the pulmonary vascular resistance; Pi, linearly extrapolated intercept of (Ppa – Pia)/Q plots at zero flow; Slope, slope of (Ppa – Pia)/Q plots.

<sup>a</sup>p < .05; <sup>b</sup>p < .01 compared with baseline. Values are expressed as mean ± se (n = 10).

| Table 2. Steady-flow hemodynamic data in dogs with microembolic lung injury, before and after administration of increasing doses of dobutamine |
|---|---|---|---|---|
| Variables | ALI | Dobu 5 | Dobu 10 | Dobu 15 |
| HR, beats/min−1 | 143 ± 10 | 160 ± 12 | 172 ± 16<sup>a</sup> | 191 ± 16<sup>b</sup> | 204 ± 14<sup>b</sup> |
| Q, L/min·m−2 | 3.5 ± 0.3 | 3.5 ± 0.3 | 3.5 ± 0.3 | 3.5 ± 0.3 | 3.6 ± 0.3 |
| Psa, mm Hg | 84 ± 5 | 86 ± 6 | 85 ± 7 | 75 ± 5<sup>a</sup> | 76 ± 5<sup>a</sup> |
| Ppa, mm Hg | 29 ± 1 | 28 ± 1 | 28 ± 1 | 26 ± 1 | 27 ± 1 |
| Pla, mm Hg | 12 ± 1 | 12 ± 1 | 12 ± 1 | 12 ± 1 | 12 ± 1 |
| Pe, mm Hg | 21 ± 1 | 20 ± 1 | 19 ± 1 | 19 ± 1 | 19 ± 1 |
| Ra, % | 52 ± 2 | 52 ± 2 | 53 ± 2 | 53 ± 2 | 51 ± 2 |
| Pi, mm Hg | 8.0 ± 1.4 | 7.3 ± 1.2 | 7.5 ± 1.3 | 7.0 ± 1.4 | 7.1 ± 1.2 |
| Slope, mm Hg | 3.1 ± 0.4 | 3.5 ± 0.3 | 3.6 ± 0.3 | 3.1 ± 0.3 | 2.6 ± 0.2 |

ALI, acute lung injury; Dobu 5, 10, 15, and 20 dobutamine infusion at 5, 10, 15, and 20 μg·kg−1·min−1; HR, heart rate; Q, cardiac index; Psa, mean systemic arterial pressure; Ppa, mean pulmonary arterial pressure; Pla, left atrial pressure; Pe, pulmonary capillary pressure; Ra, arterial component of the pulmonary vascular resistance; Pi, linearly extrapolated intercept of (Ppa – Pia)/Q plots at zero flow; Slope, slope of (Ppa – Pia)/Q plots.

<sup>a</sup>p < .05; <sup>b</sup>p < .01 compared with baseline. Values are expressed as mean ± se (n = 10).
at any dose or experimental circumstance on the partitioning of PVR or on right ventricular afterload.

**Pulmonary Vascular Pressure/Flow Relationships.** Dobutamine has been reported to decrease PVR in experimental (1, 5) and clinical (4, 6) pulmonary hypertension. Accordingly, dobutamine is believed to act as a pulmonary vasodilator and has been used as such, for example, to evaluate the reversibility of pulmonary hypertension in patients with advanced left heart failure considered for cardiac transplantation (6). However, PVR is a composite variable whose implicit assumption is that the relationship between the transpulmonary pressure difference (Ppa – Pla) and Q is linear and passes through the origin. In various pulmonary hypertensive states, multipoint (Ppa – Pla)/Q plots have been shown to be well described by a linear approximation over physiologic ranges of flows but to present with positive extrapolated pressure intercepts. This is commonly explained by a closing pressure higher than Pla that acts as an effective outflow pressure (20). When (Ppa – Pla)/Q plots present with a positive extrapolated pressure intercept, PVR cannot discriminate any more between active and passive, flow-dependent, changes in Ppa (20). Another methodological problem with the use of PVR at variable flow is that an increased flow per se may cause release of endothelial vasodilating mediators (21). Therefore, possible vasodilating properties of a drug are better examined at controlled flow. The present results suggest that previously reported decreases in PVR after dobutamine are often attributable to an increase in flow rather than to an intrinsic pulmonary vasodilator property of this drug.

In the present study, pulmonary vascular pressure vs. flow plots were generated rapidly, in <10 secs, to avoid the effects of low flow-induced sympathetic nervous system activation (15). So obtained extrapolated pressure intercepts were slightly positive, by 1–3 mm Hg, and the slopes had a value around 1 mm Hg L⁻¹ m⁻², in keeping with previously reported values for the normal canine (22) or human (23) pulmonary circulation. Microembolic lung injury increased both slopes and extrapolated pressure intercepts of (Ppa – Pla)/Q plots, also in keeping with previous observations (14). It is of interest that, although dobutamine had no effect on PVR at low maintained constant, slight vasoconstrictive (baseline) or vasodilating (embolic pul-

![Graph](image.png)

**Figure 1.** Composite pulmonary vascular impedance (PVI) spectra before and under dobutamine (Dobu) 20 μg·kg⁻¹·min⁻¹, at baseline (filled circles) and after induction of microembolic pulmonary hypertension (open circles). In both experimental conditions, the only effect of dobutamine (stippled lines) was a shift of the ratio of pressure and flow moduli to higher frequencies. Microembolic pulmonary hypertension increased 0 Hz impedance, did not affect first harmonic impedance, and decreased phase angle and characteristic impedance.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Dobu 5</th>
<th>Dobu 10</th>
<th>Dobu 15</th>
<th>Dobu 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z_0$, dynes·sec·cm⁻⁵·m⁻²</td>
<td>337 ± 19</td>
<td>338 ± 19</td>
<td>322 ± 16</td>
<td>344 ± 10</td>
<td>331 ± 24</td>
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<tr>
<td>$Z_1$, dynes·sec·cm⁻³·m⁻²</td>
<td>66 ± 8</td>
<td>72 ± 7</td>
<td>76 ± 7</td>
<td>73 ± 7</td>
<td>79 ± 6</td>
</tr>
<tr>
<td>$Z_c$, dynes·sec·cm⁻³·m⁻²</td>
<td>81 ± 8</td>
<td>80 ± 9</td>
<td>82 ± 9</td>
<td>77 ± 8</td>
<td>80 ± 8</td>
</tr>
<tr>
<td>Ph1, rad</td>
<td>$-0.11 ± 0.15$</td>
<td>$-0.08 ± 0.16$</td>
<td>$-0.01 ± 0.17$</td>
<td>0.03 ± 0.17</td>
<td>0.14 ± 0.14</td>
</tr>
<tr>
<td>$f_{min}$, Hz</td>
<td>2.8 ± 0.5</td>
<td>4.1 ± 0.9</td>
<td>4.4 ± 1.0</td>
<td>7.5 ± 1.2</td>
<td>6.4 ± 1.1</td>
</tr>
<tr>
<td>Wtot, mW·m⁻²</td>
<td>209 ± 28</td>
<td>229 ± 32</td>
<td>240 ± 37</td>
<td>236 ± 37</td>
<td>233 ± 31</td>
</tr>
<tr>
<td>Wosc/Wtot, %</td>
<td>27 ± 3</td>
<td>32 ± 3</td>
<td>37 ± 3</td>
<td>31 ± 4</td>
<td>36 ± 3</td>
</tr>
</tbody>
</table>

$Z_0$, 0 Hz impedance (total resistance); $Z_1$, first harmonic impedance; $Z_c$, characteristic impedance; Ph1, first harmonic phase angle; $f_{min}$, first minimum of the ratio of pressure and flow moduli; Wtot, total hydraulic work; Wosc/Wtot, oscillatory hydraulic work to total hydraulic work ratio.

* $p < .01$; compared with baseline. Values are expressed as mean ± se (n = 10). ** $p < .05$.
Table 4. Pulsatile flow hemodynamic data in dogs with microembolic lung injury before and after administration of increasing doses of dobutamine

<table>
<thead>
<tr>
<th>Variables</th>
<th>ALI</th>
<th>Dobu 5</th>
<th>Dobu 10</th>
<th>Dobu 15</th>
<th>Dobu 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z_w, dyne-sec-cm⁻²m²⁻¹</td>
<td>710 ± 64</td>
<td>665 ± 58</td>
<td>660 ± 56</td>
<td>640 ± 55</td>
<td>630 ± 45</td>
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<tr>
<td>Z_l, dyne-sec-cm⁻³m⁻²</td>
<td>70 ± 4</td>
<td>67 ± 4</td>
<td>65 ± 5</td>
<td>55 ± 5</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>Z_c, dyne-sec-cm⁻³m⁻²</td>
<td>60 ± 5</td>
<td>60 ± 4</td>
<td>61 ± 5</td>
<td>59 ± 5</td>
<td>59 ± 5</td>
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<tr>
<td>Ph₁, rad</td>
<td>-0.69 ± 0.11</td>
<td>-0.58 ± 0.12</td>
<td>-0.50 ± 0.12</td>
<td>-0.29 ± 0.16</td>
<td>-0.23 ± 0.15</td>
</tr>
<tr>
<td>f_meas, Hz</td>
<td>4.8 ± 0.4</td>
<td>5.8 ± 0.7</td>
<td>5.5 ± 1.0</td>
<td>5.3 ± 1.0</td>
<td>6.1 ± 1.1</td>
</tr>
<tr>
<td>Wtot, mW/m²</td>
<td>255 ± 31</td>
<td>247 ± 34</td>
<td>262 ± 36</td>
<td>249 ± 35</td>
<td>263 ± 37</td>
</tr>
<tr>
<td>Wosc/Wtot, %</td>
<td>13 ± 1</td>
<td>16 ± 2°</td>
<td>19 ± 2°</td>
<td>20 ± 2°</td>
<td>20 ± 2°</td>
</tr>
</tbody>
</table>

Z_w, 0-Hz impedance (total resistance); Z_l, first impedance; Z_c, characteristic impedance; Ph₁, first harmonic phase angle; f_meas, first minimum of the ratio of pressure and flow moduli; Wtot, total hydraulic work; Wosc/Wtot, oscillatory work to total hydraulic work ratio.

*p < .05; †p < .01 compared with baseline. Values are mean ± se (n = 10).

Volume hyperten-son (Ppa−Ppaao) vs. pulmonary blood flow (Q) minus occluded Ppa vs. pulmonary blood flow (Q) at baseline (open circles) and after induction of microembolic pulmonary hypertension (open circles), at 0, 5, 10, 15, and 20 mg·kg⁻¹·min⁻¹ dobutamine (Dobu) in each experimental condition (stippled lines). Dobutamine shifted (Ppa−Ppao)Q plots to higher pressures at 15 and 20 mg·kg⁻¹·min⁻¹ at baseline. Microembolic pulmonary hypertension shifted (Ppa−Ppao)Q plots to higher pressures. Dobutamine shifted (Ppa−Ppao)Q plots to lower pressures at 20 mg·kg⁻¹·min⁻¹ after induction of microembolic pulmonary hypertension.

Figure 2. Composite plots of mean pulmonary artery pressures (Ppa) vs. pulmonary blood flow (Q) at baseline (open circles) and after induction of microembolic pulmonary hypertension (open circles), at 0, 5, 10, 15, and 20 mg·kg⁻¹·min⁻¹ dobutamine (Dobu) in each experimental condition (stippled lines). Dobutamine shifted (Ppa−Ppao)Q plots to higher pressures at 15 and 20 mg·kg⁻¹·min⁻¹ at baseline. Microembolic pulmonary hypertension shifted (Ppa−Ppao)Q plots to higher pressures. Dobutamine shifted (Ppa−Ppao)Q plots to lower pressures at 20 mg·kg⁻¹·min⁻¹ after induction of microembolic pulmonary hypertension.

Partitioning of PVR. A variety of methods based on more or less complex reference electric analogs have been previously reported for the estimation of Pc by the analysis of Ppa decay curves after pulmonary arterial occlusion (25). We applied a biexponential fitting and recalculation of a derived Pca decay curve based on assumptions of changes in arterial and venous resistances and compliances (16, 17). We found at baseline an arterial resistance accounting for 60% of total PVR, in keeping with previous studies, which used a biexponential fitting (16, 17, 21). Microembolic lung injury slightly decreased the arterial component of PVR, suggesting that the site of resistance explored by the occlusion method may be vessels of around the same diameter as the injected glass beads, around 100 μm, or slightly larger. These results are in keeping with a previous study in which Pca was calculated from a single exponential fitting of the Ppa decay curve (14). Absence of effect of dobutamine of normal or abnormal distribution of PVR supports the notion that dobutamine either was without effect or selectively acted at the site of resistance only.

Pulmonary Vascular Impedance. Pulmonary hypertension usually is associated with an increase in impedance at 0 Hz (which is equivalent to PVR calculated without left atrial pressure, or total PVR), a shift of the first minimum of the ratio of pressure and flow moduli to higher frequencies, a more negative low-frequency phase angle, and an increased Zc (12). These changes are explained by the com-
Dobutamine at doses up to 10 μg·kg⁻¹·min⁻¹ has no flow-independent effect on the normal or the acutely hypertensive pulmonary circulation.

Combined effects of increased resistance, decreased compliance, and increased wave reflection (12). Pulmonary hypertension secondary to acute lung injury secondary to the injection of small glass beads (26, 27), or oleic acid (16), reproduces all these changes in the PVZ spectrum, except for a decreased Zc (26, 27). Since Zc is a ratio between inertness and compliance, this apparently paradoxical effect has been explained by predominant proximal arterial dilation, which may have an adaptive value as it decreases the pulsatile hydraulic load imposed on the right ventricle (26, 27). Our results show that dobutamine does not affect the PVZ spectrum, except for a shift of Ppa/Q moduli to higher frequencies, which might be attributed to an increased heart rate (12). Administration of norepinephrine has been shown to decrease pulmonary artery distensibility independently of the level of intravascular pressure (28), and stimulation of thestellate ganglion in dogs has been reported to increase Zc without associated change in PVR (29), suggesting an α-adrenergic receptor-mediated decrease in pulmonary arterial compliance. The present results indicate that dobutamine up to 20 μg·kg⁻¹·min⁻¹ has no such effects on the pulmonary circulation. Dobutamine is a synthetic catecholamine with prominent β-adrenergic effects, resulting in cyclic adenosine monophosphate-mediated inotropism, chronotropism, and vasodilation (30). In the present experiments, dobutamine decreased iso-flow systemic arterial pressure, in keeping with expected β-adrenergic receptor-mediated systemic vasodilation. Dobutamine has been previously shown to increase systemic arterial compliance and to decrease wave reflection, improving left ventricular-vascular coupling in patients with left heart failure (13). In the present controlled flow conditions, no such effect of dobutamine could be evidenced on the pulmonary circulation. Dobutamine also has α-adrenergic effects (30), which may result in pulmonary vasoconstriction after administration of propranolol to block β-adrenergic receptors (10). Stimulation of α-adrenergic receptors could account for dobutamine-induced shift of (Ppa – PpaO)/Q to higher pressures at the highest given doses in the present experiments at baseline.

Both microembolic lung injury and dobutamine increased heart rate. Although this effect decreases the pulsatile component of hydraulic load (12), as also observed in the present experiments, it is not expected to affect the PVZ spectrum. The concept of impedance rests on the assumption that the pulmonary circulation acts as a linear system (12). It previously has been established that changes in heart rate over the range observed in the present study do not affect indexes of the PVZ spectrum (except for a necessary shift of the first minimum and maximum of Ppa/Q moduli to higher frequencies related to increased baseline heart rate) (31).

Dobutamine increased the Wosc/Wₜ means ratio, which could suggest a deterioration right ventriculovascular matching by loss of an increased amount of energy to generate pulsations at the same level of mean flow. This effect probably results from an isotropic action of dobutamine, without increased cardiac output because of the controlled flow experimental design.

Intrapulmonary Shunt. Microembolic lung injury, like acute respiratory distress syndrome and various acute lung injury models, is associated with altered gas exchange because of an increase in pulmonary shunt (14). When altered gas exchange in acute lung injury is mainly caused by an increased shunt, calculated venous admixture only slightly overestimates shunt measured by an independent reference method such as by the infusion of sulfur hexafluoride (14). In the present study, shunt estimated by venous admixture over the whole range of doses of dobutamine tested after induction of microembolic lung injury did not change, in keeping with the notion that dobutamine did not affect the distribution of pulmonary blood flow as could have occurred as a consequence of altered hyperoxic vasoconstriction.

Clinical Implications. Because of previously reported species- and model-specific differences in the pulmonary vascular effects of dobutamine, it is uncertain whether the present results can be directly transposed to patients with pulmonary hypertension. Thus, the notion that dobutamine has no flow-independent effects on the pulmonary circulation at doses up to 10 μg·kg⁻¹·min⁻¹ remains to be validated in clinical practice.

ACKNOWLEDGMENTS

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REFERENCES

11. Furman WR, Sumner WR, Kennedy TP, et al: Comparison of the effects of dobutamine,

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3. PARTITIONING OF PULMONARY VASCULAR RESISTANCE

3.1. The concept of effective pulmonary capillary pressure

Fluid filtration across pulmonary capillaries is governed by the Starling equation as follows [1].

\[ Q_f = K_{fc} \cdot [(PCP - P_{int}) - K_d \cdot (\pi_{cap} - \pi_{int})] \]

Qf: fluid filtration
Kfc: capillary filtration coefficient = product of capillary hydraulic conductivity and capillary surface area
PCP – Pint: hydrostatic pressure gradient between capillaries and interstitium
\( \pi_{cap} – \pi_{int} \): oncotic pressure gradient between capillaries and interstitium
Kd: reflection coefficient to proteins; being \( \approx 0 \) when microvascular wall is extremely permeable to proteins and approaching one when when microvascular wall is impermeable to proteins.

The lungs protect themselves from the onset of pulmonary edema by a dynamic interplay of the different driving forces. For example, when filtration increases as a consequence of increased pulmonary capillary pressure (PCP), a decrease in interstitial oncotic pressure drives the fluid back into the capillaries. Interstitial followed by alveolar edema develops when the Starling forces are no more in equilibrium. Hydrostatic pulmonary edema occurs when PCP acutely exceeds 20 mm Hg [2]. Microvascular lung injury increases capillary permeability to proteins and lung edema appears even at lower PCP values. This type of edema is named low pressure or permeability edema [2]. PCP and pulmonary capillary permeability are the main determinants of pulmonary edema formation [2]. Gaar et al. originally developed the estimation of PCP in West’s lung zone III by applying the isogravimetric technique to an isolated dog lung preparation [3]. This complex and time-consuming technique remains the gold standard method for the comparison with other estimation’s techniques of PCP. More recently Hakim et al. estimated PCP with the double occlusion technique in isolated dog lungs and they founded an excellent agreement with the PCP measured by the isogravimetric method [4]. The double occlusion technique provides the experimental basis for bedside estimation of PCP by the analysis of PAP decay curve after single pulmonary artery occlusion following balloon’s inflation at the tip of PAC [5]. The typical PAP decay curve is characterised by a rapid pressure decrease (filling of the
capillary compartment from the arterial compartment) followed by a slower pressure drop (emptying of the capillary compartment into the venous compartment) with an inflection point in between as shown in Figure 1. The visual inspection method of the PAP decay curve gave accurate estimates of PCP identified as the inflection point between rapid and slow pressure drops [6]. PCP can also be estimated by several methods based on less or more complex mathematical analyses of the PAP decay curve [7]. A mono-exponential fitting of the PAP decay curve with back extrapolation to the moment of occlusion provided a valid estimate of PCP, but with a possible over-estimation as remodelled smallest arterioles get integrated into the capillary-venous compartment of the applied mathematical model [8]. The estimation of PCP can be further improved by a dual exponential fitting procedure of the PAP decay curve, even though the uncertainty about overlapping of arterial and capillary-venous compartments may persist in case of remodelling of the smallest arterioles [9]. The resulting compartmental resistances (arterial and venous) and compliance (capillaries) values are used to generate a capillary pressure decay curve and estimate PCP at the instant of occlusion [9]. PCP is normalised to PAPm because there is a phasic pressure variation within the cardiac cycle [10]. A typical PAP decay curve is presented in the following figure.

**Figure 1.** Biexponential curve fitting for estimation of pulmonary capillary pressure (Pcap) by intersection of the fast and the slow components of the pressure decay curve, or by extrapolation of the exponential fitting of the slow component of the pressure decay curve to the moment of occlusion. Reproduced from Souza R, et al. Pulmonary capillary pressure in pulmonary hypertension. Critical Care 2005; 9: R132-R138; Open Access (permission not required).
The arterial component of pulmonary vascular resistance (PVR) is calculated as \((PAPm - PCP) \cdot CO^{-1}\) and expressed as the percentage of PVR calculated as \((PAPm - PAOP) \cdot CO^{-1}\). We previously used this approach to further characterise the elevated PVR in order to identify the site of increased resistance in a canine model of acute lung injury. We founded that PCP increased from \(12 \pm 1\) mm Hg to \(15 \pm 1\) mm Hg (\(p < 0.01\)) following the induction of oleic acid lung injury, but the partitioning of PVR remained unchanged suggesting an unaffected longitudinal distribution of resistances [11]. In order to obtain accurate and precise estimates of PCP, regardless of the fitting procedure chosen, the tip of PAC must be positioned in West’s lung zone III and pressure tracings must be recorded at end-expiration when intrathoracic pressure approximates atmospheric pressure. Special attention should be reserved for obese and patients with COPD given the relevant intrathoracic pressure swings across the respiratory cycle in these subjects [12]. In the medical literature the term pulmonary capillary wedge pressure (PCWP) is widely mentioned. PCWP is obtained by wedging a PAC with a deflated balloon and is therefore a misleading term as shown in Figure 2, because PCWP is different from PCP and different from PAOP or PAWP. The working group on “definitions and diagnosis of PH” of the 5th WSPH suggested to abandon the term PCWP and to prefer the term pulmonary artery wedge pressure (PAWP) for pulmonary venous pressure [13]. However, this unique acronym does not allow to understand if the measurement was a truly wedged or occluded PAP. In general, an occluded PAP is better for the estimation of LAP as venous resistance does not affect the measurement.

![Figure 2](image.png)

Figure 2. Occluded pulmonary artery pressure versus pulmonary capillary wedge pressure.
3.2. Clinical usefulness in partitioning of pulmonary vascular resistance

Kafi et al. applied the occlusion pressure analysis with a mono-exponential fitting of the PAP decay curve to a small series of patients (n = 11) with severe PAH (PAPm 52 ± 3 mmHg; FC II-III). PCP was markedly increased (29 ± 3 mmHg) potentially causing hydrostatic pulmonary edema with an apparent normal longitudinal distribution of resistances, suggesting a peripheral location of the main site of elevated PVR [8]. This PCP estimation probably reflected an increased pressure of the distal pulmonary arterial tree than an increased pressure in lung capillaries. We used the pulmonary artery occlusion technique in a larger number of patients with PAH (n = 36) and in patients with CTEPH (n = 4) and PVOD (n = 2) with a bi-exponential fitting procedure. PCP was higher than normal in PAH (26 ± 1 mmHg), but lower than previously reported by mono-exponential function [8]. The arterial component of the PVR was increased in CTEPH (77 ± 3%) and decreased in PVOD (42 and 43%) as compared to PAH (63 ± 1%) [14]. We concluded that the occlusion pressure analysis may be helpful in identifying the site of predominantly increased PVR in PH patients but does not allow to clearly discriminate among the different considered PH groups. This finding is only partially explained by the small sample size of our cohort (four patients with CTEPH and two patients with PVOD). More recently Kim et al., based on the same partitioning of PVR, assessed the presence of preoperative (before pulmonary thromboendarterectomy (PTE)) concomitant distal microvascular disease by comparing pre- and postoperative pulmonary hemodynamics and by determining the operative risk of PTE in patients with CTEPH (n = 26). Pre-interventional upstream resistance (R$_{up}$ = (PAPm-PCP)/(PAPm-PAOP)) values correlated inversely with postoperative total pulmonary resistance index (TPRi) and postoperative PAPm ($r^2 = 0.79$ and 0.75, respectively; both $p < 0.001$) whereas TPRi and PAPm before and after surgery correlated poorly ($r^2 = 0.10$ and 0.09, respectively). All postoperative deaths (n = 4), due to right heart failure (RHF) from persistent PH, occurred in patients with preoperative $R_{up} < 60\%$. Patients with lower $R_{up}$ appear to be at increased risk for persistent PH and death after PTE due to concomitant small-vessel disease [15]. The occlusion pressure analysis seems a promising method in identifying the presence of small-vessel disease in patients with CTEPH and may be helpful for preoperative risk-assessment and for patients’ selection for medical therapy as alternative to surgery. To further test the validity of the analysis of PAP decay curve to discriminate proximal vasculopathy from small-vessels disease Toshner et al. studied a cohort of 59 patients with CTEPH, IPAH and connective tissue disease (CTD)-associated PAH. $R_{up}$ is increased in operable CTEPH (mean 87.3%; 95%-
CI 84.1 to 90.5%) as compared with inoperable CTEPH (mean 75.8%; 95%-CI 66.8 to 84.7%; p = 0.048), and IPAH/CTD-PAH (mean 77.1%; 95%-CI 71.9 to 82.3%; p = 0.003). The receiver operating characteristic curve of $R_{up}$ (area under the curve 0.75; p < 0.001) by a cut-off value of 79.3% gave a 100% sensitivity (95%-CI 73.5 to 100%) and a 57.1% specificity (95%-CI 28.9 to 82.3%) for discriminating operable from inoperable CTEPH despite accurate pressure decay curve analysis was not obtainable in up to 20% of subjects. Moreover the occlusion pressure technique was performed in a subgroup of CTEPH patients (n = 7) in different lung lobes obtaining quite different $R_{up}$ results, suggesting a heterogeneous distribution of the disease [16]. While the occlusion pressure analysis has been validated and can be easily performed during routine bedside RHC, further studies are still required before it becomes part of routine invasive assessment of PH given the above mentioned limitations of this technique [16].

3.3. References

1. Starling EH. The Linacre lecture on the law of the heart. London: Longman’s; 1918


12. LeVarge BL, Pomerantsev E, Channick RN. Reliance on end-expiratory wedge pressure leads to misclassification of pulmonary hypertension. Eur Respir J 2014; 44: 425-434


3.4. Personal contribution to the partitioning of pulmonary vascular resistance:

**Single arterial occlusion to locate resistance in patients with pulmonary hypertension**


**ABSTRACT:** The purpose of this study was to determine the site of increased resistance using the arterial occlusion technique in patients with severe pulmonary hypertension.

Pulmonary vascular resistance was partitioned in arterial and venous components based on double exponential fitting analysis of the pulmonary artery pressure decay curve: after balloon occlusion in 36 patients with pulmonary arterial hypertension (PAH); at baseline and during the inhalation of 20 parts per million of nitric oxide (NO); in four patients with chronic thromboembolic pulmonary hypertension; and in two patients with pulmonary veno-occlusive disease.

In the patients with PAH, at baseline, mean pulmonary artery pressure was 56±2 mmHg (mean±SE), with an arterial component of resistance of 63±1%. Inhaled NO did not change the partition of resistance. The arterial component of resistance amounted on average to 42% and 77% in the patients with veno-occlusive disease and the patients with thromboembolic pulmonary hypertension, respectively. However, the partitioning of resistance did not discriminate between these three diagnostic categories.

The occlusion technique may help to locate the predominant site of increased resistance in patients with severe pulmonary hypertension, but does not allow for a satisfactory differential diagnosis on an individual basis.

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The occlusion technique can be used in intact animals and patients for the partitioning of pulmonary vascular resistance (PVR) into an arterial segment (PVRa) and a capillary-venous segment, and for the determination of an effective pulmonary capillary pressure (Pc) [1, 2]. The method identified a hydrostatic mechanism, with an important role accounting for early high-altitude pulmonary oedema [3]. The single arterial occlusion technique applied to a small series of patients with primary pulmonary hypertension (PPH) showed a longitudinal distribution of resistance that appeared similar to that found in normal pulmonary circulation, with a PVRa ~55% of PVR [4]. This was interpreted as being compatible with pathological changes that dominate at the site of the smallest arterioles [4]. A surprise finding was an absolute value for Pc of ~30 mmHg, potentially associated with increased capillary filtration. Lung oedema is not known to be a frequent occurrence in patients with PPH [5].

In the study by Kafi et al. [4], pulmonary artery pressure (Ppa) decay curves after arterial occlusion were analysed using a single exponential fitting procedure derived from a simple model of the pulmonary circulation made up of arterial and venous resistances around a capillary capacitance [6]. Theoretically, this approach can be improved using a double exponential fitting based on a more realistic model of the distribution of arterial, capillary and venous resistances and capacitances [7].

It was therefore of interest to compare both methods in a larger number of patients to check whether previously described increased Pc might be a methodological artefact. Not only patients with "pure" PPH, but also with pulmonary arterial hypertension (PAH), as defined by a recent World Health
Organization-sponsored consensus conference [8], were included. The study sought to determine whether $P_{ea}$, as computed with optimal methodology, might be better correlated with clinical state than traditionally measured $P_{pa}$ and PVR. For the purpose of comparison, $P_{ea}$ was also measured by arterial occlusion in two patients with pulmonary veno-occlusive disease (PVOD) and in four patients with chronic thromboembolic pulmonary hypertension (CTEPH). An increased venous resistance would be expected to increase $P_{ea}$ at a given $P_{pa}$, and to prolong the $P_{pa}$ decay curve after occlusion. Conversely, an increase in proximal resistance, as seen in CTEPH, would be expected to shorten the $P_{pa}$ decay curve after occlusion, leading to decreased $P_{ea}$ at a given $P_{pa}$.

Methods

Patients

Forty-two patients, 12 males and 31 females aged 52±14 yrs (mean±sd) gave informed consent to this study. The study was approved by the institutional review boards of the Erasmus University Hospital (Brussel, Belgium), and the Katholieke Universiteit Leuven (Leuven, Belgium) and the UCSD Medical Center (San Diego, CA, USA) and conformed with the principles outlined in the Declaration of Helsinki. All of the patients had a $P_{pa}$ of >25 mmHg at rest. Thirty-six patients fitted into the diagnostic criteria of PAH as defined by a recent World Health Organization-sponsored consensus conference that extended the concept of PPH to associated conditions, including collagen vascular diseases, congenital systemic-to-pulmonary shunts, human immunodeficiency virus (HIV) infection, anorexia intake, and portal hypertension [9]. From those 36 patients, 19 had PH, 11 had pulmonary hypertension (PH) associated with anorexigen, three had portal PH, and three had PH associated with scleroderma. Two patients, a 16-yr-old male and a female aged 43 yrs, were suffering from PVOD. This diagnosis rested on radiological signs of interstitial and alveolar oedema, which were markedly aggravated in the male shortly after an attempt at prostacyclin therapy. The diagnosis of PVOD was confirmed in the female by an open lung biopsy. Four patients had an angiographically diagnosed CTEPH. Their pre-operative tracings were included in the present study on the basis of absent or minimal PH, with a mean $P_{pa}$ of 22 mmHg (range 19–26 mmHg) after surgical thromboendarterectomy, indicating a predominantly proximal increase in PVR. All of the patients were severely dyspnoeic and in New York Heart Association functional class III. None of the patients were being treated with prostacyclin analogues at the time of right heart catheterisation.

Procedures and measurements

Right heart catheterisation was performed without premedication, with the patient lying supine and breathing room air. A balloon-tipped, flow-directed, pulmonary catheter (131HF7; Baxter Healthcare Corp., Irvine, CA, USA) was inserted into an internal jugular vein under local anaesthetic and floated, under continuous pressure wave monitoring, into a pulmonary artery to measure $P_{pa}$, pulmonary artery occluded pressure ($P_{paO}$), $P_{ea}$ (computed from the $P_{pa}$ decay curve), right atrial pressure ($P_{ra}$) and pulmonary blood flow (Q). Systemic arterial pressure was determined intermittently by an automated blood pressure cuff. Heart rate was determined from a continuously monitored electrocardiographical lead. Transcutaneous arterial oxyhaemoglobin saturation was continuously monitored by pulse oxymetry.

Pulmonary vascular pressures were measured using disposable transducers (TruWave; Baxter Healthcare Corp.) connected to a bedside haemodynamic and electrocardiographical monitoring system (Sirecust 404; Siemens, Erlangen, Germany). The pressure transducers were zero referenced at mid-chest, and vascular pressures were obtained at end-expiration. Q was measured using the thermodilution technique as a mean of at least three successive measurements (COM-2; Baxter Healthcare Corp.). Inhaled nitric oxide (NO) was supplied from a pure NO source tank (Oxyhrique, Machelen, Belgium) and delivered through a tight face-mask. The inspired fraction of NO was monitored by chemiluminescence after calibration against standard NO concentration (42 chemiluminescence NO-NO2-NOx analyser; Thermo Environmental Instruments Inc., Franklin, MA, USA). The pulmonary vascular pressure signals were sampled at 200 Hz using an analogue-to-digital converter (DAS 8-PGA; Keithley-Metabyte, Taunton, MA, USA), and stored and analysed on a personal computer.

Pulmonary capillary pressure measurements

$P_{ea}$ was computed in triplicate from $P_{paO}$ decay curves after inflation of the balloon of the pulmonary artery catheter. For this measurement, the patients were asked to stop breathing at the end of a normal tidal volume for 10 s. All $P_{pa}$ signals were filtered using a two-pole digital low-pass filter with a cut-off at 18 Hz. The $P_{paO}$ decay curves were analysed by two different methods. First, by fitting the data between 0.2–2 s post-occlusion with a mono-exponential equation and by deriving the pressure 152 ms after the moment of occlusion [6, 9]. Second, by fitting the data between the moment of occlusion and the stabilisation of the pressure tracing at the level of the $P_{paO}$ with a bi-exponential equation, and by the calculation of $P_{ea}$ with the exact solution for a three-compartment model of the pulmonary circulation formalised by BACONNIER et al. [7], with a normalisation procedure to mean $P_{paO}$ [10]. PVRa was calculated as ($P_{paO}$–$P_{ra}$)/Q and expressed as the percentage of PVR, calculated as ($P_{paO}$–$P_{pa}$)/Q.

Clinical evaluation

The clinical state of all of the PAH patients was assessed by a score made up of the following 16
symptoms and signs: fatigue, dyspnoea, orthopnoea, jugular vein distension, peripheral oedema, syncope, dizziness, palpitation, chest pain, loud second heart sound, third heart sound, fourth heart sound, right ventricular heave, systolic murmur, diastolic murmur and hepatomegaly [11].

**Study protocol**

As soon as steady-state conditions (stable heart rate and \( P_{Pa} \) for 20 min) were ensured, a baseline set of haemodynamic measurements was obtained. The measurements were repeated after a 20-min equilibration period under inhalation of 20 parts per million of NO in 22 of the PAH patients. This dose of NO is two times the dose previously shown to offer a maximum pulmonary vasodilating effect in patients with PPH [12].

**Statistical analysis**

Results are presented as mean±SEM. Comparisons of haemodynamic variables at baseline and during inducible NO administrations in the same patients were made by paired t-test. Linear correlations were calculated between haemodynamic variables and the signs and symptoms score.

**Results**

As shown in table 1, the pulmonary haemodynamic profile of the PAH patients was similar to that previously reported in large series of patients with PPH, that is, very high \( P_{Pa} \), moderately increased \( P_{ma} \), normal \( P_{Pao} \) and increased \( Q \) [5, 11]. \( P_{e} \) calculated from mono-exponential fitting was increased to 34±1 mmHg, with a PVRa of 48±2%. \( P_{e} \) calculated from bi-exponential fitting was lower (p<0.01), but still increased to an average of 26±1 mmHg, with a PVRa of 63±1%. All further reported \( P_{e} \) values were calculated from double exponential fitting procedure. Inhaled NO slightly decreased PVR, with small but significant decreases in \( P_{Pa} \) and \( P_{ma} \). Inhaled NO did not change the partition of PVR.

The \( P_{Pa} \) decay after occlusion was prolonged in the patients with PVOD and was shorter in the patients with CTEPH (fig. 1). In comparison with the patients with PAH, those with PVOD had increased \( P_{e} \) and decreased PVRa. In patients with CTEPH, \( P_{e} \) was decreased and PVRa increased, but the measurements did not allow a clear discrimination between PAH, PVOD and CTEPH (fig. 2).

In the PAH patients, there was no correlation between \( P_{Pa} \), \( P_{Pao} \) or \( P_{e} \) and the clinical score, while \( P_{Pa} \) was directly correlated with the clinical score (\( r=0.384, p<0.05 \)). \( P_{e} \) was correlated with \( P_{Pao} \) (\( r=0.79, p<0.001 \)) and \( P_{Pa} \) (\( r=0.76, p<0.001 \)).

**Discussion**

The present results show that compared to PAH, PVRa is increased in CTEPH and decreased in PVOD, but that isolated measurement of PVRa does not allow a differential diagnosis between these three types of severe PH.

**Measurement of pulmonary capillary pressure versus pulmonary artery occlusion pressure**

Inflation of the balloon at the tip of a pulmonary artery catheter to measure \( P_{Pao} \) creates a downstream stop-flow phenomenon extending to same diameter veins. Therefore, \( P_{Pa} \) generally gives a satisfactory estimate of left atrial or end-diastolic left ventricular pressure. Wedging a pulmonary artery catheter without balloon inflation yields a pulmonary artery wedge pressure, sometimes called a pulmonary capillary wedge pressure or (wrongly) a pulmonary capillary pressure, which measures the pressure of same diameter veins. Increased venous resistance may increase pulmonary artery wedge pressure relative to \( P_{Pao} \). The measurement of an effective pulmonary capillary pressure, \( P_{e} \), requires the analysis of a \( P_{Pa} \) decay curve after balloon occlusion [1, 2].

| Table 1. — Haemodynamics at baseline and during inhalation of 20 parts per million nitric oxide (NO) in patients with pulmonary arterial hypertension and at baseline in four patients with chronic thromboembolic pulmonary hypertension (CTEPH) and two patients with pulmonary veno-occlusive disease (PVOD) |
|--------------------------------------|--------|--------|--------|
| Baseline                            | NO     | CTEPH  | PVOD   |
| Subjects n                          | 36     | 22     | 4      | 2      |
| HR beats·min⁻¹                      | 78±2   | 77±3*  | 63±6   | 71, 89 |
| Q L·min⁻¹·m⁻¹                       | 2.0±0.1| 2.2±0.1| 2.1±0.2| 1.5, 1.5|
| \( P_{Pa} \) mmHg                   | 56±2   | 49±3***| 47±5   | 50, 56 |
| \( P_{ma} \) mmHg                   | 6±1    | 6±1**  | 7±2    | 7, 8   |
| \( P_{Pao} \) mmHg                  | 11±1   | 12±1   | 12±2   | 12, 12 |
| PVR dyn·s⁻¹·cm⁻⁵·m⁻²                 | 1908±126| 1480±147***| 1352±128| 2052, 2347|
| \( P_{e} \) mmHg                    | 26±1   | 25±2   | 21±2   | 34, 37 |
| PVRa %                              | 63±1   | 63±2   | 77±3   | 42, 43 |

Data are presented as mean±SEM unless otherwise stated. HR: heart rate; Q: pulmonary blood flow; \( P_{Pa} \): mean pulmonary arterial pressure; \( P_{Pa} \): right atrial pressure; \( P_{Pao} \): pulmonary artery occluded pressure; PVR: pulmonary vascular resistance; \( P_{e} \): pulmonary capillary pressure; PVRa: arterial component of the PVR. *: p<0.05 compared with baseline; **: p<0.01 compared with baseline; ***: p<0.001 compared with baseline.
Computing of pulmonary capillary pressure

Based on pulmonary circulation, modelled as an electrical circuit made of a capillary capacitance between the arterial and venous resistances (R-C-R), the $P_{pa}$ decay curve after balloon occlusion can be fitted with a mono-exponential function, and $P_c$ can be calculated by extrapolation to the moment of occlusion or shortly thereafter [6]. There is, however, a concern that $P_c$ estimated from a mono-exponential fitting might overestimate capillary pressure, as measured by double occlusion or by the reference isogravimetric method [13, 14]. Direct micropuncture measurements compared with single and double occlusion determinations suggest that $P_c$ estimated from a mono-exponential fitting may be affected by small arterioles resistance in addition to capillary-venous resistance [15].

A better fit of $P_{pa}$ decay curves after balloon occlusion is obtained with a bi-exponential function [16]. Since both the arterial and venous segments of the pulmonary circulation can be characterised by resistive and compliant properties, BACONNIER et al. [7] formalised a three-compartment C-R-C-R-C model, and proposed an exact solution to compute $P_c$ from the bi-exponential fitting of the $P_{pa}$ decay curve. As there is a phasic variation of $P_{ec}$ within the cardiac cycle [17], $P_c$ may be better normalised to mean $P_{pa}$ [10]. In the present study, this method of calculation led to lower $P_c$ values than previously found using a mono-exponential fitting in PPH patients [3, 18]. However, it is uncertain whether any contribution of the smallest size pulmonary arterioles to calculated $P_c$ is excluded.

The present results confirm that $P_c$ computed from mono-exponential fitting is very high in PAH [4].
However, $Pc$ derived from bi-exponential fitting was still higher than normal. Based on reported measurements of $Ppa$ and $PpaO$ in normal subjects, and a normal PVR of $\approx 60\%$ [3], $Pc$ should not normally exceed 16 mmHg. $Pc$ values that increased above 20 mmHg could be expected to be associated with an increased extravascular lung water [3]. However, as lung oedema is not known as a usual feature of PAH [5], it is most likely that high $Pc$ measured in PAH would be caused by the effect of increased smallest arteriolar resistance. An alternative, though less likely, explanation would be that the lungs of PAH patients, like patients with left heart failure, would be adapted to chronically increased capillary filtration pressure by capillary remodelling and increased lymphatic flow.

Mechanisms of increased pulmonary capillary pressure in pulmonary arterial hypertension

Histological studies in PPH show various combinations of medial hypertrophy, concentric or eccentric intimal fibrosis, and complex arteritis, plexiform or dilatation lesions in $\approx 30\%$ of cases, in situ thrombosis [19]. These histological features seem nonspecific for PPH and are described in a variety of secondary forms of PAH, such as PAH associated with anoxigen intake [19], CREST syndrome [20], HIV infection [21] and chronic liver disease [22]. The lesions appear to predominate in small, $<500-1,000$ $\mu$m diameter, arterioles, but it is not entirely clear whether they might extend to more proximal portions of the pulmonary artery tree, nor whether there might be coexistent lesions of small pulmonary veins.

Spontaneously hypertensive Wistar Kyoto rats that are used as a model of PH show increased muscularity in small pulmonary veins as well as in arteries [23]. In a series of 19 patients with PPH, intimal and/or adventitial increased thickness of the pulmonary venous walls was found in half of them [24]. Venous involvement is also present in PAH associated with CREST syndrome [20]. It has been estimated that 5–25% of patients with clinically diagnosed PPH present with predominant venoocclusive lesions at careful pathological examination of biopsy or autopsy specimens [25]. PVOD has also been described in patients infected with HIV [21]. Therefore, the present finding of increased absolute values of $Pc$ with a "normal" longitudinal distribution of the PVR, may reflect that venous involvement is more important than previously assumed in patients with PAH. Detailed morphological studies will be needed to assess whether the variability of recorded $Pc$ in the present study might reflect variability in this venous involvement in PAH.

Effects of inhaled nitric oxide in pulmonary arterial hypertension

These data show that inhaled NO decreases PVR without changing its partition. Inhaled NO has been reported in isolated perfused lungs of various species after different vasoconstrictor stimuli either to unalter the longitudinal distribution of resistances [26] or to act predominantly at precapillary level [27]. Inhaled NO did not affect the longitudinal distribution of resistances in experimental micro-embolic PH [28] but decreased the capillary-venous component of PVR in acute respiratory distress syndrome [29]. Inhaled NO diffuses easily through the alveolo-capillary membrane before its inactivation by haemoglobin, and probably dilates the smallest arterioles and venules adjacent to the alveolar space, provided there is a component of active constriction. These results confirm that in most patients with PAH, this component of vasoconstriction is minimal, and that inhaled NO dilates both arterioles and venules.

Clinical and haemodynamic correlations

In the present study, the signs and symptoms score was correlated with PVR and not $Ppa$ or $Pc$. This is in keeping with previous studies showing that PVR or Q are better correlated with exercise or functional capacity in PAH patients than $Ppa$ [30]. There were significant correlations between $Pc$ and $Ppa$ or $PpaO$. This is explained by upstream transmission of left heart filling pressures, and by the fact that increased capillary-venous resistance necessarily increases both $Ppa$ and $Pc$.

Clinical implications

There is only one previously reported patient with PVOD and $Pc$ measured using the occlusion method [31]. The present results do not agree with that study's suggestion that an increased $Pc$ is diagnostic of PVOD. Only two patients with PVOD could be included in the present study, precluding meaningful statistical comparisons with patients with PAH. This is explained by the fact that the disease is very rare, with an estimated incidence of 0.1–0.2 cases per million persons per year [25]. In addition, these patients are often critically ill and unstable at the time of diagnosis, making the collection of sufficient quality arterial occlusion data problematic.

Most patients with CTEPH present with some degree of persistent PH after successful thromboendarterectomy [32]. In this study, a small series of four such patients, selected for minimal residual PH, had a $Pc$ less elevated on average than in patients with PAH, but still higher than normal, suggestive of peripheral small vessel involvement. Whether the occlusion technique has the potential of helping the identification of patients with CTEPH at risk of postoperative PH is currently under investigation, with promising preliminary results [33].

Conclusions

In patients with pulmonary arterial hypertension, pulmonary capillary pressure measured with the occlusion technique is higher than normal and may be due to a previously assumed unimportant venous involvement. The single arterial occlusion technique helps to locate the site of predominantly increased pulmonary vascular resistance in severe pulmonary hypertension, but does not discriminate between pulmonary
arterial hypertension, pulmonary veno-occlusive disease and chronic thromboembolic pulmonary hypertension.

Acknowledgements. The authors thank the staff of the Intensive Care Unit and the staff of the Coronary Care Unit of the Erasmus University Hospital (Brussels, Belgium) for their help with patient care. M-T. Gauthier and P. Jespers helped in the preparation of this report.

References


4. PULSATILE PULMONARY HEMODYNAMICS

4.1. The concept of pulmonary vascular impedance

A right heart catheterization (RHC) with measurements of pressures and flow, and calculation of PVR is recommended as the reference method for diagnostic confirmation of suspected PH, evaluation of disease severity, and in determining prognosis and response to treatment [1, 2]. The fluid-filled thermodilution PAC provides satisfactory determinations of only PAPm and mean Q [3, 4]. This "steady-flow" hemodynamic approach imposes a simplification that neglects the natural pulsatility of the pulmonary circulation [5, 6]. Even when PVR is optimally estimated from multi-points pressure-flow plots [7] the use of PVR as a measure of the opposition to flow presented to the right ventricle (RV) ignores two important characteristics in an oscillatory system: vascular compliance and wave reflection [8]. This limitation is important because it has recently been better realized that RV function is a major determinant of functional state, exercise capacity and prognosis in PH [9]. It has been previously shown that this non-pulsatile hemodynamic approach underestimates right ventricular hydraulic load by one third to one half in healthy subjects and possibly more in patients with PH [6]. Recently Saouti et al. assessed RV total and oscillatory hydraulic power in IPAH patients (n =35) and in 14 control subjects using PAC-derived pressure and magnetic resonance imaging (MRI)-derived flow determinations [10]. Total power increased from 0.29 ± 0.10 W in controls to 0.52 ± 0.14 W in moderate IPAH to 0.73 ± 0.24 W in severe IPAH (p < 0.0001 for all comparisons). Interestingly oscillatory hydraulic power remained a constant fraction (approximately 23%) of total power independently of PAP values. This finding seems useful in permitting to derive total power from PAPm and mean Q by a simple formula: [total power = 1.33 x (PAPm x mean Q)], because this power estimation does not require to record instantaneous pressure and flow signals. Right ventricular (RV) afterload can be estimated by RV wall tension occurring during RV ejection in accordance with a transposition of LaPlace’s law of spheric structures, which is problematic to assess in clinical practice [11]. Pulmonary vascular impedance (PVZ) is determined by a dynamic interplay between PVR, vascular compliance, reflected waves and blood inertance during RV ejection and represents indeed the most accurate available quantification of right ventricular afterload [6, 12, 13]. Experimental animal studies showed, at a given level of PH (assessed by a non-oscillatory hemodynamic approach), dissociation between changes in PVR and PVZ according to the type of PH [14-16]. This discrepancy is relevant to dynamic components of right ventricular afterload, which may be quite different in accordance with the type of PH. Here is probably the explanation for previously observed poor correlation between level of PH (assessed by PAPm or PVR) and right heart
failure (RHF) in patients with PH [17], and for the clinical failure of vasodilators, which decrease PVR in the treatment of PH [18]. For the assessment of the pulsatile pulmonary hemodynamic, it is necessary to record instantaneous pressure and flow waves simultaneously in the frequency domain rather than in the time domain. By applying the Fournier analysis these waves can be decomposed into their respective series of harmonics at multiples of the heart rate frequency. This spectral analysis is possible given the behaviour of the pulmonary circulation as a nearly linear system: in fact a purely sinusoidal flow oscillation produces a purely sinusoidal pressure oscillation of the same frequency [12]. The ratio of pressure harmonics to flow harmonics defines PVZ and unlike PVR cannot be expressed as a single numerical value but can be displayed as a graphic spectrum of pressure/flow moduli and phase angle, both as a function of frequency as shown in Figure 1.

![Figure 1](image.png)

**Figure 1.** Pulmonary vascular impedance (PVZ) spectrum. A.: instantaneous pulmonary flow and pressure measurements. B: PVZ spectrum following decomposition of pressure and flow waves into their respective harmonics. PVZ as the ratio of pressure harmonics to flow harmonics. with estimated characteristic impedance \((Z_c)\) at high frequencies. C: \(Z_c\) estimation in the time domain as the slope of the linearized early PAPs/Q curve by Dujardin JPL. Adapted from Brimioulle and Naeije in Pneumologie, Flammarion 1996, cap 12; with permission

Normally, PVZ spectrum decreases rapidly from a high value a 0 Hz to a first minimum at 2-4 Hz and
increases again to a first maximum at 6-8 Hz followed by smaller fluctuations at higher frequencies. Phase angle at low frequencies is negative indicating that flow leads pressure, whereas at higher frequencies the phase is near zero [13, 19]. PVZ at zero Hz frequency (PVZ₀) is the ratio of PAPm to mean Q, corresponding to total PVR (PVR without inclusion of LAP). At high frequencies when impedance values are relatively constant and phase angle approximates zero, wave reflections are reasonably assumed to be negligible and this PVZ is called characteristic impedance (PVZ_C), which reflects the ratio of inertial elements to compliant elements in proximal pulmonary arteries. PVZ_C can also be calculated in the time domain instead in the frequency domain as the slope of the linearized early PAPs/Q curve [20]. Resistance vessels influence low frequency PVZ spectrum, intermediate pulmonary vessels influence mid-range frequency PVZ spectrum and proximal vessels influence high frequency PVZ spectrum. A reflection coefficient (RC) can be estimated from the difference between PVZ₀ and PVZ_C as followed [6]:

\[
RC = \frac{(1 - PVZ_C/PVZ_0)}{(1 + PVZ_C/PVZ_0)}
\]

Alternatively, separation of instantaneous pressure and Q waves into their forward and backward components can be used to quantify wave reflection [21]. Total hydraulic power (work performed per unit time) is estimated by integrating the product of instantaneous pressure multiplied by flow, steady power as the product of PAPm and mean Q and pulsatile power by subtracting steady power from total hydraulic power [6]. The pulsatile nature of blood flow makes that more energy is used to move a given volume of blood per minute that would be used if the heart somehow generates a non-pulsatile flow. Steady flow is physiologically useful in pumping blood forward whereas pulsatile power is “wasted” in arterial pulsations [12]. A pressure/flow ratio increase at all frequencies suggests a reduced distensibility of proximal arteries. A shift of the first minimum and maximum moduli to higher frequencies signals an increased wave velocity or a change in the dominant reflection sites. An increase in the magnitude of the frequency-dependent oscillations is indicative of increased distal reflections and a more negative phase at low frequencies suggests a more pronounced effect of reflected pressure waves on PAPs [6, 12].

Measurement and interpretation of PVZ spectra are complex and difficult. Computers models have been developed to present PVZ data in a more simple and concise form. Simple electric models (lumped parameter models) such as 3- to 4-element Windkessel take into account resistance and compliance, but not wave reflection. These models provide a reasonable description of the hemodynamic properties of the pulmonary circulation [22, 23].
4.2 Pulmonary vascular impedance in pulmonary hypertension

4.2.1 Pulmonary vascular impedance in intact animal models

Given the inverse relationship between animal size and resting heart rate the chosen animal model affects the frequency range of PVZ spectra. Furthermore different animal species present different PVZ pattern following the same pathological insult. For instance, experimental distal pulmonary embolization with autologous blood clots and glass beads increases PVZ_C in minipigs and goats but decreases PVZ_C in dogs [24, 25]. The dog represents an attractive animal model because human PVZ pattern (calculated using Hi-fidelity PAP catheter with an electromagnetic flow catheter) are entirely similar to those in dog. The minimal value of impedance modulus and of phase cross-over in human occur at similar frequencies to that in dog, despite the considerable differences in size of body and of lungs [12]. Chronic pulmonary venous hypertension increases PVZ_0 and PVZ_C, whereas acute venous hypertension increases PVZ_0 by unchanged PVZ_C [26]. Acute pulmonary hypertension by proximal vascular constriction increases both PVZ_0 and PVZ_C, but only PVZ_0 increases when PAP is increased to the same levels by distal embolization [15, 27]. We previously used PVZ computation to better characterize RV afterload in an experimental canine model of acute lung injury [28]. After inducing an oleic acid lung injury we observed an increased PVZ_0 (from 267 ± 19 to 426 ± 35 dyn·s·cm⁻⁵·m²; p < 0.01) a decrease in PVZ_C (from 104 ± 8 to 75 ± 6 dyn·s·cm⁻⁵·m²; p < 0.01) and a decreased oscillatory component of the hydraulic load (29 ± 3 to 22 ± 3%; p < 0.01). The expected increase in RV afterload induced by acute lung injury is limited by the distal localisation of increased resistance and by a decreased PVZ_C. These findings are in keeping with the clinical observation that RHF was not identified as independent predictor of mortality in patients with early ARDS (n = 145) ventilated with a lung protective strategy [29].

4.2.2 Pulmonary vascular impedance in humans

PVZ is not commonly investigated at the bedside. The computation of PVZ needs an invasive approach with high-fidelity technology, which is too demanding and difficult to integrate in daily clinical practice. The fluid-filled thermodilution PAC is generally thought to be inadequate for instantaneous pressure measurements given the low frequency response and for instantaneous Q measurements because thermodilution requires several cardiac cycles. There are only few reports on PVZ calculation in humans due to its complexity and the inherent technical limitations of commercially available high-fidelity catheters [6, 12]. “Normal” PVZ spectra in adult humans were
obtained from patients undergoing diagnostic cardiac catheterization who were found to have no pulmonary vascular and no heart diseases [12]. Chronic pulmonary hypertension in severe mitral stenosis is associated with an increase in resistance, in elastance and in low-frequency impedance [30]. Similar changes have been reported in patients with IPAH [31] and in those with severe congestive heart failure [32]. Resting left ventricular ischemia-induced acute pulmonary hypertension during coronary angioplasty resulted in decreased PVZ₀, increased PVZ₁ and unchanged characteristic impedance [33], whereas exercise induced myocardial ischemia was associated with an increased PVZᵄ [34]. Yet there have been two reports on the feasibility of bedside PZV computation in patients with PAH from PAP measured with fluid-filled PAC, and pulmonary flow-velocity measured by trans-thoracic Doppler echocardiography (TTE) [35, 36]. The derived PVZ indices appeared in agreement with previously reported high-fidelity technology measurements [31] and sensitive to pharmacological interventions [35, 36]. Interestingly, in one of these studies, performed in a pediatric patient population with PAH, PVZ showed superiority over PVR alone for the prediction of clinical outcomes [36]. However, the bedside method has not been rigorously validated against reference high-fidelity approach. We therefore compared PVZ computation using a simple bedside approach (PAC and TTE for pressure and flow determinations, respectively) with the reference method (high-fidelity Millar catheter and ultrasonic flow probe) in eight anesthetized dogs with two different types of pulmonary hypertension (proximal by pulmonary arterial ensnarement versus distal by microembolisation) at different pressure levels each one [27] using linear regression and Bland-Altman agreement analyses [37]. Impedance metrics (PVZ₀, PVZ₁, PVZᵄ, RC and steady hydraulic power) were highly correlated (r² ≥ 0.95; p < 0.001) between the two methods. Bedside measurements slightly overestimated PVZ₀, PVZ₁, PVZᵄ, RC and steady hydraulic power (bias of 11 dyne.s.cm⁻⁵.m⁻²; 13 dyne.s.cm⁻⁵.m⁻²; 0.6 dyne.s.cm⁻⁵.m⁻²; 0.6 and 6 mW.m⁻² respectively) and the 95% limits of agreement with the gold standard method were relatively small: 79 dyne.s.cm⁻⁵.m⁻²; 32 dyne.s.cm⁻⁵.m⁻²; 18 dyne.s.cm⁻⁵.m⁻²; 7 and 57 mW.m⁻² respectively. For first harmonic phase angle and pulsatile hydraulic power the correlation was poor (r² = 0.34 and 0.6 respectively) and bedside measurements underestimated these two variables. These last observations are due to the inherent time latency in PAP recording of fluid-filled catheters compared to high-fidelity ones. These results confirm that is possible to derive valid estimates of pulsatile pulmonary hemodynamic, except for first harmonic phase angle and pulsatile hydraulic power, with simple bedside tools commonly employed in daily clinical practice. This is relevant because in recent years it has been better recognized that RV function is a major determinant of symptomatology and prognosis of severe PH [9, 38] and thereafter an improved assessment of RV afterload is desirable. With the rapid technological developments of user-friendly devices and the growing availability of bedside software for data acquisition and
analysis, these pulsatile hemodynamic measurements are likely to become part of daily clinical practice.

4.3 References


10. Saouti N, Westerhof N, Helderman F, et al. Right ventricular oscillatory power is a constant fraction of total power irrespective of pulmonary artery pressure. Am J Respir Crit Care Med 2010; 182: 1315-1320


4.4 Personal contribution to pulmonary vascular impedance:

Continuous versus Pulsatile Pulmonary Hemodynamics in Canine Oleic Acid Lung Injury

ALBERTO PAGNEMENTA, YVES BOUCKAERT, PIERRRE WAUTHY, SERGE BRIMOULLE, and ROBERT NAEIJE

Laboratory of Physiology, Faculty of Medicine, Free University of Brussels, Brussels, Belgium

Pulmonary hypertension occurs commonly in the acute respiratory distress syndrome (ARDS), but associated right ventricular failure is relatively rare. We tested the hypothesis that this apparent contradiction is explained by a peripheral location of the increased pulmonary vascular resistance (Rpv). Experimental ARDS was induced in eight dogs by injection of oleic acid (0.07 ml/kg). Changes in Rpv were evaluated by measurements of pulmonary artery pressure (Ppa) at several levels of flow (Q), which was altered by manipulation of venous return. The analysis of Ppa decay curves after arterial balloon occlusion was used to partition Rpv into arterial and venous segments. Right ventricular afterload was evaluated by determination of pulmonary vascular impedance (Zpv), which was calculated from spectral analysis of Ppa and Q waves. Oleic acid lung injury was associated with an increase in both the slope and the extrapolated pressure intercept of Ppa/Q plots, no change in the partitioning of Rpv, no change in time-domain indices of wave reflection or in pulmonary arterial compliance, and a decrease in both the characteristic impedance and pulsatile component of total right ventricular hydraulic load. We conclude that the site of increased Rpv in oleic acid lung injury is the smallest pulmonary arterioles, which, together with a decreased characteristic impedance, contributes to minimize right ventricular afterload.

Pulmonary hypertension occurs frequently in the acute respiratory distress syndrome (ARDS), but right ventricular failure is relatively uncommon, and rarely identified as a cause of death (1–5). This apparent contradiction may be explained not only by a generally moderate increase in pulmonary artery pressure (Ppa), but also by the increase in pulmonary vascular resistance (Rpv) occurring peripherally. In both clinical (6) and experimental (7) ARDS pulmonary artery pressure is affected very little by changes in pulmonary blood flow (Q), which is probably due to an increased closing pressure of small extraalveolar vessels (8). Partitioning of Rpv by the occlusion method to calculate an effective capillary pressure (Pc') has shown arterial and venous components that were not greatly different from normal in clinical (9) and in experimental (10) ARDS, in keeping with an increase in small vessel resistance. Experimental ARDS induced by the injection of small glass beads has been shown to affect pulmonary vascular impedance (Zpv) spectra by decreased or unchanged characteristic impedance (Zc) and a minimal effect on wave reflection, thereby limiting right ventricular afterload (11–13). However, until now there has been no study combining all these methodological approaches to evaluate the functional state of the pulmonary circulation in oleic acid-induced acute lung injury.

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Correspondence and requests for reprints should be addressed to R. Naeije, M.D., Ph.D., Laboratory of Physiology, Erasme Campus, CP 604, 808, Lennik road, B-1070 Brussels, Belgium. E-mail: naeije@ucl.ac.be

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METHODS

Preparation

Eight mongrel dogs (mean weight, 25 kg; range, 16 to 35 kg) were included in the present study, which was approved by the Committee on the Care and Use of Animals in Research of the Brussels Free University School of Medicine. The dogs were anesthetized with morphine (0.1 mg/kg) and α-chloralose (80 mg/kg), followed by a continuous infusion of α-chloralose at the rate of 20 mg/h supplemented with hourly boluses of morphine (0.1 mg/kg). Paralysis was obtained with pancuronium bromide (0.2 mg/kg per hour). The dogs were ventilated (Elema 900 B servo-ventilator, Siemens Elema, Solna, Sweden) via auffed endotracheal tube with an inspired O2 fraction (Fio2) of 0.4 to 1.0 to maintain arterial oxygen saturation (SaO2) > 90%, a respiratory rate of 10 breaths/min, a tidal volume (VT) of 15–25 ml/kg adjusted to maintain arterial PCO2 between 35 and 45 mm Hg, and a positive end-expiratory pressure (PEEP) of 5 cm H2O. Periodic deep inspirations were administered to prevent atelectasis formation. Body temperature was maintained at 36.5–38.5 °C, using an electric heating pad. When metabolic acidosis occurred, it was corrected by a slow infusion of sodium bicarbonate. Throughout the experiments 0.9% NaCl was infused at about 10 ml/kg per hour to maintain a left atrial pressure (Pla) between 5 and 10 mm Hg.

A balloon-tipped flow-directed pulmonary catheter (model 131H-7F; Baxter Edwards, Irvine, CA) was inserted through the left external jugular vein and positioned by the pressure wave form into a branch of the pulmonary artery for measurements of occluded Ppa (Ppao), Pc' computed from the Ppa decay curve after arterial balloon occlusion, Q, and central temperature, and for mixed venous blood sampling. A polyethylene catheter was inserted in the abdominal aorta via the right femoral artery for measurements of systemic arterial pressure (Psa) and for arterial blood sampling. A balloon catheter (Percor Stat-DL 10.5F;Datascope, Paramus, NJ) was advanced into the inferior vena cava through a right femoral venotomy. Inflation of the balloon produced a titratable decrease in Q by reducing venous return. Thrombus formation along the balloon catheter was prevented by intravenous administration of sodium heparin (100 U/kg) just before the insertion. A large-bore polyethylene cannula was inserted into the left femoral artery and vein to act as an arteriovenous fistula, in order to increase Q by opening the fistula and increasing venous return.

A left lateral thoracotomy was performed. A balloon tipped flow-directed pulmonary catheter (model 131H-7F; Baxter Edwards) was inserted in the left atrium via the atrial appendage to measure left atrial pressure (Pla). A 16- to 24-mm nonconstricting ultrasonic flow probe (TI10; Transonic Systems, Ithaca, NY) was positioned around the main pulmonary artery for the measurement of instantaneous pulmonary blood flow (Q). The Transonic flowmeter system is linear to 60 Hz, with a flat amplitude response to 35 Hz. A SF high-fidelity manometer-tipped catheter (model SPC 350; Millar Instruments, Houston TX) was introduced through the right ventricle into the main pulmonary artery,
and its tip was positioned just distal to the flow probe for the measurement of instantaneous Ppa. The frequency response of the microanometer system is flat beyond 200 Hz. The chest was tightly closed, pleural air was evacuated, and the lungs reexpanded with several large volume inspirations.

### Measurements

Heart rate (HR) was determined from a continuous electrocardiogram. Psa, Ppa, Paa, Pla, and Pce were measured with Statham P50 transducers (Gould, Oxnard, CA). The vascular pressure and flow signals were displayed on a monitor (Sirecust 404; Siemens, Erlangen, Germany) and recorded on a six-channel recorder (model 2600; Gould, Instruments Division, Cleveland, OH). The pressure transducers of the fluid-filled catheters were zero referenced at midchest, and vascular pressures were recorded at end expiration. Q was measured by thermohalination as a mean of at least three successive measurements (CO-set; Baxter Edwards, Santa Ana, CA). The zero Q from the ultrasonic flow probe was adjusted to the end-diastolic value, assumed to be zero. The instantaneous pulmonary pressures and flow signals were sampled at 200 Hz with an analog/digital converter (DAS 8-PGA; Keithley-Metabyte, Taunton, MA), and stored and analyzed on a personal computer. Zpva was calculated from the Fourier series expression for pressure and flow signals as previously reported (15).

Five end-expiratory heartbeats were analyzed for each data collection interval. Pressure and flow harmonics with amplitude of <1% of pressure and of flow pulse amplitude were considered as noise and excluded from Zpva calculations. The Zpva modulus was computed as the ratio between pressure and flow moduli, and its phase computed as the difference between flow and pressure phases. The impedance at 0 Hz (Z0) was taken as the total resistance (Ppa/Q) and the characteristic impedance (Zc) was calculated as the average of impedance moduli between 2 and 15 Hz. The first harmonic modulus (Z1) and the first harmonic phase angle (Pbph) were also derived from Zpva spectra. Total hydraulic power (Whot) was calculated as the integral of the instantaneous product of pressure multiplied by flow. Steady hydraulic power (Ws) was calculated as the product of mean pressure and mean flow, and oscillatory power (Wosc) as the difference between total and steady power.

To quantify wave reflection, the recorded instantaneous pressure waves were separated into their forward and backward components, according to:

\[ P' = P - Pm \]
\[ P' = (P + Zc \cdot Q')/2 + Pm \]
\[ Q' = Q - Qm \]
\[ Q' = (Q - Zc \cdot Q')/2 \]

where P and Q are the recorded pressure and flow waves, Pm and Qm the mean pressure and flow, and P' and Pb' are forward and backward waves (15). The equations show that P is the sum of Pm and Pb. The backward or reflected wave was characterized by its amplitude (the difference between the maximal and minimal values) and by the time intervals between the electrocardiographic R wave and the following events: the foot of the wave (i.e., the starting inflection point), the upward zero crossing, the peak, and the downward zero crossing of the wave (15, 16). The energy transmission ratio (ETR) was calculated as the ratio between the hydraulic power in the measured wave and the hydraulic power in the forward wave (17). Pulmonary vascular compliance was estimated by the ratio of stroke volume (SV) to pulse pressure (PP) (18). Stroke volume was calculated as Q/HR and PP was calculated as the difference between maximum and minimal values of instantaneous Ppa.

Pce was computed three times from the Ppa decay curve after inflation of the balloon of the pulmonary artery catheter. For this measurement the dogs were disconnected from the ventilator at end expiration for 15 s. The Ppa decay curve was analyzed by a dual exponential fitting procedure, which includes a rapidly decreasing exponential (filling of the capillary from the arterial compartment) and a slowly decreasing exponential (emptying of the capillary compartment into the venous compartment) (19). The resulting compartment resistance and compliance values were used to generate a capillary pressure decay curve and estimate Pce at the instant of occlusion (19). Pce was normalized to mean Ppa (20). The arterial component of Zpva (Ra) was calculated as (Ppa - Pce)/Q and expressed as the percentage of Zpva calculated as (Ppa - Ppao)/Q. Arterial and mixed venous blood gases were measured immediately after drawing the samples by an automated analyzer (ABL 2; Radiometer, Copenhagen, Denmark) and corrected for temperature.

### Experimental Protocol

As soon as the animals were in steady state conditions (stable HR, Psa, Ppa, and Q for 20 min) a baseline set of hemodynamic and blood gas measurements was obtained, and instantaneous Ppa and flow signals were sampled for Zpva calculations. A first Ppa/Q plot was obtained by a rapid inflation of the inferior vena cava balloon. This fast flow-pressure curve was obtained by filling the caval balloon in order to reduce flow by approximately 50% in less than 10 s to prevent sympathetic activation (21).

The same procedure was repeated 90 min after the administration of oleic acid (0.07 ml/kg; Sigma, St. Louis, MO) as a slow injection (5 min) into the right atrium.

### Statistical Analysis

Results are expressed as means ± SEM. Linear regression analysis was performed on the Ppa/Q coordinates, obtained by the rapid inflation of the inferior vena cava balloon to compute a slope and an extrapolated pressure intercept (Pi) for each of them. To obtain composite Ppa/Q plots, Ppa was recalculated from the regression analysis from individual dogs and interpolated at the Q of 2 and 5 L min⁻¹ m⁻². Hemodynamic data and blood gas results were analyzed by paired t test (22).

### RESULTS

The Ppa/Q relationships were linear in all experimental situations with correlation coefficients of 0.98 ± 0.01 at baseline and 0.97 ± 0.01 after induction of oleic acid lung injury.

Oleic acid lung injury was associated with a decrease in Pao2/FiO2 from 397 ± 41 to 86 ± 18 mm Hg (p < 0.01). Arterial PCO2 increased from 39 ± 1 to 47 ± 2 mm Hg (p < 0.01), with a decrease in arterial pH from 7.40 ± 0.01 to 7.36 ± 0.03 (p < 0.05) and a decrease in mixed venous PO2 from 48 ± 2 to 33 ± 2 mm Hg (p < 0.01).

As shown in Table 1, oleic acid lung injury induced moderate decreases in Ppa and decreases in Q, decreased Psa, and slightly increased Pce. Effective capillary pressure increased from 12 ± 1 to 15 ± 1 mm Hg (p < 0.01), but the partitioning of Rppa was unchanged (Figure 1). Both the extrapolated pressure intercept Pi and the slope of the Ppa/Q plots were significantly increased after oleic acid administration (Table 1, Figure 2).

The effects of oleic acid lung injury on indices of pulsatile pulmonary hemodynamics are shown in Table 2. Z0 increased by 60%, with no change in Z1 and a decrease in Zc. The first minimum frequency (fmin) of the Zpva spectrum shifted toward higher frequencies and the phase angle decreased.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Oleic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats min⁻¹</td>
<td>142 ± 8</td>
<td>145 ± 8</td>
</tr>
<tr>
<td>Q, L min⁻¹ m⁻²</td>
<td>5.1 ± 0.3</td>
<td>4.1 ± 0.4²</td>
</tr>
<tr>
<td>Psa, mm Hg</td>
<td>109 ± 5</td>
<td>90 ± 8</td>
</tr>
<tr>
<td>Ppa, mm Hg</td>
<td>16 ± 1</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>Pia, mm Hg</td>
<td>9 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>Pva, mm Hg</td>
<td>3.7 ± 0.6</td>
<td>6.4 ± 0.5¹</td>
</tr>
<tr>
<td>Slope, mm Hg L⁻¹ min⁻²</td>
<td>2.8 ± 0.2</td>
<td>4.3 ± 0.3²</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: HR = heart rate; Pi = linearly extrapolated pressure intercept of Ppa/Q plots at zero flow; Psa = left atrial pressure; Ppa = mean pulmonary arterial pressure; Pia = mean systemic arterial pressure; Q = cardiac index; Slope = slope of Ppa/Q plots.

1 p < 0.01 as compared with baseline.

2 p = 0.01 as compared with baseline.
PP remained unchanged. Wtot did not change, but Wosc/Wtot decreased, along with a decreased ETR. A typical Zpva spectrum in a dog before and after injection of oleic acid is shown in Figure 3.

As shown in Table 3, the time-domain indices of wave reflection were unaffected by oleic acid lung injury. Typical pulmonary artery pressure waveforms decomposed into forward and backward components, before and after oleic acid lung injury, are shown in Figure 4.

DISCUSSION

The present results show that oleic acid lung injury is associated with an increase in Rpva but no change in compliance or in wave reflection. Characteristic impedance is decreased, resulting in an improved energy transfer from the right ventricle to the pulmonary circulation.

Pulmonary Vascular Pressure-Flow Relationships

In the initial report of pulmonary hypertension in patients with ARDS, pulmonary hemodynamic measurements were presented as Ppa versus Q and Rpva versus Q, which disclosed an apparent independence of pulmonary vascular pressures and flows, and a flow dependency of Rpva (6). These observations were tentatively explained by a closing pressure higher than Ppa accounting for increased Ppa in clinical ARDS (6). Studies on experimental ARDS induced in intact dogs by the injection of oleic acid have confirmed a relative independence of Ppa and Q, with a positive extrapolated pressure intercept of linear (Ppa - Ppa/Q) relationships (7). This observation, together with the finding that upstream transmission to Ppa of progressively increased Ppa occurred at values higher than the extrapolated pressure intercept of Ppa/Q plots, confirmed the hypothesis that pulmonary hypertension in oleic acid lung injury is accounted for by an increased closing pressure (7). In the same experimental model, it could be shown that alveolar pressure does not affect Ppa, measured at constant Q and Ppa, until it exceeds the pressure intercept of Ppa/Q plots, suggesting that the site of closure would be at the small extraalveolar vessels (8). In the present study, Ppa/Q plots were generated with rapid, less than 10-s changes in flow, to prevent low Q-mediated sympathetic nervous system-induced pulmonary vasoconstriction, which could have increased the extrapolated pressure intercept and decreased the slope of Ppa/Q plots (21). The present results based therefore on passive, autonomic nervous system-independent, hemodynamic measurements confirm that the pressure intercept of Ppa/Q plots is increased in oleic acid ARDS, compatible with increased small vessel closure accounting for pulmonary hypertension.

However, the concept of closing pressure derives from a Starling resistor model of the circulation, which is difficult to prove exclusively on the basis of Ppa and Qa measurements at variable flow (23, 24). It has been shown that viscoelastic models, which do not postulate vascular closure, may provide valid alternative explanations (23, 24). Alternatively, pulmonary hypertension in the present experiments was due not only to an increased pressure intercept but also to an increased slope

![Figure 1](image1.png)

**Figure 1.** Pressure drop across the arterial (open columns) and the venous (hatched column) segments at: Base - baseline; OA - 90 min after oleic acid administration (n = 8). Numbers inside the arterial columns are the percentages of the pressure drop across the arterial segment (arterial component of the pulmonary vascular resistance, Rpva). Oleic acid lung injury did not affect the partitioning of Rpva.

![Figure 2](image2.png)

**Figure 2.** Composite plots of mean pulmonary artery pressure (Ppa) versus pulmonary blood flow (Q) at: Base = baseline; OA = 90 min after oleic acid administration (n = 8). Ppa was interpolated at the Q of 2 and 5 L/min/m \(^2\) and is presented as the mean ± SEM. *p < 0.001 between oleic acid-induced lung injury and baseline. Oleic acid lung injury was associated with an increase in both slope and pressure intercept of Ppa/Q plots.

![Figure 3](image3.png)

**Figure 3.** Representative pulmonary vascular impedance (Zpva) spectra in a dog at baseline (solid line) and after oleic acid (OA) lung injury (dashed line). After OA administration, pressure at 0 Hz increased from 344 to 423 dyn s cm \(^{-2}\); characteristic impedance decreased from 115 to 83 dyn s cm \(^{-2}\); the frequency of the first minimum shifted from 3.4 to 6.1 Hz and the low-frequencies phase angle decreased.

---

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Oleic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z0, dyn s cm (^{-1}) m (^2)</td>
<td>267 ± 19</td>
<td>426 ± 31*</td>
</tr>
<tr>
<td>Z1, dyn s cm (^{-1}) m (^2)</td>
<td>73 ± 10</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>Zc, dyn s cm (^{-1}) m (^2)</td>
<td>104 ± 8</td>
<td>75 ± 6†</td>
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<tr>
<td>fmin, Hz</td>
<td>0.25 ± 0.05</td>
<td>−0.05 ± 0.06†</td>
</tr>
<tr>
<td>Wtot, mW m (^{-1})</td>
<td>237 ± 36</td>
<td>222 ± 41</td>
</tr>
<tr>
<td>Wosc/Wtot, %</td>
<td>29 ± 3</td>
<td>22 ± 3*</td>
</tr>
<tr>
<td>ETR, %</td>
<td>87 ± 3</td>
<td>65 ± 3†</td>
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<tr>
<td>SV/Pp, ml/mm Hg</td>
<td>1.99 ± 0.20</td>
<td>1.92 ± 0.26</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SEM (n = 8).

---

*Definitions of abbreviations: ETR = energy transmission ratio; fmin = frequency of first minimum; Ppa = first harmonic phase angle; SV/Pp = stroke volume to pulse pressure ratio; Wosc/Wtot = oscillatory hydraulic work to total hydraulic work ratio; Wtot = total hydraulic work; Z0 = 0-Hz impedance (total resistance); Z1 = first harmonic impedance; Zc = characteristic impedance.

---

* p < 0.01 as compared with baseline.
TABLE 3
TIME-DOMAIN INDICES OF PRESSURE WAVE REFLECTION IN DOGS BEFORE AND AFTER OLEIC ACID ACUTE LUNG INJURY

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Oleic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Amp, mm Hg} )</td>
<td>4.8 ± 0.4</td>
<td>1.7 ± 0.3*</td>
</tr>
<tr>
<td>( \text{t_{back}, ms} )</td>
<td>259 ± 17</td>
<td>269 ± 19</td>
</tr>
<tr>
<td>( \text{t_{peak}, ms} )</td>
<td>296 ± 13</td>
<td>301 ± 18</td>
</tr>
<tr>
<td>( \text{t_{peak}, ms} )</td>
<td>360 ± 14</td>
<td>345 ± 16</td>
</tr>
<tr>
<td>( \text{t_{peak}, ms} )</td>
<td>467 ± 24</td>
<td>394 ± 23†</td>
</tr>
</tbody>
</table>

Definition of abbreviations: \( \text{Amp} \) = amplitude of backward wave; \( \text{t_{back}} \) = time to foot of backward wave; \( \text{t_{peak}} \) = time to end of positive backward wave; \( \text{t_{peak}} \) = time to peak of backward wave; \( \text{t_{peak}} \) = time to positive backward wave.

* Values are expressed as means ± SEM (n = 8).
† \( p < 0.05 \) as compared with baseline.

Partitioning of Rpvα
A variety of methods based on more or less complex reference electrical analogs have been previously reported for the estimation of \( \text{Pc}^* \) by the analysis of Ppa decay curves after pulmonary arterial occlusion (25). We applied a biexponential fitting and recalculation of a derived \( \text{Pc}^* \) decay curve based on assumptions of changes in arterial and venous resistances and compliances (19). We found a basal arterial resistance accounting for 60% of total Rpvα, in keeping with previous studies, which used a biexponential fitting (26). Oleic acid injury increased both components of Rpvα without affecting its partitioning, suggesting unchanged longitudinal distribution of resistances. It has been previously shown, using different techniques including microcatheter, small retrograde catheter, and arterial and venous occlusion in isolated perfused dog lungs, that arterial occlusion measures pressures in vessels that are >50 \( \mu \text{m} \) and <1,000 \( \mu \text{m} \) in diameter, and probably close to 100 to 150 \( \mu \text{m} \) in diameter (27). Thus, oleic acid lung injury increases Rpvα at the periphery of the pulmonary arterial tree. This interpretation is compatible with the major arteriolar and capillary structural damage found on microscopic examination of the lungs of dogs with oleic acid lung injury (28) as well as of patients with ARDS (29).

Pulmonary Vascular Impedance
Previous studies of acute lung injury induced by the injection of small (150- to 200-\( \mu \text{m} \)) glass beads in dogs have reported an increase in \( \text{Zc} \) in the minimum of Ppa/\( \Omega \) moduli to higher frequencies, and an increase in low-frequency phase angle negativity, with either no change or a decrease in \( \text{Zc} \) (11–13, 17). Similar changes have been observed in dogs with small (<3-mm-diameter) blood clot pulmonary embolic pulmonary hypertension (15). Pulmonary hypertension is less severe in canine oleic acid lung injury (14) and in patients with ARDS (1). The present results, showing that oleic acid lung injury increases \( \text{Zc} \) but decreases \( \text{Zc} \), are in keeping with previous studies of acute microembolic lung injury in pigs (11–13). Both \( \text{Zc} \) and \( \text{Zc} \) increase in pigs with acute lung injury induced by bronchoalveolar lavage (30), or with small blood clot pulmonary embolism (15), but these results are explained by more muscularized and reactive large porcine pulmonary arteries (15).

Long-standing pulmonary hypertension increases both \( \text{Zc} \) and \( \text{Zc} \) (31). Acute proximal obstruction of the pulmonary arterial tree increases \( \text{Zc} \) (11, 13, 17). Acute increases in \( \text{Zc} \) may be humorally mediated. The administration of norepinephrine decreases pulmonary artery distensibility at normal as well as at high intravascular pressures (32). Stimulation of the stellate ganglion in dogs increases \( \text{Zc} \) without changing Rpvα (33). The serotonin antagonist ketanserin (which also has some \( \alpha \)-adrenergic blocking effects) blocks the \( \text{Zc} \) increase induced by constriction of the left main pulmonary artery (17). Whether the absence of an increase or even decrease in \( \text{Zc} \) in acute lung injury might have an active component is unclear. It would be of interest to use a pharmacological tool to test for reversibility of decreased \( \text{Zc} \). Obvious candidate mediators of an active decrease in \( \text{Zc} \) would be nitric oxide (NO) and prostacyclin, but inhibition of NO synthase or cyclooxygenase increases Rpvα in oleic acid lung injury (34), so that associated changes in \( \text{Zc} \) would be of uncertain interpretation.

Characteristic impedance is a ratio between the inertance and compliance of the proximal pulmonary arterial tree (31). The increase in Ppa in oleic acid lung injury is moderate, and would not therefore be expected to change \( \text{Zc} \) by a major effect on proximal arterial dimensions. On the other hand, any increase in Ppa would tend to passively decrease compliance. In spite of unchanged SW/PP calculations, it is thus possible that an active increase in compliance contributed to the decreased \( \text{Zc} \) in the present experiments. An indirect argument in favor of increased compliance is given by the observed decrease in the amplitude of the reflected wave. Absence of other time-related indices of wave reflection has already been observed in acute small blood clot pulmonary embolism (15) and may simply be related to the distal nature of pulmonary vascular obstruction (11, 13).

In the present experiments, oleic acid lung injury did not increase heart rate, which could have decreased the pulsatile component of hydraulic load (35). Therefore, unchanged or increased compliance, together with unchanged or decreased wave reflection, were the only possible causes of a decreased pulsatile component of the hydraulic load, in agreement with previous studies on acute canine microembolic lung injury (11–13). A decrease in the pulsatile component of hydraulic load decreases pulmonary artery pulse pressure, and therefore decreases right ventricular systolic wall tension, or afterload (31). Decreased ETR, also previously reported in acute canine blood clot embolic pulmonary hypertension (15, 17), can be interpreted as a reduction in the amount of energy necessary for a given amount of forward flow and thus also a decrease in the amount of hydraulic work imposed on the right heart.

Limitations of the Present Study
Oleic acid lung injury is not a perfect representation of clinical ARDS. Both conditions have a large number of pathological and physiological similarities, but oleic acid causes the initial lung injury directly, without requiring inflammatory cells or their products to mediate the initial damage, while ARDS is most often related to sepsis and associated inflammation (14).
In addition to this difference in etiology, oleic acid lung injury also tends to improve after several hours (14), so that it cannot be used to evaluate the effects of pulmonary hypertension on right ventricular function after one to several day’s duration of ARDS. It is possible that in most patients with ARDS, right ventricular remodeling has already occurred at the time of diagnosis of pulmonary hypertension, improving right ventriculovascular coupling. This could be another reason why right heart failure is a relatively rare cause of mortality in ARDS (1–5).

**Clinical Implications**

The pulsatile components normally make up one-third of total hydraulic power output of the right ventricle, as compared with only one-tenth of left ventricular output (31, 35, 36). The right ventricle is thin-walled and has a crescent shape, which limit its capacity to maintain stroke volume in the presence of even moderate increases in pulmonary artery pressures. Right ventricular ejection thus carries a higher component of reactance (i.e., inertia and elastance) than that of the left ventricle, making it more sensitive to relatively smaller changes in Zpva (36).

That mean Ppa or Rpa is a poor predictor of outcome in patients with ARDS (2, 3) may be understandable since steady flow hemodynamic measurements do not take right ventricular pulsatile hydraulic load into consideration. It is of interest that a large-scale study showed systolic Ppa, not mean Ppa, to be a predictor of mortality (3). Is it possible that those patients with ARDS who present with increased mortality due to right heart failure also present with increased Zc, due to progression of disease or other causes that decrease proximal pulmonary arterial compliance and/or increase wave reflection.

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**References**


Proximal pulmonary arterial obstruction decreases the time constant of the pulmonary circulation and increases right ventricular afterload

Alberto Pagnamenta, Rebecca Vanderpool, Serge Brimioule, and Robert Naeije
1 Department of Physiology, Faculty of Medicine, Free University of Brussels, Brussels, Belgium; and 2 Department of Intensive Care, Erasme Academic Hospital, Brussels, Belgium

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Pagnamenta A, Vanderpool R, Brimioule S, Naeije R. Proximal pulmonary arterial obstruction decreases the time constant of the pulmonary circulation and increases right ventricular afterload. J Appl Physiol 114: 1586–1592, 2013. First published March 28, 2013; doi:10.1152/japplphysiol.00333.2013.—The time constant of the pulmonary circulation, or product of pulmonary vascular resistance (PVR) and compliance (Ca), called the RC-time, has been reported to remain constant over a wide range of pressures, etiologies of pulmonary hypertension, and treatments. We wondered if increased wave reflection on proximal pulmonary vascular obstruction, like in operable chronic thromboembolic pulmonary hypertension, might also decrease the RC-time and thereby increase pulse pressure and right ventricular afterload. Pulmonary hypertension of variable severity was induced either by proximal obstruction (pulmonary arterial narrowing) or distal obstruction (microembolism) eight anesthetized dogs. Pulmonary arterial pressures (Ppa) were measured with high-fidelity micromanometer-tipped catheters, and pulmonary flow with transonic technology. Pulmonary ensnarement increased mean Ppa, PVR, and characteristic impedance, decreased Ca and the RC-time (from 0.46 ± 0.07 to 0.30 ± 0.03 s), and increased the oscillatory component of hydraulic load (Wosc/Wtot) from 25 ± 2 to 29 ± 2%. Pulmonary microembolism increased mean Ppa and PVR, with no significant change in Ca and characteristic impedance, increased RC-time from 0.53 ± 0.09 to 0.74 ± 0.05 s, and decreased Wosc/Wtot from 26 ± 2 to 13 ± 2%. Pulse pressure increased more after pulmonary ensnarement than after microembolism. Concomitant measurements with fluid-filled catheters showed the same functional differences between the two types of pulmonary hypertension, with, however, an underestimation of Wosc. We conclude that pulmonary hypertension caused by proximal or distal obstruction is associated with a decreased RC-time and increased pulsatile component of right ventricular afterload.

noticeable exception is pulmonary hypertension secondary to left ventricular failure (24). In these patients, RC-time is decreased because of a stiffer pulmonary arterial tree caused by increased pulmonary venous pressure (16).

Proximal pulmonary arterial obstruction has been shown to increase wave reflection, which increases pulse pressure (PP) at any given level of mean Ppa (mPpa) (7, 8, 26). This finding has been confirmed in patients with chronic thromboembolic pulmonary hypertension (CTEPH) (4, 17, 18). Increased wave reflection with disproportionate increase in systolic Ppa (sPpa) relative to mPpa would add to the effects of increased pulmonary arterial stiffness in decreasing calculated Ca and RC-time and thereby increase RV afterload at any given level of PVR (6, 26).

We, therefore, investigated the effects of proximal pulmonary vascular obstruction by pulmonary arterial ensnarement, and of distal pulmonary vascular obstruction by the injection of microbeads in anesthetized dogs. Pulmonary vascular function was quantified in both time and frequency domain using high-fidelity but also standard fluid-filled catheter equipment and trans-thoracic echocardiography, as used in clinical practice to allow for optimal translation. The results show that purely proximal increase in PVR decreases RC-time and increases RV afterload.

METHODS

Preparation. Eight mongrel dogs (mean weight 30 kg; range, 19–48 kg) were included in the present study, which was approved by the Committee on the Care and Use of Animals in Research of the Brussels Free University School of Medicine. Anesthesia was induced with propofol (10 mg/kg), and thereafter the dogs were anesthetized with α-chloralose (20 mg/h) and repeated morphine boluses (0.1 mg/kg) and paralyzed with pancuronium bromide (0.2 mg·kg⁻¹·h⁻¹) to maintain anesthesia and apnea. The dogs were ventilated (Elena 900 B servo-ventilator, Siemens Elema, Solna, Sweden) via a cuffed endotracheal tube in the volume control mode. The inspired O₂ fraction was 0.4. The respiratory rate was 10 breaths/min, the tidal volume was 15–25 ml/kg, adjusted to maintain arterial Pco₂ between 35 and 45 Torr, and the positive end-expiratory pressure was 5 cmH₂O. Periodic deep inspirations were administered to prevent atelectasis formation. Body temperature was maintained at 36–38°C using an electric heating pad. When metabolic acidosis occurred, it was corrected with a slow infusion of sodium bicarbonate. Physiological saline was infused at 300 ml/h, with rate adaptation to maintain right and left ventricular filling pressures and blood pressure within normal limits.

A balloon-tipped flow-directed pulmonary catheter (model 131H-7F; Baxter Edwards, Irvine, CA) was inserted in the main pulmonary artery through the left external jugular vein for measurements of mPpa, sPpa, and diastolic Ppa (dPpa), right atrial pressure, cardiac output (Q), central temperature, and for mixed venous blood sampling. A polyethylene catheter was inserted in the abdominal aorta via
the right femoral artery for measurements of systemic arterial pressure (Psa) and for arterial blood sampling. In all of the animals, left lateral thoracotomy in the fourth intercostal space was performed. The tip of a Swan-Ganz catheter (model 131H-7F; Baxter Edwards, Irvine, CA) was inserted in the left atrium via the atrial appendage to measure left atrial pressure (Pla). A 16- to 24-mm no-constricting ultrasonic flow probe (T101, Transonic Systems, Ithaca, NY) was positioned around the main pulmonary artery for the measurement of instantaneous pulmonary Q. The transonic flowmeter system is linear to 60 Hz, with a flat amplitude response to 35 Hz. A 5F high-fidelity manometer-tipped catheter (model SPC 350, Millar Instruments, Houston, TX) was introduced through the RV into the main pulmonary artery, and its tip was positioned just distal to the flow probe for the measurement of the instantaneous Ppa. The flow response of the manometer system is flat beyond 200 Hz. The chest was tightly closed, and some large inspirations were then performed to reexpand the lungs, but no attempt was made to restore a negative pleural pressure.

**Measurements.** Heart rate (HR) was determined from a continuous-ly monitored electrocardiographic lead. Ppa and pulmonary arterial flows were measured with the high-fidelity microtransducer-tipped catheters and the ultrasonic flow probe, respectively. Psa, Pla, and also Ppa were measured using Gould Statham P50 transducers (Gould, Oxnard, CA). The vascular pressure and flow signals were displayed by using a monitoring system (Sirecust 404, Siemens, Erlangen, Germany) and recorded on a six-channel Gould recorder (model 2600S, Gould, Instruments Division, Cleveland, OH). The pressure transducers of fluid-filled catheters were zero referenced at midchest, and vascular pressures were obtained at end expiration. Mean Q was measured using the thermodilution technique as a mean of at least three successive measurements (CO-set, Baxter; Edwards, Santa Ana, CA). The measurements of Ppa were measured using the ultrasonic flow probe. The zero Q from the ultrasonic flow probe was adjusted to the end-diastolic value, assumed to be zero. The instantaneous pulmonary pressures and flow signals were sampled at 200 Hz using an analog-to-digital converter (RTI 800, Analog Device), stored, and analyzed on a personal computer. Instantaneous pulmonary flow was also measured by transthoracic Doppler echocardiography using a 3.5-MHz probe (SONOS 2000, Palo Alto, CA) with the dog in a lateral position. Pulsed-Doppler velocity was recorded in the RV outflow tract using the short-axis parasternal view, as previously described (10). Sampling frequency and gain setting were optimized to obtain the best flow-velocity envelope. All transthoracic Doppler echocardiographies were performed by the same investigator (A. Pagnamenta). Ppa and flow signals were recorded after the Swan-Ganz catheter was withdrawn to the same position as the high-fidelity catheter, as close as possible to the pulsed Doppler pulmonary artery flow-velocity sampling site. The signals were visually checked for quality and then were synchronized by an ECG artifact and recorded on a paper of 100 mm/s using the built-in printing system of the echocardiograph. Pressure and flow-velocity were “manually” scanned (UnGraph for Windows, Biosoft, Cambridge, UK), digitized at a sampling rate of 200 Hz, and analyzed on a personal computer. For each dog, a series of thermodilution Q and concomitant average Doppler flow velocities were used to calculate a conversion factor for the flow-velocity tracings into volume flow.

**Calculations.** Pulmonary vascular impedance (PVZ) was calculated from the Fourier series expressions for pressure and flow signals (20, 26). Between three and six end-expiratory heartbeats were analyzed for each data-collection interval. Pressure and flow harmonics with amplitude of <1% of pressure and off flow pulse amplitude were excluded from PVZ calculations. The PVZ modulus was computed as the ratio between pressure and flow moduli, and its phase was computed as the difference between pressure and flow phases. The impedance at 0 Hz (Zo) was taken as the total resistance (mPpa/Q), and the characteristic impedance (Zc) was calculated as the average of impedance moduli between 2 and 15 Hz. From the PVZ spectra, we also derived the first harmonic modulus (Z1) and the first harmonic phase angle (Φ1). Total hydraulic power (Wtot) was calculated as the integral of the instantaneous product of pressure times flow. Steady hydraulic power (Ws) was calculated as the product of mean pressure by mean flow, and Wosc as the difference between total and steady power.

Pulmonary arterial Ca was calculated from the ratio between stroke volume (SV) and PP. The RC-time constant was found by fitting the function, Ca = RC-time/TPVR to the pulmonary arterial banding and embolization data, where TPVR is the total PVR (mPpa/Q). This analysis was done with MATLAB 7.13, R2011b (The MathWorks, Natick, MA).

Arterial and mixed venous blood gases were measured by an automated analyzer (ABL 2, Radiometer, Copenhagen, Denmark) immediately after the samples were drawn and corrected for temperature.

**Protocol.** As soon as the animals were in steady-state conditions (stable HR, Psa, Ppa, and Q for 20 min), a first baseline set of all hemodynamic and blood-gas measurements was obtained. Instantaneous Ppa and flow signals were sampled for PVZ calculations. Thereafter, the same measurements were repeated during the following conditions:

1. After ensnarement of the right-end left pulmonary arteries distal to the intravascular catheter tips, at two different Ppa levels: mPpa of 22 mmHg and mPpa of 27 mmHg. Attempts at higher Ppa caused too much hemodynamic instability and were thus omitted. Care was taken to avoid proximal pulmonary arterial tree distortion by the ensnarement.
2. At baseline 2: after waiting sufficient time to be sure that there was no residual effect of proximal constriction assessed by a return of HR, Psa, and Ppa values to baseline levels.

One to three grams of 100-μm glass beads (Sigma, St. Louis, MO) were then slowly administered into the right atrium in around 20 min. The embolization was carried out until mPpa reached 35 mmHg and then stopped, allowing mPpa to stabilize in 20–30 min at a value around 25 mmHg. A second embolization was carried out until mPpa reached 45 mmHg and then stopped, allowing mPpa to stabilize in 20–30 min at a value around 35 mmHg.

**Statistics.** Results are expressed as mean values ± SE. Hemodynamic data and blood-gas results were analyzed by a repeated-measures analysis of variance. When the F-ratio of the analysis of variance reached a P < 0.05 critical level, modified t-tests were used to compare two different situations (27). A P critical level < 0.05 of the modified t-tests was accepted as indicating statistical significance. PVZ calculated using the fluid-filled catheter and echocardiography and PVZ calculated with the high-fidelity catheter and ultrasonic flow probe were compared by correlation analysis and by Bland-Altman agreement analysis by calculating the bias (mean of the difference between the two methods) and the 95% limits of agreement (2 standard deviations around the mean difference) (1).

**RESULTS**

Effect of pulmonary artery ensnarement and microembolization on pulmonary hemodynamics. See Table 1. Progressive ensnarement increased mPpa and HR, decreased Q, while Pla remained unchanged. Ensnarement increased mPpa with a proportional increase in sPpa (1.8 × mPpa) and a small effect on dPpa (0.3 × mPpa) pressure (Fig. 1). All measurements returned to baseline after relief of ensnarement, with the exception of a slight decrease in Pla, which was compensated for by fluid-filling. There were no significant differences between the two baselines. Progressive microembolization increased mPpa, HR, and Pla, decreased Psao, and Q remained unchanged. Acute microembolism increased mPpa with an increase in sPpa that was proportionally less than after ensnarement (1.3 × mPpa), while dPpa increased more (0.8 × mPpa). This resulted in a larger PP in the ensnare-
Table 1. Steady hemodynamic data in eight dogs at baseline, two levels of progressive ensnarement of the pulmonary arteries, a second baseline, and two levels of progressive microembolization of the distal pulmonary circulation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline 1</th>
<th>Ensnarement 1</th>
<th>Ensnarement 2</th>
<th>Baseline 2</th>
<th>Embolization 1</th>
<th>Embolization 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>138 ± 8</td>
<td>151 ± 6</td>
<td>157 ± 6*</td>
<td>127 ± 10</td>
<td>164 ± 7†</td>
<td>157 ± 3†</td>
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<td>Psa, mmHg</td>
<td>118 ± 7</td>
<td>120 ± 6</td>
<td>124 ± 6</td>
<td>120 ± 7</td>
<td>107 ± 10†</td>
<td>109 ± 10†</td>
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<td>mPpa, mmHg</td>
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<td>27 ± 2*</td>
<td>17 ± 2</td>
<td>26 ± 1†</td>
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<td>sPpa, mmHg</td>
<td>28 ± 4</td>
<td>38 ± 6</td>
<td>44 ± 5*</td>
<td>27 ± 3</td>
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<td>44 ± 7†</td>
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<td>dPpa, mmHg</td>
<td>11 ± 2</td>
<td>12 ± 1</td>
<td>11 ± 1</td>
<td>10 ± 2</td>
<td>19 ± 1†</td>
<td>26 ± 3†</td>
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<td>Pla, mmHg</td>
<td>7 ± 2</td>
<td>6 ± 2</td>
<td>8 ± 2</td>
<td>5 ± 2</td>
<td>8 ± 2†</td>
<td>9 ± 2†</td>
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<td>Q, 1·min⁻¹·m⁻²</td>
<td>4.5 ± 0.9</td>
<td>3.8 ± 0.6</td>
<td>3.6 ± 0.6*</td>
<td>3.4 ± 0.6</td>
<td>3.2 ± 0.4</td>
<td>3.5 ± 0.5</td>
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<td>SV, ml</td>
<td>33 ± 4</td>
<td>25 ± 3</td>
<td>20 ± 1*</td>
<td>27 ± 3</td>
<td>21 ± 2</td>
<td>24 ± 3</td>
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<td>Ca, ml/mMHg</td>
<td>2.1 ± 0.2</td>
<td>1.1 ± 0.1*</td>
<td>0.7 ± 0.1*</td>
<td>1.9 ± 0.3</td>
<td>1.6 ± 0.2</td>
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<tr>
<td>RC-time, s</td>
<td>0.46 ± 0.07</td>
<td>0.35 ± 0.03</td>
<td>0.30 ± 0.03*</td>
<td>0.53 ± 0.09</td>
<td>0.74 ± 0.05</td>
<td>0.83 ± 0.12†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 dogs. HR, heart rate; Psa, mean systemic arterial pressure; mPpa, mean pulmonary arterial pressure; sPpa, systolic pulmonary arterial pressure; dPpa, diastolic pulmonary arterial pressure; Pla, left atrial pressure; Q, cardiac output; SV, stroke volume; Ca, compliance; RC, pulmonary vascular resistance-Ca. *P < 0.05 compared with baseline 1. †P < 0.05 compared with baseline 2.

ment model at the same mPpa (PP_{ensnarement} = 1.5 mPpa - 1 vs. PP_{embolism} = 0.5 mPpa + 3.7).

With progressive ensnarement, SV decreased from 33 to 20 ml as a result of decreased Q and increased HR. Microembolization increased HR, but, with no change in Q, there was no significant change in SV. The result was that, with progressive ensnarement, Ca decreased but stayed approximately the same with microembolism (Table 1). The RC-time decreased with ensnarement and increased with microembolism (Fig. 2).

Effect of pulmonary artery ensnarement and microembolization on PVZ. See Table 2. There were no significant differences in the baseline measurements before and after progressive ensnarement. Progressive ensnarement increased Z0, Z1, and Zc, with no change in the Ph1. Wot increased with unchanged Wosc/Wot. Progressive microembolization increased Z0 and had no effect on Z1 and Zc. The first minimum frequency of the PVZ spectrum shifted toward higher frequencies. The Ph1 decreased, and Wot increased, but Wosc/Wot decreased.

Contrasted effects of ensnarement and microembolism on PVZ spectra of three animals at the same severity of pulmonary hypertension (Z0) with marked increase in the ratios of pressure and flow moduli over the entire range of the spectrum are illustrated in Fig. 3.

Validation of instantaneous pressure and flow measurements with fluid-filled catheters and transhoracic Doppler echocardiography. There were significant correlations between high-fidelity and fluid-filled catheter methods for PP and mPpa (Fig. 4) and the impedance metrics, Z0, Z1, Zc, RC, and WS (Fig. 5 and Table 3). From the Bland-Altman analysis, there was little bias between the methods for PP and mPpa, fluid-filled catheter measurements overestimated Z0, Z1, Zc, and WS, but the 95% limits of agreement with the reference method were relatively small (Fig. 4 and Table 3). The fluid-filled catheter-derived measurements underestimated both the Ph1 and the Wosc (Table 3). For these two variables, there was a poor correlation between the methods.

DISCUSSION

The present results show that the time constant of the pulmonary circulation is shortened in pulmonary hypertension caused by proximal obstruction compared with distal obstruc-

![Fig. 1. Correlation between systolic mean pulmonary arterial pressure (mPpa) and diastolic mPpa in pulmonary hypertension induced by proximal obstruction (ensnarement) and distal obstruction (microembolism).](image1)

![Fig. 2. The inverse relationship between compliance (Ca) and total pulmonary vascular resistance (TPVR). In the ensnarement model, the RC-time is decreased (0.39 s, R² = 0.61, P = 0.001) compared with the microembolization model (0.61 s, R² = 0.41, P = 0.004).](image2)
Table 2. Pulsatile hemodynamics at baseline, two levels of progressive ensnarement of the pulmonary arteries, a second baseline, and two levels of progressive microembolization of the distal pulmonary circulation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline 1</th>
<th>Ensnarement 1</th>
<th>Ensnarement 2</th>
<th>Baseline 2</th>
<th>Embolization 1</th>
<th>Embolization 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z, dyn·s·cm⁻²·m⁻²</td>
<td>376 ± 52</td>
<td>498 ± 31</td>
<td>655 ± 53*</td>
<td>436 ± 69</td>
<td>712 ± 79</td>
<td>864 ± 171†</td>
</tr>
<tr>
<td>Z₁, dyn·s·cm⁻³·m⁻²</td>
<td>85 ± 9</td>
<td>176 ± 18*</td>
<td>362 ± 31*</td>
<td>86 ± 11</td>
<td>66 ± 5</td>
<td>110 ± 23</td>
</tr>
<tr>
<td>Z₂, dyn·s·cm⁻³·m⁻²</td>
<td>113 ± 8</td>
<td>181 ± 15*</td>
<td>267 ± 11*</td>
<td>108 ± 8</td>
<td>89 ± 7</td>
<td>95 ± 15</td>
</tr>
<tr>
<td>Ph₁, rad</td>
<td>0.07 ± 0.11</td>
<td>0.07 ± 0.08</td>
<td>0.07 ± 0.09</td>
<td>0.06 ± 0.11</td>
<td>-0.29 ± 0.16†</td>
<td>-0.67 ± 0.09†</td>
</tr>
<tr>
<td>Wtot, mW/m²</td>
<td>264 ± 72</td>
<td>290 ± 83</td>
<td>326 ± 56*</td>
<td>175 ± 44</td>
<td>230 ± 36</td>
<td>308 ± 61†</td>
</tr>
<tr>
<td>Wosc/Wtot, %</td>
<td>25 ± 2</td>
<td>28 ± 2</td>
<td>29 ± 2*</td>
<td>26 ± 2</td>
<td>16 ± 7</td>
<td>14 ± 2†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 dogs. Z₀, 0-Hz impedance (total resistance); Z₁, first harmonic impedance; Z₂, characteristic impedance; Ph₁, first harmonic phase angle; Wtot, total hydraulic work; Wosc/Wtot, oscillatory hydraulic work-to-total hydraulic work ratio. *P < 0.05 compared with baseline. †P < 0.05 compared with baseline.

Fig. 3. Average impedance (Z) spectra in 3 dogs at baseline and with identical or very close 0-Hz impedance (Z₀) after induction of pulmonary hypertension with either ensnarement or microembolism. Ensnarement shifted the entire impedance spectrum to higher ratios of pressure and flow moduli. Vertical and horizontal bars indicate SE.

et al. (6) showed that isolated decrease in Ca at unchanged PVR increased RV systolic pressure with late systolic peak and increased PP. Calvin et al. (3) showed that a proximal pulmonary arterial obstruction increased both Z₀ and Z₂, whereas, with a distal obstruction, Z₀ remains unchanged or decreased. Because Z₂ is a ratio between inertance and Ca, the decrease of Z₂ in pulmonary hypertension on distal small arteriolar obstruction was tentatively explained by a compensatory dilatation of the proximal arterial tree (3). Fitzpatrick and Grant (7) showed that pulmonary arterial ensnarement increased both Z₀ and Z₂ and decreased Ca, while the application of positive end-expiratory pressure to compress peripheral vessels, and thus increased peripheral resistance, increased Z₀ but had negligible effects on Z₂ and Ca. In the present experiments, Z₂ increased after pulmonary arterial ensnarement and was unchanged after microembolism, but with directional changes in Ca. The reason why Ca was preserved in microembolic pulmonary hypertension is unclear. Even though the mPpa in these animals increased from 30–35 mmHg, this did not appear sufficient to affect the slope of diameter-pressure relationships. Active neurohumoral mechanisms contributing to the observed changes cannot be excluded, even though this has been explored in only one study, which showed a decrease in Z₀ during pulmonary arterial ensnarement after the administration of the serotonin receptor blocker ketanserine (7). Decreased Ca and increased Z₂ in pulmonary arterial banding can be explained by the combined effects of mechanical interference of the maneuver and wave reflection on proximal constriction.

In the present experiments, increased mPpa and PVR were accompanied by an increase in total pulmonary arterial hydraulic work, indicating increased RV afterload. However, the pulsatile component of hydraulic work increased after pulmonary arterial ensnarement and decreased after microembolism. A faster HR could have decreased the pulsatile component of hydraulic work (15). However, there were no significant differences in HR between our two pulmonary hypertension models. Thus increased pulsatile hydraulic work after ensnarement is to be explained by contrasting changes in low- and high-frequency impedance and associated changes in Ca.

The RC-time was markedly shorter in “proximal” pulmonary hypertension as a model of operable CTEPH, compared with “distal” pulmonary hypertension as a model of PAH. This is in contrast to clinical studies that reported constant RC-time and oscillatory component of hydraulic load independently of type of pulmonary hypertension (21, 23). These differences between experimental and clinical pulmonary hypertension
may be explained by better control of the site of obstruction in the present experiments, while pulmonary vasculopathy in CTEPH tends to spread over the entire pulmonary arterial tree (9). It may be noted that there was a longer RC-time at baseline before the injection of microbeads. This may be related to previous ensnarement, even though care was taken to observe return of HR, mPpa, and Q to baseline. The RC-time number is a product of two ratios and, therefore, sensitive to small changes in either one of its several components, in relation to incompletely recovered stability or unnoticed changes in depth of anesthesia. Ppa after ensnarement and before microbead injection was decreased, by an average of 2 mmHg within limits of normal, illustrating imperfect maintenance of hemodynamic stability by fluid loading. However, such a small decrease in Ppa without other hemodynamic alterations would be unlikely to affect the RC-time. We, therefore, believe that the difference in RC-time between the two pulmonary hypertension models is true, as it was enhanced over time with progressive increase in pulmonary pressures.

sPpa, dPpa, and mPpa are tightly correlated, with simple formulas to predict one from another that seem applicable to any type of pulmonary hypertension (5). This remains true only if Cais predictable at any level of PVR and RC-time remains constant. A recent study reported on a decreased RC-time in heart failure (24), which is explained by increased pulmonary wedge pressure causing a decrease in Cais at any level of PVR (16). The present results report on exclusive proximal obstruction as another cause of decreased RC-time and show the associated increase in Ppa and oscillatory arterial hydraulic work. Previously reported equations to predict mPpa from sPpa, which are used in Doppler echocardiographic studies of the pulmonary circulation, have to be used with great caution in case of decreased Cais or increased ZC.

Instantaneous pulmonary arterial flow velocity can be measured by transthoracic pulsed Doppler echocardiography and converted into volume flow using a conversion factor obtained by conventional thermodilution Q measurement (10, 11). It has been generally assumed that the frequency response of fluid-filled thermodilution Swan-Ganz catheters that are used for routine right heart catheterization would be insufficient for accurate instantaneous pressure measurements, especially at high HRs like in the present study (25). However, the present results confirm that realistic pressure and flow measurements to be used in the calculation of PVZ can be obtained using simple
Fig. 5. Linear regression (left) and Bland-Altman analysis (right) for $Z_0$ (top) and characteristic impedance ($Z_c$; bottom) between the values obtained with the high-fidelity catheter and ultrasound flow probe, and the fluid-filled catheter and echocardiography.

**Table 3.** Linear regression and Bland-Altman analysis for impedance metrics obtained with the high-fidelity and fluid-filled catheter methodology.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression</th>
<th>Bland-Altman</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>$R^2$</td>
</tr>
<tr>
<td>$Z_0$, dyn cm$^{-1}$ m$^{-2}$</td>
<td>0.90</td>
<td>0.99</td>
</tr>
<tr>
<td>Ph1, rad</td>
<td>0.41</td>
<td>0.34</td>
</tr>
<tr>
<td>Ws, mW/m$^2$</td>
<td>0.93</td>
<td>0.95</td>
</tr>
<tr>
<td>$W_{osc}$, mW/m$^2$</td>
<td>1.81</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Ws, steady hydraulic power.

shown canine and human PVZ spectra are remarkably similar except for body size-related differences in the high-frequency impedance of humans (19). Given that PVZ is more descriptive of the pulmonary circulation, it is interesting there are only a few reports on the PVZ spectra in humans (20). This is likely due to the difficulty of placement of the high-fidelity micromanometer-tipped catheter in the pulmonary artery and cost. However, as we show in this paper, it is possible to measure meaningful PVZ magnitudes using tools that are commonly used in reference pulmonary hypertension centers. A limited number of clinical studies that have used fluid-filled catheters and echocardiography to measure PVZ have demonstrated sensitivity to pharmacological interventions (10, 11) and, in one pediatric study (11), prognostic relevance.

To what extent the ensmare of the pulmonary arteries and microembolism are microembolism is not a new model of CTEPH and PAH is not exactly known. Successful pulmonary endarterectomy does not always reverse pulmonary hemodynamics to normal, indicating more widespread vasculopathy than generally assumed (8). Pulmonary arterial hypertension may be associated with secondary proximal arterial remodeling. Therefore, caution should be exerted in the clinical extrapolation of the present results.
In conclusion, the site of increased PVR in pulmonary hypertension affects the time constant of the pulmonary circulation. Purely proximal obstruction like in purely operable CTEPH may be added to heart failure as a cause of shortened RC-time and relative increase in RV afterload.

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Present address of A. Pagnamenta: Dept. of Intensive Care, Mendrisio Regional Hospital, Mendrisio, Switzerland.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES

5. RIGHT VENTRICULAR-PULMONARY ARTERIAL COUPLING

Although PAH is a disease that primarily affects the pulmonary vasculature the symptomatology and outcome of patients with PAH are principally determined by right ventricular (RV) function [1-3]. Moreover RV function is also a major independent prognostic factor in patients with PH-LHD, advanced pulmonary diseases and congenital heart diseases [4]. Accurate quantification of RV total hydraulic load by pulmonary vascular impedance (PVZ) without taking into account the adaptation of the RV to the increased afterload is a simplification that neglects the important dependency of right ventricular function on pulmonary arterial function. Accordingly, the concept of right ventricle-pulmonary circulation unit emerges requiring to study pulmonary circulation and RV function simultaneously [5]. This approach seems not only to be valid and useful from a physiological/pathophysiological point of view but also from a therapeutic perspective [2]. The normal RV is a thin-walled flow generator coupled with a high compliance low resistance system, the pulmonary circulation [6, 7]. RV pressures are significantly lower than LV pressures under normal conditions [8], and the pulmonary circulation has a much lower vascular resistance, greater artery compliance and a lower waves reflection as compared with the systemic circulation [9]. Thereafter the RV is more sensitive to afterload changes than the LV [10]. In fact, an acute increase in RV afterload such as produced by proximal arterial constriction in order to mimic massive pulmonary embolism induces an acute RV dilatation followed by a rapid pump failure [11]. On the contrary a more gradual increase in RV afterload allows the RV to adapt and to remodel, like the LV faced to an increased LV afterload [12]. In experimental setting ventricular remodeling is usually differentiated in two patterns: adaptive (or homeometric adaptation) and maladaptive (or heterometric adaptation) remodelling. Concentric hypertrophy with preserved systolic and diastolic function, and unchanged ventricular volumes characterizes adaptive remodelling, which is observed in patients with Eisenmenger syndrome. Eccentric hypertrophy with impaired systolic and diastolic function, and increased ventricular volumes characterizes maladaptive remodelling, which is observed in patients with IPAH and CTD-associated PAH [2, 13]. At the 5th WSPH held in 2013 the following definition of right heart failure (RHF) was endorsed. “RHF is a dyspnoea fatigue syndrome with eventual increased systemic venous pressure caused by suboptimal flow output of the RV in response to metabolic demand as a consequence of elevated RV afterload” [2]. More recently the International Right Heart Failure Foundation proposed the following definition of RHF: “RHF is a clinical syndrome due to an alteration of structure and/or function of the right heart circulatory
system that leads to sub-optimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures – at rest or with exercise” [14].

5.1. Right ventricular pressure-volume loops

The best available load-independent assessment of cardiac contractility in vivo is the maximal elastance (Emax) or the maximum slope of a pressure-volume loop during the cardiac cycle [12, 15, 16]. For the LV Emax is equal to end-systolic elastance (Ees) as measured at the left upper corner of a square-shaped pressure-volume loop [17]. Under normal conditions, given the low pulmonary vascular impedance the RV pressure-volume loop has a triangular shape rather than a square one and Ees may be unreliable because Emax occurs before the end of RV ejection [18]. The manipulation of venous return by inflation of a vena cava inferior balloon generates a family of pressure-volume loops permitting to derive an accurate Emax as illustrated in Figure 1.
Figure 1. A: a normal right ventricular pressure-volume loop is of triangular shape, with maximum elastance (or Ees, point A) occurring before the end of systole (point B). B: a decrease in venous return allows for the recording of a family of right ventricular pressure-volume loops and the use of end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) to define systolic and diastolic function. Reproduced from Maughan WL, et al. with permission.

The shape of the RV pressure-volume loop changes as a consequence of increased impedance in PH so that RV pressure at Emax approximates peak systolic pressure [19]. Bedside instantaneous pressure and volume measurements of the RV are not actually available for routine assessment of Emax. RV Emax determinations with conductance catheters and vena cava inferior balloon obstruction have been reported in normal subjects [20]. Emax measurements using conductance catheters and a family of pressure-volume loops by manipulating venous return using a Valsalva manoeuvre have been recently reported in patients with PAH [21]. Afterload as it is “seen” by the RV can be calculated as arterial elastance (Ea), which is graphically derived on a pressure volume loop by dividing pressure at Emax by stroke volume [12]. The ratio of Emax to Ea defines RV-arterial coupling as presented in Figure 2. The optimal coupling of the RV to the pulmonary circulation occurs at Emax/Ea ratios of 1.5-2, corresponding to the optimal energy transfer form the RV to the pulmonary circulation [12].
**Figure 2.** Cartoon illustrating right ventricular pressure-volume loops at varying levels of preload decline. The slope of the line connecting the end-systolic pressure points is the end-systolic elastance ($E_{ES}$), a load-independent measure of contractility. The $E_{ES}$ can be compared with effective arterial elastance ($E_A$) to assess coupling of right ventricular contractility to pulmonary vasculature load. Reproduced from Tedford RY\textsuperscript{37} with permission.

5.2. Single-beat method for measurement of right ventricular elastance

Given the complex geometry of the RV, instantaneous measurements of RV volumes may be quite problematic. Furthermore manipulations of venous return to generate families of pressure-volume curves require the insertion of an inferior vena cava balloon. Due to these intrinsic limitations a single-beat approach has been primarily developed for the LV [22] and thereafter for the RV [23] as valuable alternative to ventricular pressure-volume loop for the assessment of ventriulo-arterial coupling because the single-beat method does not require the measurement of absolute RV volumes. This approach is based on a maximum pressure (Pmax) assessment from a simple sinusoidal extrapolation of the early and late parts of a RV pressure curve, an integration of pulmonary Q, and synchronisation of the signals. Emax is estimated from the slope of a tangent from Pmax to the pressure-volume curve as presented in Figure 3. Pmax corresponds to the pressure the RV would generate during a non-ejecting beat at end-diastolic volume (maximal isovolumic pressure). Ea is graphically derived on a pressure volume loop as the absolute slope of the drawn line from end-systole to end-diastole. The contractility corrected for afterload or the RV-arterial coupling is defined as previously mentioned by the Emax/Ea ratio.
Figure 3. Single-beat method for measurement of right ventriculo-arterial coupling in an anesthetized dog. A. good agreement between directly measured maximum right ventricular (RV) pressure (Pmax) when the pulmonary arterial trunk is clamped during one heart beat (black line) and extrapolated Pmax (gray line). The slightly lower observed Pmax is explained by proximal pulmonary arterial compliance. B: Pmax is calculated from early and late portions of the RV pressure curve, end-systolic elastance (Ees) or arterial elastance (Ea) graphically determined from Pmax and relative changes in volume and pressure during systole. Reproduced from Brimioulle S, et al.\textsuperscript{23} with permission.
5.3. Simplified and alternative methods to assess RV-arterial coupling

a) Volume method: given the common pressure term, a ratio of elastances can be simplified as a ratio of volumes as followed: from $E_{\text{max}}/E_{\text{a}} = (\text{ESP}/\text{ESV})/(\text{ESP}/\text{SV})$ to $\text{SV}/\text{ESV}$. The $\text{SV}/\text{ESV}$ ratio is based on two incorrect assumptions. First, the ESP-ESV relationship is linear and crosses the origin [24], but ventricular volume at zero filling pressure is clearly different from zero, and therefore ESP-ESV relationship underestimates $E_{\text{max}}$. Second, $E_{\text{es}}$ as previously mentioned does not coincide with $E_{\text{max}}$. However, recently Vanderpool et al. found in a cohort study of heterogeneous patients ($n = 50$) with PH that $\text{SV}/\text{ESV}$ is the only independent predictor of transplantation-free survival [25].

b) Pressure method: this method is based on $P_{\text{max}}$ calculation from a RV curve obtained during a RHC, $P_{\text{APm}}$ as surrogate of ESP and RV volumes measurements by MRI. $E_{\text{max}}$ is calculated as followed: $E_{\text{max}} = (P_{\text{max}} - P_{\text{APm}})/(\text{EDV}-\text{ESV})$. $V_0$ is the extrapolated volume intercept of the linear fit of a multipoint maximum elastance pressure-volume relationship and assumed to be zero it allows to simplify $(P_{\text{max}} - P_{\text{APm}})/(\text{EDV}-\text{ESV})$ to $P_{\text{max}}/P_{\text{APm}} - 1$ [24]. This estimated $E_{\text{max}}$ is more preload dependent as previously estimated [24]. The pressure method of RV arterial coupling was recently not identified as independent predictor of transplantation-free survival [25].

c) The pump function graph: originally developed for the LV in a pump function curve $\text{SV}$ is plotted against mean ventricular pressure [26]. This representation is helpful in appreciating the differentiate $\text{SV}$ changes following a decrease in PVR depending on the RV pressure: at high RV pressure $\text{SV}$ increases more than pressure decreases, whereas at low RV pressure $\text{SV}$ increases less than pressure decreases [2]. Originally used to explain more severe RHF at any level of $P_{\text{APm}}$ in SSc-PAH as compared with IPAH [27], this observation was later confirmed using $E_{\text{max}}/E_{\text{a}}$ calculations [21]. The use of the pump function curve is limited by its preload dependency and by the use of mean RV pressure or $P_{\text{APm}}$ as surrogates for RV pressure at $E_{\text{max}}$.

d) The contractile reserve: it is determined by the dynamic assessment of the contractility corrected for afterload. This ventricular reserve can be determined by pharmacologic stress test or exercise. Recently Grüning et al. assessed exercise-induced PAPs increase by stress echocardiography and maximum oxygen consumption per kg (peak $\text{VO}_2$) in 124 patients with severe IPAH and inoperable CTEPH with impaired RV function [28]. Exercise-induced PAPs increase $\leq 30$ mmHg as compared to baseline was identified as a strong independent predictor of poor survival with the highest adjusted
hazard ratio of all variables (HR = 2.84; 95%-CI 1.92 to 6.78) in the Cox proportional hazard model. Patients with an exercise-induced PAPs increase ≤ 30 mmHg and a peak VO₂ ≤ 11.4 mL · min⁻¹ · kg⁻¹ had the worst survival rate. Assessment of exercise-induced PAPs increase eventually associated with peak VO₂ determination can contribute to monitor treatment response in PAH/CTEPH patients with possible early identification of insufficient/inadequate therapeutic management.

5.4. Resistance compliance time

The simplest clinical measure of pulmonary vascular compliance (Ca) is the ratio between stroke volume (SV) and pulse pressure (PP = PAPs-PAPd) [29]. The product of PVR multiplied by Ca defines the RC-time. Reuben found in a heterogeneous patients population (n = 35) with PH, some of which with normal PAPm values, that the PVR and Ca followed a highly predictable inverse hyperbolic relationship [30]. Any change in PVR implies an inverse change in Ca permitting to estimate Ca from PVR using a simple formula. This finding was further confirmed in subjects without PH and over a wide variety of forms, severities and treatments of PH with a corresponding near-constant RC-time [31-33]. This observation is notably in contrast with what is happening in the systemic circulation where systemic vascular resistance and compliance can vary independently of each other and consequently RC-time does not remain constant [34]. The constant RC-time of the pulmonary circulation may be explained by two mechanisms. First, an increased PVR leads to an increased intravascular pressure, which in turn results in stiffer arteries inducing a reduction in compliance [35]. Second, compliance properties are widespread over the entire pulmonary arterial tree and not only confined to the proximal vessels as in the systemic circulation [36, 37]. A constant RC-time implies that Ca becomes more relevant than PVR in determining RV afterload when PAPm and PVR are only moderately elevated [38]. Another important consequence of the pulmonary R-C dependence is the proportionality of pressures: a highly correlated linear relationship (r² = 0.98) was found between PAPm and PAPs and between PAPm and PAPd [39, 40]. The proportionality between PP and PAPm implies that the RV pulsatile load remains a constant fraction of total hydraulic power independently of PAP values [41]. Knowing steady power as the product of PAPm and mean Q, RV total hydraulic power can be easily estimated (total power = 1.3 x steady power). The fixed relationship between PVR and Ca is helpful in understanding the different impact of a reduction in PVR on Ca depending on the “baseline” PVR value as shown in Figure 4.
Figure 4. Comparison of the consequence of a decrease of 0.3 mm Hg · s · ml⁻¹ in R (PVR) for a patient with a low baseline R (*Patient A*) and in a patient with a high baseline R (*patient B*). Although the decrease in R is equal in both patients, patient A will have a corresponding increase of 60% in C (Ca), whereas Patient B will have an increase of only 16%. Reproduced from Lankhaar JT, et al.³¹ with permission.

In a canine model of proximal CTEPH (pulmonary arterial ensnarement) we found a shorter RC-time associated with an increase in RV afterload (RC-time: 0.30 ± 0.03 s from a baseline value of 0.46 ± 0.07 s; p < 0.05) compared with a model of distal CTEPH (microembolization) (RC-time: 0.83 ± 0.12 from a baseline value of 0.53 ± 0.09 s; p < 0.05) suggesting that the site of increased resistance affects the time constant of the pulmonary circulation probably through altered wave reflection [42].

In a recently published large retrospective analysis RC-times were compared in patients with proximal CTEPH (n= 91) before and after PEA, distal CTEPH (n = 53) and IPAP (n=78) [43]. RC times were found to be highest in IPAP patients (0.63 ± 0.14 s) followed by distal CTEPH (0.55 ± 0.12 s) and lowest in proximal CTEPH patients (0.49 ± 0.11 s) with statistically significant differences among the three cohorts of patients after adjustment for covariates (age, PAOP, PAPm). Despite a postoperative normalization of pulmonary artery pressures (PAPm: 20.4 ± 3.3 mm Hg) in proximal CTEPH patients, RC-time declined further following successful PEA (from 0.49 ± 0.11 s to 0.38 ± 0.11 s; p < 0.0001) instead of improving as expected. One proposed explanation of this finding is that PEA induced structural changes, which altered compliance properties of pulmonary vessels. Another exception of the consistent resistance compliance relationship was observed in patients with elevated pulmonary venous pressure. In a large clinical database Tedford et al. observed in patients with chronic LHF and elevated PAOP (≥ 20 mm Hg) a disproportionate decline in
compliance not driven by SV with a consequently shift of the RC relation downward to the left [44]. They also examined a subgroup of patients (n= 207) with LHF and 2 RHCs at different times points with different PAOP values (PAOP ≤ 10 mmHg and PAOP ≥ 20 mm Hg, respectively). Furthermore, 24 patients with early-stage LHF with preserved ejection fraction and normal resting PAOP (≤ 15 mmHg), which increased (≥ 25 mmHg) during supine exercise were assessed. Interestingly, an increase of PAOP in the same subjects at different times points or during exercise was associated with reduced RC-times (0.43 ± 0.15 s to 0.28 ± 0.12 s and 0.43 ± 0.17 s to 0.26 ± 0.10 s, respectively; both p < 0.001) suggesting increased pulsatile load. These interesting findings possibly highlight the previously underestimated deleterious effects of post-capillary pulmonary hypertension on RV function, but the definitive impact of elevated PAOP on RV afterload remains uncertain.

5.5. RV-arterial coupling in animal models and in humans

RV-arterial coupling derived from Emax/Ea ratio has been studied in different models of PH [16]. Preserved coupling by increased RV contractility to match increased Ea occurred in experimental animal models of hypoxia [45], distal pulmonary embolism [45], proximal pulmonary artery constriction [45], early sepsis [46] and short-term (three months) persistent ductus arteriosus [47]. Decreased Emax/Ea ratio due to insufficient adaptive increase in contractility occurred in experimental animal models of late endotoxic shock [46], and in long-term (six months) persistent ductus arteriosus [48]. In a dog model of heart failure induced by seven weeks of overpacing we observed a profound deterioration in RV-arterial coupling despite a mild increase of PAPm (Ees/Ea from 1.4 ± 0.1 to 0.8 ± 0.1; p < 0.05; PAPm from 17 ± 1 to 23 ± 1 mm Hg; p < 0.05) as a consequence of an absent adaptive increase in contractility (Ees from 1.2 ± 0.1 to 1.4 ± 0.1). Inhaled nitric oxide and nitroprusside decreased total PVR (from 669 ± 69 to 540 ± 41 dyne.s.cm⁻⁵.m⁻² and to 561 ± 32 dyne.s.cm⁻⁵.m⁻², respectively; both p < 0.05) without affecting Ees/Ea ratios. Milrinone, on the other hand decreased total resistance (from 669 ± 69 to 519 ± 87 dyne.s.cm⁻⁵.m⁻²; p < 0.05) and restored right ventriculo-arterial coupling (Ees/Ea from 0.8 ± 0.1 to 1.6 ± 0.2; p < 0.05) through a predominantly increase in contractility [49]. Different pharmacological interventions have been tested in experimental PH by assessing their impact on Emax/Ea ratio [16]. Low-dose dobutamine increased coupling by an inotropic effect with a slight decrease in afterload [50]. Low-dose norepinephrine improved Emax/Ea ratio without affecting Ea [50]. Levosimendan administration was associated with improved RV-arterial coupling by a combined effect of increased contractility and decreased afterload [51]. PAH-targeted medications improved RV-arterial coupling through pulmonary vasodilation without convincing evidence of positive inotropic effects in various
experimental PH models [16]. Measurements of the Emax/Ea ratio have been reported in a limited number of patients with PAH. Kuehne et al. measured pressures and volumes with fluid-filled RHC and MRI respectively in six patients with relatively early IPAH and in six controls subjects and assessed RV-arterial coupling by the single-beat method [52]. Patients with IPAH compared to controls presented a three-fold improvement in contractility consequently to an increased Ea (Ea from 0.6 ± 0.3 to 2.7 ± 0.6 mmHg mL⁻¹; p < 0.01) with an impaired RV-arterial coupling (Emax/Ea: from 1.9 ± 0.4 to 1.1 ± 0.3, p < 0.01). However RV volumes were not increased suggesting at least a resting adaptive remodelling. Tedford et al. measured RV pressures and volumes with conductance catheters and assessed Emax by a family of pressure-volume loops generated using a validated Valsalva manoeuvre (validation against inferior vena cava obstruction) in five patients with IPAH, seven patients with scleroderma (SSc)-associated PAH and seven patients with SSc but without PAH (SSc-no-PAH) [21]. RV-arterial coupling was preserved in patients with IPAH and patients with SSc-no-PAH (2.1 ± 1.0 and 2.3 ± 1.2, respectively) but was depressed in patients with SSc-PAH to 1.0 ± 0.5 (p = 0.03 and p = 0.016 as compared with IPAH and with SSc-no-PAH, respectively). McCabe et al. measured pressures and volumes with conductance catheters and assessed RV-arterial coupling with pressure/volume loops in ten patients with CTEPH, in seven patients with chronic thromboembolic disease but without PH and seven control subjects [53]. Emax/Ea ratios were preserved in controls and in patients with chronic thromboembolic vascular disease without PH (1.46 ± 0.30 and 1.27 ± 0.36, respectively) but were reduced to 0.60 ± 0.18 in patients with CTEPH (p < 0.05 compared with both groups). Until now there are no published clinical trials investigating the effects of different drugs on RV-arterial coupling in PH patients. Experimental and clinical studies on RV-arterial coupling suggest the predominant role of adaptive remodelling of RV confronted with increased afterload at least in resting conditions. Maladaptive remodelling will first occur by too high RV afterload maintained for a prolonged time or in the presence of a systemic disease [16].

5.6. References


5. Champion HC, Evangelos ED, Michelakis D, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications Circulation 2009; 120: 992-1007


35. Milnor WR. In: Hemodynamics (2nd Ed.), edited by Williams and Wilkins, 1989


41. Saouti N, Westerhof N, Helderman F, et al. Right ventricular oscillatory power is a constant fraction of total power irrespective of pulmonary artery pressure. Am J Respir Crit Care Med 2010; 182: 1315-1320


5.7. Personal contributions to right ventricular-pulmonary arterial coupling:

Early right ventriculo-arterial uncoupling in borderline pulmonary hypertension on experimental heart failure

Alberto Pagnamenta,1 Céline Dewachter,1 Kathleen McEntee,1 Pierre Fecker,1 Serge Brimiouille,2 and Robert Naeije1
1Department of Physiology, Faculty of Medicine, and 2Department of Intensive Care, Erasme Academic Hospital, Free University of Brussels, Brussels, Belgium

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Pagnamenta A, Dewachter C, McEntee K, Fecker P, Brimiouille S, Naeije R. Early right ventriculo-arterial uncoupling in borderline pulmonary hypertension on experimental heart failure. J Appl Physiol 109: 1080–1085, 2010. First published August 5, 2010; doi:10.1152/japplphysiol.00467.2010.—Pulmonary hypertension on heart failure (HF) limits exercise capacity and survival probably because of associated right ventricular (RV) failure. This study investigated the mechanisms of RV function adaptation to early pulmonary hypertension in experimental HF. Seven weeks of rapid ventricular pacing in six dogs induced a HF characterized by cardiomegaly and decreased left ventricular ejection fraction. Compared with right control dogs, pulmonary hypertension was borderline, with a mean pulmonary artery pressure increased to only 23 ± 2 (means ± SE) mmHg. However, the pulmonary vascular impedance spectrum was globally shifted to higher pressures, with an increase in 0 Hz impedance (resistance) to 662 ± 69 vs. 455 ± 41 dyne·sec·cm⁻⁵·m² in controls (P < 0.01) and in characteristic impedance to 183 ± 20 vs. 104 ± 7 dyne·sec·cm⁻⁵·m² in controls (P < 0.01). There was no change in RV end-systolic elastance (Ees), but arterial elastance (Ea) was increased to 1.8 ± 0.3 vs. 0.9 ± 0.1 mmHg/ml in controls so that RV-arterial coupling defined by the Ees-to-Ea ratio (Ees/Ea) was decreased to 0.8 ± 0.1 vs. 1.5 ± 0.1 in controls (P < 0.01). Inhaled nitric oxide, 40 ppm or 5 µg·kg⁻¹·min⁻¹ nitropresside iv, did not affect Ees/Ea. Fifty milligrams (iv) of milrinone increased Ees/Ea to 1.6 ± 0.2 by an isolated increase in Ees. We conclude that overpacing-induced HF is accompanied by a borderline pulmonary hypertension but profound RV-arterial uncoupling explained by the failure of RV systolic function to adapt combined effects of increased pulmonary arterial resistance and elastance.

overpacing; pulmonary vascular resistance; pulmonary vascular impedance; right ventricular function

PULMONARY HYPERTENSION IS A COMMON COMPLICATION OF HEART FAILURE (HF) (15). In these patients, pulmonary arterial pressure (Ppa) is increased as a passive consequence of upstream transmission of left atrial pressure (Pla), but there may be an increased gradient between Ppa and Pla because of additional effects of pulmonary vascular tone and remodeling (15, 21). Pulmonary hypertension in HF has been identified as an independent predictor of decreased exercise capacity and survival, and this is likely explained by an associated afterload-induced alteration in right ventricular (RV) function (13, 15, 23). Uncoupling of RV function from the pulmonary circulation could contribute to exercise ventilation inefficiency, which has been shown in recent years to be of great clinical and prognostic relevance in HF (33).

The gold standard for the evaluation of patients with pulmonary hypertension is right heart catheterization with measurements of right atrial and pulmonary vascular pressures and cardiac output (22). However, these measurements neglect the natural pulsatility of the pulmonary circulation and cannot, therefore, provide a complete description of all the forces opposing pulmonary arterial flow (5). The correct evaluation of RV hydraulic load, or afterload, can be provided pulmonary vascular impedance (PVZ), calculated from a spectral analysis of pulmonary arterial pressure and flow waves and actually determined by a dynamic interaction between resistance, compliance, and wave reflection (5). As for RV function, this is best globally defined by a pressure-volume relationship and adaptation to afterload estimated from the ratio of end-systolic elastance (Ees) and arterial elastance (Ea) (31). It has indeed been demonstrated that RV function adaptation to afterload is initially systolic, with maintenance of an optimal Ees-to-Ea ratio (Ees/Ea) ~1.5, allowing for flow output at a minimal amount of energy cost (31).

Because of the prognostic impact of both pulmonary hypertension and altered RV function in HF, we thought it of interest to investigate the mechanisms of abnormal coupling of the RV to the pulmonary circulation in an experimental model of the disease. We reported previously on a few weeks of overpacing in dogs to induce severe dilated cardiomyopathy, characterized by marked cardiomegaly and decreased ejection fraction, but only mild increase in pulmonary vascular pressures and resistance (23, 28). We specifically sought to determine whether mild pulmonary hypertension in HF would nevertheless be a cause of RV-arterial uncoupling by either an underestimation of afterload or inherent limitation systolic function.

METHODS

A total of 14 beagle dogs (11–15 kg) were included in the study. HF was induced by 7 wk of overpacing in six of them. The other eight dogs served as controls. The investigation was approved by the Institutional Animal Care and Use Committee of the Free University of Brussels and was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996).

The overpacing model of HF. The overpacing was instituted as follows. After pretreatment with midazolam (0.1 mg/kg iv) and methadone (0.3 mg/kg iv), anesthesia was induced and maintained with propofol (5 mg/kg followed by 5 mg/kg · h⁻¹). The animals were ventilated with an inspired O₂ fraction (FiO₂) of 0.4, a respiratory rate of 12 breaths/min, and a tidal volume adjusted to maintain CO₂ expiratory pressure between 30 and 35 mmHg. Under sterile operating conditions, a transthoracic bipolar pacemaker lead (Fineline II, model 4471; Guidant, Brussels, Belgium) was surgically implanted in the RV apex under fluoroscopic control, and a multiprogrammable

Address for reprint requests and other correspondence: R. Naeije, Laboratory of Physiology, Faculty of Medicine, Free University of Brussels Erasme Campus, CP 604, 808, Lennik Rd., B-1070 Brussels, Belgium (e-mail: naeije@ulb.ac.be).
pulse generator (Insignia; Guidant) was inserted in the cervical region
in a subcutaneous pocket and connected to the pacemaker lead. After
a 2-wk recovery period, the dogs were subjected to 7 wk of rapid RV
pacing with weekly increments: 180, 200, 220, and 240 beats/min for
the 4 last wk, as described previously (23, 28). Progression of HF was
monitored on a weekly basis, with dogs in sinus rhythm (30 min after
transient inactivation of the pacemaker) by clinical examination and
transthoracic echocardiography (Pandion; Pie Medical Benelux,
Zaventem, Belgium).

Invasive hemodynamic measurements. Just before the invasive
experiments, the ventricular pacemaker was deactivated in the dogs
with tachycardiomypathy. The dogs were anesthetized with mor-
phine (0.1 mg/kg) and α-chloralose (80 mg/kg), followed by a
continuous infusion of α-chloralose at the rate of 20 mg/h supple-
mented with morphine (0.5 mg·kg⁻¹·h⁻¹). Paralysis was obtained
with pancuronium bromide (0.2 mg·kg⁻¹·h⁻¹). The dogs were ven-
tilated (Elema 900 B servo-ventilator; Siemens Elema, Solna, Swe-
den) via a cuffed endotracheal tube with a FIO₂ of 0.4, a respiratory
rate of 10 breaths/min, a tidal volume of 15–25 ml/kg adjusted to
maintain arterial P O₂ between 35 and 45 mmHg, and a positive
end-expiratory pressure of 5 cm H₂O. End-expiratory pressures re-
mained at 5 cm H₂O and peak inspiratory pressures between 30 and
35 cm H₂O. Periodic deep inspirations were administered to prevent
atelectasis formation. Body temperature was maintained at 36–38°C
using an electric heating pad. When metabolic acidosis occurred, it
was corrected with a slow infusion of sodium bicarbonate. Through-
out the experiments, NaCl 0.9% was infused at ~10 ml·kg⁻¹·h⁻¹ to
maintain a P Ha between 5 and 10 mmHg.

A balloon-tipped, flow-directed pulmonary catheter (Model 131H-
7F; Baxter Edwards, Irvine, CA) was inserted through the left external
jugular vein and positioned using the pressure wave form into a branch
of the pulmonary artery for measurements of Ppa, right atrial
pressure (Pra), cardiac output (Q), and central temperature and for
mixed venous blood sampling. A polyethylene catheter was inserted
in the abdominal aorta via the right femoral artery for measurements
of systemic arterial pressure (Psa) and for arterial blood sampling.

A left lateral thoracotomy was performed. A balloon-tipped, flow-
directed pulmonary catheter (model 131H-7F) was inserted in the left
atrium via the atrial appendage to measure Pla. A 16- to 24-mm
nonconstricting ultrasonic flow probe (TI01; Transonic Systems,
Ithaca, NY) was positioned around the main pulmonary artery for the
measurement of instantaneous pulmonary Q. The Transonic flowme-
ter system is linear to 60 Hz, with a flat amplitude response to 35 Hz.
A 5F high-fidelity manometer-tipped catheter (model SPC 350; Millar
Instruments, Houston, TX) was introduced through the RV into the
main pulmonary artery, and its tip was positioned just distal to the
flow probe for the measurement of instantaneous Ppa. Another 5F
high-fidelity manometer-tipped catheter (model SPC 350) was intro-
duced into the RV for the measurement of instantaneous RV pressure
(Prv). The frequency response of the micromanometer system is flat
beyond 200 Hz. The chest was tightly closed, pleural air was evacu-
ated, and the lungs were reexpanded with several large volume
inspirations.

Measurements. Heart rate (HR) was determined from a continuous
electrocardiogram. Vascular pressures were measured using Gould
Statham P50 transducers (Gould, Oxnard, CA). The pressure and flow
signals were displayed on a monitor (Sirecust 404; Siemens, Erlangen,
Germany) and recorded on a six-channel Gould recorder (model
2600S; Gould, Instruments Division, Cleveland, OH). The pressure
transducers of the fluid-filled catheters were zero-referenced at mid-
chest, and vascular pressures were recorded at end expiration. Q was
measured by thermodilution as a mean of at least three successive
measurements (CO-set; Baxter Edwards, Santa Ana, CA). The zero Q
from the ultrasonic flow probe was adjusted to the end-diastolic value,
assumed to be zero. The instantaneous RV and pulmonary pressures
and flow signals were sampled at 200 Hz using an analog/digital
converter (DAS 8-PGA; Keithley-Metabyte, Taunton, MA), stored,
and analyzed on a personal computer.

Pulmonary vascular resistance (PVR) was calculated as (Ppa −
Ppa)/Q and corrected for body surface area. PVZ was calculated from
the Fourier series expressions for pressure and flow signals, as
reported previously (10). Five end-expiratory heartbeats were ana-
lized for each data collection interval. Pressure and flow harmonics
with amplitude of <1% of pressure and of flow pulse amplitude were
considered as noise and excluded from PVZ calculations. The PVZ
modulus was computed as the ratio between pressure and flow moduli
and its phase computed as the difference between flow and pressure
phases. The impedance at 0 Hz (Z0) was taken as the total resistance
(Ppa/Q), and the characteristic impedance (Zc) was calculated as the
average of impedance moduli between 2 and 15 Hz.

A single-beat method was used to calculate Ees, pulmonary artery
effective elastance (Ea) from instantaneous RV pressure curves, and
synchronized pulmonary blood flows, as reported previously (4). The
method relies on the measurement of a relative change in RV volume
by the integration of pulmonary flow and on the calculation of
maximal RV pressure (Pmax) from the early and late systolic portions
of the RV pressure curve (4). Practically, four to nine good quality
beats are sampled at the end of expiration and integrated into a single
during the Fourier transform and subsequent automatic analysis
by the software. We previously showed a good agreement between
calculated Pmax and the Pmax of a nonjecting beat (4). Ventricular-
arterial coupling efficiency was assessed by Ees/Ea.

Arterial and mixed venous blood gases were measured immediately
after the samples were drawn by an automated analyzer (ABL 2;
Radiometer, Copenhagen, Denmark) and corrected for temperature.

Experimental protocol. As soon as the animals were in steady-state
conditions (stable HR, Psa, Ppa, and Q) for 20 min, a first baseline set
of all hemodynamic and blood gas measurements was obtained, and
instantaneous Ppa, Prv, and flow signals were sampled for PVZ, Ees,
and Ea calculations.

In the animals with HF, the same measurements were repeated in
the following sequence: 10 min after the institution of 40 ppm inhaled
nitric oxide (iNO), control after return of HR, Psa, and Ppa values
to baseline levels; 10 min after the institution of continuous intravenous
nitropressure progressively increased to 5 μg·kg⁻¹·min⁻¹, control
after return of HR, Psa, and Ppa values to baseline levels; and 10 min
after administration of a single intravenous bolus of 50 μg·kg⁻¹ mili-
none given over 1 min.

The dose of 40 ppm iNO was based on previous studies that
showed it most effective to decrease pulmonary vascular tone without
systemic hemodynamic effects in experimental animals (10). NO was
supplied from a pure NO source tank (Oxyhydrade, Machelen,
Belgium) and delivered through the endotracheal tube. The inspired
fraction of NO was monitored by chemiluminescence after calibration
against standard NO concentration (model 42 chemiluminescence
NO-NO₂-NOx analyzer; Thermo Environmental Instruments, Frank-
lin, MA). Inspired or expired NO₂ remained <1 ppm.

The dose of 5 μg·kg⁻¹·min⁻¹ nitropressure was chosen because of
its maximal effects on pulmonary vascular tone without excessive
decrease in Psa (10).

The dose of 50 μg/kg milrinone as a bolus has previously been
reported in studies on the reversibility of PVR in patients with HF
evaluated for cardiac transplantation (12, 27).

Statistical analysis. Results are expressed as means ± SE. The
statistical analysis consisted in a repeated-measures analysis of vari-
ance. When the F ratio of the analysis of variance reached a P < 0.05
critical level, modified t-tests were used to compare two different
situations (34).

RESULTS

There were no significant differences in arterial blood gases
between HF dogs and controls (Table 1). The different phar-
macological interventions had no effect on arterial blood gases, except for a decrease in arterial Po$_2$ (PaO$_2$) following the administration of milrinone (Table 1). There were no differences in any measurements between the baseline and control without pharmacological interventions, and therefore, only one of these series of measurements is reported in the tables.

**Effects of over pacing-induced cardiomyopathy.** Compared with the controls, over pacing-induced HF was associated with increased HR and decreased Q (Table 1). Pulmonary vascular pressures, Ppa, and PVR were increased, and Psa was decreased. The increase in Ppa in dogs with HF was marginal, corresponding to “borderline” pulmonary hypertension, as recently defined by a Ppa between 20 and 25 mmHg (15).

Over pacing-induced HF was associated with increases in Zo, first harmonic impedance (Z$_1$), Zc, and Ea, with no change in Ees and a decrease in Ees/Ea (Table 2).

Typical changes in PVZ spectrum and RV-arterial coupling are illustrated in Fig. 1.

**Effects of pharmacological interventions.** iNO had no hemodynamic effect except for a decrease in Ppa and Zo (Tables 1 and 2). Nitroprusside increased HR and decreased Psa, Ppa, Ppa, Ppa, PVR, and Zo but had no effect on Zc, Ees, Ea, and Ees/Ea. Milrinone increased HR and Q, decreased Ppa, Ppa, Psa, PVR, Zc, Zc, and Zc had no effects on Ea, and increased Ees/Ea by a marked increase in Ees (Fig. 1).

**DISCUSSION**

The present results show that 1) over pacing-induced HF in dogs is associated with a deterioration in RV-arterial coupling because of the absence of adapted increase in RV contractility in the presence of borderline pulmonary hypertension and 2) increased afterload in pulmonary hypertension on HF may be markedly underestimated by the exclusive use of steady-flow pressure and resistance measurements.

Pulmonary hypertension secondary to HF is explained by upstream transmission of pulmonary venous pressure, with variable participation of increased resistance on both increased tone and vascular remodeling (15, 23). Accordingly, mean Ppa is correlated to Ppa, either directly measured or indirectly estimated by an occluded or wedged Ppa (11, 26), and decreases proportionally to decreased Ppa after cardiac transplantation (26). Increased PVR in HF is related to disturbed endothelial NO and endothelin-1 signaling (23), which is already significant in early-stage HF, with only mild increases in Pta, Ppa, and PVR (9, 29) like in the present study.

Both increased Ppa and decreased RV ejection fraction have been shown to be potent predictors of survival in HF (11). Irreversible increases and Ppa and PVR are predictors of increased mortality after cardiac transplantation (7, 17). These observations support the notion that the prognosis in HF patients is largely dependent on the adaptation of RV function to increased afterload (13, 23). However, RV afterload cannot be determined accurately from steady-flow hemodynamic measurements (5). A quantification of RV afterload requires instantaneous pressure, flow, and volume measurements for the determination of a PVZ spectrum or calculation of a pulmonary Ea (5, 31). In the present study, the shift of the whole PVZ spectrum to higher ratios of pressure and flow moduli was indicative of an increased afterload caused by increases in both resistance and elastance. This was confirmed by an out-of-proportion increase in Ea. Previous studies in patients with chronically increased pulmonary venous pressure on either
mitral stenosis (19) or advanced HF (20) had reported an increase in both low- and high-frequency PVZ suggestive in increases in both pulmonary vascular resistance and elastance. The present results show that the increases in both resistance and elastance occur early in the course of the disease to increase RV afterload that is out of proportion with that estimated by single PVR or Ppa determinations.

The essence of the normal ventricular response to increased afterload is homeometric by an increase in contractility matching Ees to increased Ea (31). This has been confirmed for the RV in conditions of acute increase in afterload, after induction of hypoxic vasoconstriction (4), or chronic increase in afterload, for example, after a few months of aorta-pulmonary shunting (30). Patients with severe pulmonary arterial hypertension present with an increased RV contractility, yet not sufficient to cope with increased afterload, so that the Ees/Ea decreases, indicating pending RV failure (18). This is obviously likely to occur in earlier stages of the disease in the presence of disease processes, limiting the capability of RV systolic function to adapt (6). In the present experiments, RV function was already depressed by the overpacing, and accordingly uncoupled from the pulmonary circulation, whereas pulmonary hypertension was only borderline. Left atrial pressure was increased, but marginally, contrasting with the severity of left ventricular dysfunction typical of the overpacing-induced HF model (24). However, Ppa was measured at rest and in conditions of general anesthesia. It is thus likely that the pulmonary circulation is exposed to higher and variable Ppa in conscious and active animals with overpacing-induced HF, contributing to remodeling and increased PVZ.

iNO, nitroprusside, and milrinone are among vasodilators used to test for reversibility of increased PVR in patients with HF evaluated for cardiac transplantation (1, 7, 12, 25, 27). It is assumed that the lowest PVR obtained through pharmacological manipulation is a reasonable estimate of the afterload that the transplanted RV will have to face postoperatively (7, 17). This may not always be the case, since preoperative administration of vasodilators may fail to decrease Pta, which is the major determinant of pulmonary hypertension in HF (26). However, many vasodilators have been shown to decrease PVR in advanced HF, with variable efficacies related to a combination of effects on tone, cardiac output, and Ppa. iNO in HF decreases PVR and does not usually affect cardiac output but may increase Pta (1, 3, 14, 21). The latter has been explained by a decreased pulmonary venous resistance, allowing for an increased venous return to the failing left ventricle, rather than by identifiable negative inotropic effects (2, 14). The only effect of iNO in the present study consisted of a decrease in Ppa, PVR, and Zo, compatible with previously reported potent pulmonary vasodilating effects. However, like that reported previously in normoxic or hypoxic dogs (10), iNO had no effect on PVZ spectrum, Ees, or Ees/Ea, compatible with a site of action limited to pulmonary-resistive vessels. Nitroprusside in HF decreases systemic and pulmonary resistances and reducing pressures of both ventricles, with no change or an increase in cardiac output depending on the balance between preload and afterload reductions (7, 25). There has been a suggestion that nitroprusside might have positive inotropic effects (28), but this may be related to reflex sympathetic activation. In the present study, nitroprusside...
decreased PVR, Ppa, Pla, Ppa, and Psao without change in cardiac index, compatible with known systemic and pulmonary vasodilating properties. Nitroprusside-induced decrease in PVR was not sufficient to decrease Ea, since tone was not much elevated, and there were no effects on the spectrum of PVZ. There was no evidence for a positive inotropic effect, as indicated by unchanged Ees and Ees/Ea. Milrinone decreases PVR in HF by a combination of positive inotropic effects to increase cardiac output and a decreased pulmonary vascular tone (12, 27). In the present study, milrinone increased Ees/Ea essentially by a positive inotropic effect. There were decreases in PVR and in low- as well as high-frequency PVZ, but these effects were insufficient to affect afterload as measured by Ea. Milrinone decreased PaO2 in relation probably to a decrease in hypoxic pulmonary vascular tone and resultant increased perfusion of less well- or nonventilated lung areas. A trend toward decreased PaO2 was also apparent with nitroprusside, but this did not achieve significance. Both drugs have been shown to be potent pulmonary vasodilators (9, 10). It is interesting that iNO did not decrease in PaO2, in contrast with previously demonstrated more effective inhibition of hypoxic pulmonary vasoconstriction in normal dogs (10). Absence of associated changes in cardiac output might explain this apparent discrepancy.

In patients with severe HF, a low dose of intravenous nitroprusside (32 mg/min ± 20 SD) has been reported to decrease low-frequency PVZ, represented by Z1, indicating an improvement in pulse wave velocity. A higher dose of nitroprusside (66 mg/min ± 41 SD) decreased PVR, Zc, and wave reflections, increasing the forward flow and decreasing RV power requirement per unit forward flow (20). The absence of a significant effect of nitroprusside on the spectrum of PVZ in the present study is probably related to less severe HF and limited increase in pulmonary vascular tone. In patients with HF on severe aortic stenosis, nitroprusside increased Q, decreased Psa, and decreased celleduell Ppa (16). The hemodynamic data from these studies were modeled using theoretical pressure-volume relationships, and the results suggested a participation of positive inotropic effects (28). Nitroprusside had no effect on Ees the present study, confirming previous observations in normoxic or hypoxic dogs (10). There might have been a trend toward increased Ees, but, as already mentioned, this would be most likely related to reflex sympathetic activation, as indicated by concomitantly increased HR and decreased Psa.

Tachycardia-induced cardiomyopathy simulates idiopathic dilated cardiomyopathy rather than ischemic or hypertensive cardiomyopathy (32). Overpacing induces a global biventricular failure and may, therefore, be associated with earlier and more severe RV-arterial uncoupling. In addition, overpacing induces a severe HF in only a few weeks, which does not allow for chronic pulmonary vascular and myocardial remodeling to fully develop. All of these are important limitations to the extrapolation of the present findings to patients with HF.

Another limitation of the present study is that no dose-response curves were considered for the pharmacological interventions. Both iNO and intravenous nitroprusside were given at the maximum tolerated doses without excessive systemic hemodynamic effects, as reported previously (10), to obtain the largest possible decrease in RV hydraulic load. Dose-response curves for PVR have been reported previously over a wide range of doses of intravenous milrinone, ≤300 mg/kg, in rabbits with experimental pulmonary hypertension (8). However, in the present study, borderline blood pressure and tachycardia prevented the increase of milrinone to doses >50 μg/kg, which were used previously to test for the reversibility of PVR in HF patients evaluated for cardiac transplantation (12, 27).

In conclusion, early HF on tachycardia-induced cardiomyopathy is associated with a profound RV uncoupling despite only a mild increase in pulmonary vascular pressures. This is explained by altered systolic function of the RV in the context of the induced cardiac disease and by the underestimation of afterload by steady-flow hemodynamic evaluations.

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Present address of P. Feusler: Dept. of Internal Medicine, Centre Hospitalier Universitaire, 191 Avenue du Doyen Gaston Giraud, 34295 Montpellier, France.

Present address of A. Pagamenta: Dept. of Intensive Care Medicine, Regional Hospital Mendrisio, Via Tarconi 23, 6850 Mendrisio, Switzerland.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


6. CONCLUSION AND PERSPECTIVE

As presented in this thesis, pulmonary circulation in pulmonary hypertension can be assessed from simple methods to more complex ones. However the evaluation of PH is a multifaceted approach and the clinical utility of combining different methods remain to be determined. Recently non-invasive methods have been developed and further implemented (e.g. MRI and three-dimensional echocardiography) with promising perspectives, which require prospective validation. Invasive assessment (PAC-derived) of the functional status of the pulmonary circulation using multi-point pulmonary pressure flow coordinates generated by dobutamine or by exercise may be an attractive method for early identification of pulmonary vascular disease in selected patients with normal pulmonary hemodynamic at rest. Furthermore this approach can be helpful for the evaluation of prognosis and to determine adequacy of treatment response to medical therapy. It could also permit to identify and thereafter to define stress-induced hemodynamic treatment-goals in order to adapt medical treatment and probably to start early a combination therapy. Accurate non-invasive evaluation of multi-point pressure/flow relationships by echocardiography is desirable and preferable to invasive assessment of the functional status of the pulmonary circulation. Dobutamine stress echocardiography is preferable to exercise TTE because the latter is technically challenging and a validated exercise protocol has not been established. The clinical usefulness of routine non-invasive multi-point pressure/flow determinations requires further validation studies. Accurate and precise measurement of PAOP is of central role for the differentiation between pre- and post-capillary pulmonary hypertension with direct treatment consequences. In selected patients LHC with direct LVEDP determination could be necessary for definitive diagnosis. By spontaneous positive end-expiratory pressure such as in the setting of obstructive lung disease or obesity pre-capillary PH may be mislabelled as post-capillary. The clinical usefulness of averaging PAOP through the respiratory cycle should be tested in a clinical trial probably with the direct comparison with LVEDP measurement adjusted for oesophageal pressure as estimate of pleural pressure. Nowadays there is no gold standard method for the assessment of operability of CTEPH patients and consequently the evaluation process remains complex. In daily clinical practice a multidisciplinary team consisting of an experienced PEA surgeon, radiologists and CTEPH physicians evaluates the better treatment option. Definitive inoperability should be assessed by at least two independent experienced PEA surgeons. The analysis of the PAP decay curve by the occlusion method seems a promising technique for preoperative risk assessment and for patients’ selection for medical therapy.
However this approach should be further implemented in order to better discriminate proximal vasculopathy from peripheral involvement in CTEPH. The occlusion method can be combined with the calculation of RC-time in order to better identify the site of increased resistance. A clinical prediction rule based on imaging techniques, analysis of PAP decay curve by the occlusion method and calculation of RC-time is potentially helpful in assessing CTEPH operability but it still requires a prospective validation. Right ventricular afterload is better evaluated by the calculation of pulmonary vascular impedance. However, recently it was proposed to derive total RV hydraulic power from PAPm and mean Q by a simple formula permitting to avoid instantaneous pulmonary pressure and flow determinations. Valid estimates of pulsatile pulmonary hemodynamics can be obtained during routine right heart catheterization from PAP measured with fluid-filled PAC and pulmonary flow-velocity measured by TTE. Impedance calculation without considering the impact and the adaptation of RV faced to an increased afterload in the setting of PH gives only a partial picture of the hemodynamic situation. The pulmonary circulation and the right ventricle should no more be considered as two separate entities but they should be viewed as a unique functional unit. New treatment options should be evaluated by measurement of right ventriculo-arterial coupling. Accurate non-invasive techniques for the assessment of RV coupling and their sensitivity to pharmacologic intervention are required and should be developed. Pulmonary vasculature remains the primary target of medical therapy in PAH. However, novel therapeutic options aimed at preserving right ventricular function as well as reversing right ventricular dysfunction/failure are needed. Despite considerable progresses have been made in diagnosis and treatment of PH in recent years, clinical and experimental work is still much to be done and we have to work hard before we can give more concrete answers to our patients suffering from this devastating disease.