Title Page

Impact of Pulmonary Endarterectomy on Pulmonary Arterial Wave Propagation and Reservoir Function

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Abstract

High wave speed and large wave reflection in the pulmonary artery have previously been reported in patients with chronic thromboembolic pulmonary hypertension (CTEPH). We assessed the impact of pulmonary endarterectomy (PEA) on pulmonary arterial wave propagation and reservoir function in CTEPH patients. Right heart catheterization was performed using a combined pressure and Doppler flow sensor tipped guidewire to obtain simultaneous pressure and flow velocity measurements in the pulmonary artery in eight CTEPH patients before and 3 months after PEA. Wave intensity and reservoir-excess pressure analyses were then performed. Following PEA, mean pulmonary arterial pressure (PAPm, ~49 versus ~32 mmHg), pulmonary vascular resistance (PVR, ~11.1 versus ~5.1 Wood Units) and wave speed (~16.5 versus ~8.1 m/s), i.e. local arterial stiffness, markedly decreased. The changes in the intensity of the reflected arterial wave and wave reflection index (pre: ~28%; post: ~22%) were small and post-PEA patients with and without residual pulmonary hypertension (i.e. PAPm ≥25 mmHg) had similar wave reflection index (~20 versus ~23%). The reservoir and excess pressure decreased post-PEA and the changes were associated with improved right ventricular afterload, function and size. In conclusion, while PVR and arterial stiffness decreased substantially following PEA, large wave reflection persisted, even in patients without residual pulmonary hypertension, indicating lack of improvement in vascular impedance mismatch. This may continue to affect the optimal ventriculo-arterial interaction and further studies are warranted to determine whether this contributes to persistent symptoms in some patients.

Keywords: pulmonary hypertension, pulmonary endarterectomy, wave intensity analysis, wave reflection, arterial stiffness

New and Noteworthy

We performed wave intensity analysis in the pulmonary artery in patients with chronic thromboembolic pulmonary hypertension before and 3 months after pulmonary endarterectomy. Despite of substantial reduction in pulmonary arterial pressures, vascular resistance and arterial stiffness, large pulmonary arterial wave reflection persisted 3 months post-surgery, even in patients without residual pulmonary hypertension, suggestive of lack of improvement in vascular impedance mismatch.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by an elevated mean pulmonary arterial pressure (PAPm) ≥ 25 mmHg due to obstruction of the pulmonary arteries following an episode or recurrent episodes of pulmonary embolism (16). Left untreated, the disease progresses to right heart failure and death. The treatment of choice is pulmonary endarterectomy (PEA), which has dramatically increased the survival of CTEPH patients (15). However, despite technically successful endarterectomy, some patients remain symptomatic (6). Current hemodynamic evaluation of pulmonary hypertension (PH) mainly focusses on PAPm and pulmonary vascular resistance (PVR), i.e. the steady component of right ventricular (RV) afterload, while the pulsatile (dynamic) afterload, which is related to arterial stiffness and wave reflection, is often neglected.

Wave intensity analysis (WIA) is a time-domain based approach for the assessment of pulsatile afterload and ventricular function. It quantifies the intensity, origin, type and timing of arterial waves (41, 51). Forward traveling waves arise from ventricular contraction or relaxation, which generate forward compression (FCW) or decompression waves (FDW) that increase or decrease pressure and flow, respectively. Backward traveling waves, e.g. reflected waves, originate as a consequence of admittance (or inversely impedance) mismatching in the vasculature. Depending on the nature of the admittance mismatch, they can be backward compression waves (BCW) that increase the pressure while decreasing the flow or backward decompression waves that decrease the pressure while increasing the flow. In addition to characterizing wave intensity, direction and type, WIA can also be used to determine wave speed (i.e. local pulse wave velocity), a measure of arterial stiffness. Previous studies applying WIA in

the pulmonary artery have revealed distinctive wave characteristics in CTEPH patients. Notably, greater wave speed and wave reflection were observed indicative of increased local arterial stiffness and admittance mismatching between the proximal and distal vasculature, respectively (44, 52).

Another approach that can be used to describe the arterial system is the reservoir-excess pressure analysis (40, 59), which characterizes the measured pressure waveform in terms of a reservoir and excess pressure and is, to some extent, analogous to the 3-element Windkessel model of the circulation (58). The application of reservoir-excess pressure analysis is increasingly being used in the systemic circulation and indices derived from the analysis have been shown to predict cardiovascular events (12, 20, 38). However, only a limited number of studies have explored the reservoir-excess pressure approach in the pulmonary artery (18, 53) and these have shown increased reservoir and excess pressures in PH patients.

The influence of PEA on pulmonary arterial wave propagation and reservoir function has not been investigated previously and here, we use WIA and reservoir-excess pressure analysis to provide additional information about the RV load and pulmonary vasculature following PEA.

Methods

Ethical Approval

Study participants were selected among patients undergoing clinical investigations for CTEPH at Hammersmith Hospital, Imperial College Healthcare, United Kingdom, and Aarhus University Hospital, Denmark. Patient inclusion criteria were standardized

and an identical protocol was used at both centers to avoid bias. The same investigator (JS) collected all the data at both sites to avoid inter-observer variability. Patients were excluded if CTEPH was ruled out or if they were considered unsuitable for PEA, which was performed either at Papworth Hospital, Cambridge or Aarhus University Hospital. The study complied with the Declaration of Helsinki and was approved by the local Ethics Committees (references 13/LO/1305 and M-2013-278-13) and all participants gave written informed consent.

Study Protocol

Right heart catheterization was performed using a 6 Fr balloon flotation catheter that was advanced into the pulmonary artery via the right brachial or jugular vein. Subsequently, a combined dual-tipped pressure and Doppler flow sensor wire (Combowire, Philips Volcano, California, USA) was advanced approximately 1 cm beyond the end of the catheter (52). Doppler flow velocity signals were optimized by careful manipulation of the catheter and wire *in situ*. Once stable signals were observed, pressure and velocity data were acquired simultaneously at a sampling rate of 200 Hz for ~60 seconds together with ECG monitoring in a free breathing state in the main, left and right pulmonary arteries (PA). All patients were in sinus rhythm at the time of investigation. All investigations including routine transthoracic echocardiography and blood tests were performed before and 3 months after PEA. In addition to the included CTEPH patients, analyses were also applied to the acquired pressure and velocity data from the pulmonary arteries of patients without pulmonary vascular disease that were included in a previous study and these patients served as controls (52).

Right Ventricular Work and Afterload

The global pulmonary arterial compliance was calculated as right ventricular stroke volume (RVSV) divided by pulmonary arterial pulse pressure. PVR was calculated as the transpulmonary pressure difference, defined as the difference between PAPm and pulmonary arterial wedge pressure (PAWP), divided by cardiac output. Total pulmonary resistance (TPR) was calculated as PAPm divided by cardiac output.

RV power and energy densities, defined as the power and energy , respectively, delivered by the right ventricle to generate the stroke volume per unit cross sectional area (CSA) of the artery, are useful dimensions for comparison with wave intensity (i.e. power density) and energy density. Given the heart rate (HR) and mean flow velocity (U_{mean}), RV power/energy densities were derived from steady flow RV stroke work (RVSW) (8) using previously described formulas (Equations 1 – 3) (52).

(1) $$RV\ energy\ density = \frac{RVSW}{CSA} = \frac{(PAPm-RAP)\cdot RVSV}{RVSV\cdot HR/U_{mean}} = \frac{(PAPm-RAP)}{HR/U_{mean}}$$

Hence,

(2) $$RV\ energy\ density = (PAPm - RAP)\cdot U_{mean}\cdot CCD$$

and

(3) $$RV\ power\ density = (PAPm - RAP)\cdot U_{mean}$$

where RAP is the right atrial pressure and CCD is the duration of the cardiac cycle.

Wave Intensity Analysis

Recorded pressure (P) and velocity (U) data were processed offline using customized Matlab software (v2015a MathWorks, Massachusetts, USA). Using the R-wave on ECG as a fiducial marker, pressure and velocity signals were ensemble-averaged and

smoothed using a Savitzky-Golay differentiating filter (2nd order polynomial fit, window size 11). Hardware-related delay between pressure and velocity signals was corrected by shifting the velocity data until the beginning of the upslope of the velocity and pressure waveforms were aligned (52).

The wave speed (c) was calculated using the sum of squares method (Equation 4) (13).

$$c = \frac{1}{\rho} \cdot \sqrt{\frac{\sum dP^2}{\sum dU^2}} \quad (4)$$

Where ρ is the blood density, assumed to be 1040 kg/m^3 and the summation was taken over the entire cardiac period.

Another common approach to determine the local wave speed is the PU-loop method, where pressure is plotted against velocity and the slope of the early linear portion of the PU-curve is expected to be equal to the product of blood density and wave speed (24). This is only valid under the assumption that there is no wave reflection in early systole, i.e. that there is an early linear segment. However, in many of our subjects, the PU-loop did not display a linear initial segment and in practice, PU-loop estimates of wave speed were poorly reproducible; therefore, we chose to use the sum of squares method.

Wave intensity was separated into its forward (WI_+) and backward (WI_-) components and normalized to the duration of the cardiac cycle (CCD) to make it independent of sampling rate (52, 53) (Equation 5).

$$WI_{\pm} = \pm \left(\frac{dP \cdot CCD}{dt} \pm \rho c \cdot \frac{dU \cdot CCD}{dt} \right)^2 / (4\rho c) \quad (5)$$

Separated waves were quantified by the peak intensity of the individual waves (W/m^2) and by the cumulative area under each wave (J/m^2) corresponding to the power

and energy, respectively, carried by each wave per cross sectional area of the artery over a cardiac cycle squared. Wave reflection index (WRI) was calculated as the ratio of the BCW to FCW energy.

Reservoir-excess Pressure Analysis

The reservoir-excess pressure approach was originally developed using both pressure and flow velocity data (59). However, as flow velocity is rarely measured during clinical settings, here, reservoir-excess pressure analysis was performed using only the measured pressure (Equation 6) (2), as this method can be reproduced by most investigators. Both methods give quantitatively similar results.

(6)

$$P_r = P_0 \cdot e^{-(k_s+k_d)t} + P_\infty \frac{k_d}{k_s+k_d}\left(1 - e^{-(k_s+k_d)t}\right) + k_s \cdot e^{-(k_s+k_d)t} \int_0^t P(t') e^{-(k_s+k_d)t'} dt'$$

The reservoir pressure (P_r) varies in magnitude through changes in the resistance (R) to outflow from the reservoir, the reservoir compliance (C) and the asymptotic pressure (P_∞), which is the limit for the exponential decay of the reservoir pressure during diastole and corresponds to the pressure at which outflow through the microcirculation would be predicted to be zero assuming a mono-exponential decay (Figure 1). k_s is the rate constant for reservoir filling. It is the inverse of the product of compliance and the ratio between arterial inflow and excess pressure. This ratio is related to, but not necessarily equal to, the characteristic impedance of the pulmonary artery (by analogy

with the 3-element Windkessel model). k_d is the constant for reservoir emptying. P_0 is the pressure at time, t_0, corresponding to the end of ventricular ejection, i.e. at the time of closure of the pulmonary valve (Figure 1). This was assumed to correspond to the time of maximal negative dP/dt (1, 45). The excess pressure (P_x) is calculated as the difference between the measured pressure and the reservoir pressure.

Reservoir and excess pressures were quantified by peak P_r (minus diastolic pressure) and P_x, and the integral of P_r (minus diastolic pressure) and P_x, respectively. Note that WIA described above was applied to the measured pressure rather than the calculated excess pressure, as the validity of WIA using the excess pressure remains controversial (37, 49).

Three different estimates of the diastolic pressure decay time were calculated. The diastolic time constant, τ, i.e. the inverse of the k_d, was derived from the reservoir-excess pressure analysis. The RC-time was calculated as RC_{PVR}, defined as the product of PVR and arterial compliance (C_p) (56) and RC_{TPR}, defined as the product of TPR and C_p (27).

Statistical Analysis

Sample data are summarized as means ± SD. Differences between pre- and post-PEA data were then compared using a paired Student's t-test. WIA and reservoir parameters from the main, right and left PAs were analyzed using mixed linear models to examine the differences between pre- and post-PEA data. These data are presented as estimated marginal means and 95 % CI. Where appropriate, data were log-transformed prior to analysis to achieve normally distributed residuals. 1-way repeated measures analysis of variance (ANOVA) was performed to detect differences between τ, RC_{PVR} and RC_{TPR}.

Post-hoc tests following ANOVA employed a Bonferroni adjustment for multiple testing. Spearman's correlation analysis was performed to examine monotonic relationships between variables. Following PEA, the patients were separated into two groups *a priori*: those with residual PH and those without (i.e. a PAPm < 25 mmHg after surgery). Differences in WIA and reservoir parameters between the two groups and controls were compared using mixed linear models. The level of significance was set at $p < 0.05$. All statistical analyses were performed using Stata (v13, StataCorp, Texas, USA).

Results

Patient Characteristics

In total, 10 CTEPH patients underwent PEA. Two patients were lost to follow-up and the remaining eight patients (67 ± 9 years, 3 male) completed the post-PEA investigations. Average waiting period from the initial assessment to PEA was 4.0 ± 2.3 months and average time to first follow-up post-PEA was 3.8 ± 1.1 months. Significant symptomatic and hemodynamic improvements were achieved following PEA (Table 1). Overall, PAPm decreased by 16 ± 17 mmHg, PVR decreased by 6.0 ± 5 Wood Units and cardiac output increased by 1.3 ± 1.1 l/min (Table 1 and Supplementary Figure S1: https://osf.io/h2dwk/?view_only=765df6c79dcf4d4ab9c697be0c4701ae). RV size reduced and RV function improved (Supplementary Table S1: https://osf.io/h2dwk/?view_only=765df6c79dcf4d4ab9c697be0c4701ae).

PAPm dropped to <25 mmHg in three patients (out of 8) following PEA .These patients also had a significantly smaller right atrium and ventricle post-PEA compared

to patients with residual PH (defined as PAPm ≥25 mmHg, data not shown). In two patients, PAPm increased after PEA; in one of them the increased PAPm could be explained by increased cardiac output. The cardiac output remained the same in one patient and increased in the rest of the cohort (Supplementary Figure S1: https://osf.io/h2dwk/?view_only=765df6c79dcf4d4ab9c697be0c4701ae). Post-PEA hemodynamic outcomes did not appear to be associated with pre-operative hemodynamic measurements, RV size or function, and was unrelated to whether the patient had predominantly main/lobar or segmental artery disease.

Arterial Wave Characteristics

The pressure and flow velocity profiles and the corresponding WIA patterns from the main pulmonary artery of a patient before (Figure 2A & B) and after (Figure 2C & D) surgery are shown. This patient achieved a substantial drop in pulmonary pressures with a PAPm <25 mmHg post-PEA along with a substantial increase in flow velocity. WIA revealed three dominant systolic waves. The observed FCW in early systole and FDW in late systole were generated by RV contraction and relaxation, respectively, while the mid-systolic BCW was attributed to reflection of the preceding FCW. Following PEA, BCW did not diminish. For comparison, WIA pattern of a representative control subject (Figure 2E & F) without pulmonary vascular disease from a previous study (52) showed minimal BCW. Table 2 shows the estimated marginal means of the pooled WIA indices from the three PA branches (summary statistics for each of the branch are shown in Supplementary Table S2: https://osf.io/h2dwk/?view_only=765df6c79dcf4d4ab9c697be0c4701ae). Following PEA, wave speed significantly decreased by 8 m/s [95 % CI: 6; 11 m/s]. The intensity

of BCW and wave reflection index (WRI, defined as the ratio between BCW and FCW energy) also decreased, although the decrease in WRI (by 6 % [95 % CI: 1 ; 13 %]) did not achieve statistical significance. FCW intensity and energy density and the ratio of FCW to RV stroke power and energy densities remained essentially unchanged.

When compared to control subjects without pulmonary vascular disease (N = 10, 59 ± 14 years, 8 male) from our previous study (52), post-PEA wave speed and wave energy were much greater in patients with residual PH (Figure 3). Patients that achieved a PAPm <25 mmHg post-PEA had significantly lower wave speed than those with residual PH, although it remained significantly greater compared to controls. In contrast, post-PEA WRI in patients with a PAPm <25 mmHg was similar to patients with residual PH and it remained substantially greater than individuals without pulmonary vascular disease (Figure 3C).

Reservoir Function

Separation of the measured pressure into a reservoir pressure and an excess pressure is illustrated in Figure 4. Table 3 shows the estimated marginal means of the pooled reservoir indices from the three PA branches (summary statistics for each of the branch are shown in Supplementary Table S3: https://osf.io/h2dwk/?view_only=765df6c79dcf4d4ab9c697be0c4701ae). Both the reservoir and excess pressures decreased following PEA (Table 3, Figure 4C & D). Comparison of the morphology of the excess pressure waveform with the velocity waveform in patients with CTEPH showed that the two waveforms deviated from one another noticeably in mid-systole (Figure 4B & D) consistent with substantial wave reflection. This was not seen in controls (Figure 4F). The morphology of the flow

velocity waveform was also noticeably different in patients with CTEPH (before and after PEA) compared with controls (compare 4B, D & F).

Compared to control subjects without pulmonary vascular disease and patients without residual PH post-PEA, the reservoir, excess and asymptotic pressures were significantly greater in patients with residual PH (Figure 5). However, patients without residual PH post-PEA had a reservoir pressure (both peak and integral) that remained significantly greater compared to controls (Figure 5A). Post-PEA excess pressure of patients without residual PH was also greater compared to controls; while there was a large degree of normalization of the asymptotic pressure (Figure 5B and 5C).

Estimates of the diastolic pressure decay time, using the parameters τ, RC_{PVR} and RC_{TPR}, differed significantly from each other both pre and post-PEA. Expectedly, there was a strong correlation between RC_{PVR} and RC_{TPR}, while post-PEA τ was moderately correlated to RC_{PVR} and RC_{TPR} (Figure 6). PEA did not affect RC_{TPR} (Table 3). In contrast, τ increased and RC_{PVR} reduced following PEA. Of note, post-PEA (but not pre-PEA) τ was significantly correlated to the post-PEA asymptotic pressure.

Correlation Analyses

The correlation of changes (post-PEA minus pre-PEA values) in the WIA and reservoir indices from the main pulmonary artery to the conventionally used hemodynamic measurements, echocardiographic parameters reflecting RV size and function and B-type natriuretic peptide (BNP) was examined (Supplementary Table S4: https://osf.io/h2dwk/?view_only=765df6c79dcf4d4ab9c697be0c4701ae). Decreased wave speed was significantly correlated to changes in PVR (rho = 0.79, p = 0.02), arterial compliance (rho = -0.81, p = 0.01) and BNP (rho = 0.82, p = 0.02). The decrease

in reservoir pressure was significantly associated with the decrease in pulse pressure (rho = 0.98, $p < 0.01$) and the increase in arterial compliance (rho = -0.88, $p < 0.01$) and decreased excess pressure was significantly correlated to decreased RV diastolic diameter (rho = 0.79, $p = 0.02$), RV area (rho = 0.74, $p = 0.04$) and decreased BNP (rho = 0.82, $p = 0.02$). Decreased asymptotic pressure was significantly associated with decreased PAPm (rho = 0.95, $p < 0.01$) and decreased PVR (rho = 0.79, $p = 0.02$). In contrast, changes in wave energy and WRI were not significantly correlated to changes in any of the conventionally used hemodynamic parameters or RV size and function (Supplementary Table S4: https://osf.io/h2dwk/?view_only=765df6c79dcf4d4ab9c697be0c4701ae), although there was a moderate positive correlation between the decrease in FCW energy and decreased BNP (rho = 0.71; $p = 0.07$).

Discussion

We used WIA and reservoir-excess pressure analysis to assess the influence of PEA on pulmonary arterial wave propagation and reservoir function. Following PEA, PAPm decreased (it was below 25 mmHg in more than 1/3 of the patients). The local wave speed also decreased markedly, but wave reflection was only slightly reduced, even in patients with a PAPm <25 mmHg post-PEA. Reservoir, excess and asymptotic pressures all decreased and these changes were associated with improved RV afterload, function and size; Finally, RC_{PVR} decreased and τ increased, while RC_{TPR} appeared to be unchanged.

Impact of PEA on Wave Speed and Wave Energy

Consistent with previous studies (11, 17), significant improvements in pulmonary hemodynamics and RV function were observed 3 months post-PEA with ~34 % reduction in PAPm, ~55 % reduction in PVR and ~32 % increase in cardiac output. Corresponding to improved arterial compliance, wave speed, a measure of pulmonary arterial stiffness, decreased by ~50 %; although, it remained significantly higher than the wave speed of control subjects, even in patients with a PAPm < 25 mmHg after surgery. The contribution of arterial stiffness to RV afterload is often neglected; however, its inverse, arterial compliance, has been shown to be a strong independent predictor of mortality in pulmonary arterial hypertension patients (32, 33), and in the systemic circulation, aortic pulse wave velocity is an independent predictor of cardiovascular events (5, 29).

FCW energy represents the work done by the ventricle to generate pulse waves, while RV stroke work accounts for the energy used to maintain steady flow; both remained essentially unchanged after PEA, although there was some evidence of normalization in patients with a PAPm < 25 mmHg after surgery. The ratio of FCW to RV stroke work also remained unchanged indicating unaffected proportional contribution of the wave and mean power to the total RV hydraulic power. FCW is generated during RV ejection and consequently, its magnitude is influenced by RV preload, contractility and the properties of the pulmonary artery (23). The preserved wave energy and RV stroke work may therefore be explained by the increased cardiac output post-PEA due to decreased RV afterload.

Impact of PEA on Wave Reflection

Reflected waves are generated when the energy transmission property between the proximal and distal vasculature differs leading to an admittance (or inversely impedance) mismatch (41). Reflected compression waves that arrive in systole augment pressure and impede flow and therefore constitute an additional load on the contracting right ventricle. The normal pulmonary circulation is efficiently constructed so that it facilitates forward traveling waves and impedes backward traveling waves (60), while high intensity reflected waves are evident in CTEPH patients (44, 52). Interestingly, high intensity reflected waves were observed both pre- and post-PEA and the magnitude of wave reflection diminished only slightly following PEA. In a previous study, we have demonstrated that large wave reflection was present in patients with mildly elevated pulmonary pressures, similar to those with severely elevated pulmonary pressures and thus, we suggested that vascular impedance mismatch may occur in the initial phase of pulmonary vascular disease (52). In keeping with these previous observations, the findings from the present study suggest that despite substantial reduction in pulmonary pressures and PVR in some patients, some degree of vascular admittance mismatch persisted. This may be indicative of residual pulmonary arterial disease, which may continue to adversely affect interactions between the right ventricle and the vasculature. Persistent large wave reflection post-PEA does not imply that removal of thrombi did not influence wave energy transmission. Wave behavior in the vicinity of thrombi is poorly understood. Thrombi may act as a reflector or they may partially absorb energy. Although the net wave reflection remained large, it is difficult to establish whether the location of the reflection sites altered. Some studies (28, 44) have used the local wave speed and half of the time difference between FCW to BCW to give an estimate of the "effective" reflection site. This calculation is based on the assumption that the local wave speed is constant throughout the circulation and that

413 reflection arises form a single site; both of these assumptions are questionable (48).
414 Therefore, we have refrained from estimating the location of effective reflection site(s).
415 Whether the large wave reflection contributes to persistent exercise intolerance and
416 residual symptoms post-PEA (6, 10) remains to be determined.
417 First described by Andersen and colleagues and later confirmed by Moser and Bloor,
418 it is now widely accepted that CTEPH is a dual compartment vascular disorder (3, 35)
419 with development of various degrees of secondary small-vessel arteriopathy distal to
420 both obstructed and unobstructed large arteries. Hence, despite successful
421 endarterectomy, the impact of distal vascular remodeling, which could be irreversible,
422 may be sustained and this could contribute to persistent vascular admittance
423 mismatching. Moreover, partially occluding thrombi in the distal locations may remain
424 and fragile thrombus materials may break during surgery and travel to distal vessels
425 (39) contributing to impaired pulse wave energy transmission. Post-PEA admittance
426 mismatching may also be related to post–surgery complications such as pulmonary
427 vascular steal syndrome, where previously obstructed areas become hyperperfused,
428 while non-endarterectomized areas become hypoperfused (39) or structural damage to
429 the vessel wall during surgery. Removal of tunica intima and some of the tunica media
430 of the affected vascular segments during PEA will alter the anatomy of the vessel wall
431 and cause endothelial dysfunction. (22). Regenerated endothelium has been shown to
432 exhibit impaired nitric oxide production which causes impaired vascular responses (57).
433 Further studies are warranted to determine the pathophysiology and implications of
434 persistent vascular admittance mismatching and whether it improves during longer term
435 follow-up in the same way that gas exchange capacity improves (54) and vascular steal
436 resolves (36).
437

438 **Impact of PEA on Reservoir Function**

439

440 The reservoir-excess pressure analysis offers an additional perspective on pulmonary
441 hemodynamics. Customarily, reservoir-excess pressure analysis is applied to pressures
442 acquired by high fidelity micromanometers, as fluid-filled catheters are associated with
443 issues such as damping and insufficient frequency responsiveness. However,
444 performing reservoir-excess pressure analysis on carefully acquired data using fluid-
445 filled catheters may be possible. If so, this could facilitate the use of reservoir-excess
446 pressure analysis in research and clinical settings.

447 As RV afterload increases in pulmonary hypertension, reservoir, excess and
448 asymptotic pressures increase (18, 53) and they remain high in patients with residual PH
449 following PEA. Analogous to its systemic counterpart (42), the work done by the
450 ventricle on the reservoir work represents the energy used to charge the elastic vessels
451 in systole; this provides the driving pressure for microcirculatory flow during diastole.
452 The excess pressure is the residual pressure once reservoir pressure is subtracted. Both
453 these pressures are attributable to waves. Nevertheless, excess pressure is more
454 indicative of local conditions; thus, it is noteworthy that the decrease in excess pressure
455 was related to improved RV function and reduced RV size. Reservoir pressure also
456 decreased due to the increased arterial compliance (and reduced resistance) following
457 PEA. The reduction in reservoir pressure can be viewed as an indication of improved
458 hydraulic behavior of the pulmonary circulation as the reservoir pressure represents the
459 pressure that results in the minimum ventricular hydraulic work for a given flow
460 waveform (42). This emphasizes that arterial compliance is beneficial for the system as
461 it acts as a buffer (or a "reservoir") for pulsatile ejection.

462 The asymptotic pressure (P_∞) is an empirical parameter derived from the reservoir-
463 excess pressure model. It is assumed to represent the equilibrium pressure at which flow
464 out of the large elastic arteries would be expected to cease. This generally exceeds the
465 left atrial pressure due to the Starling-resistor characteristics of the lung and the
466 pulmonary microcirculatory vessels. It is assumed that near-zero pulmonary flow occurs
467 at end-diastole (21) consistent with a P_∞ that is close to the diastolic pressure. This
468 "critical closing pressure" is influenced by vascular smooth muscle tone, pulmonary
469 rarefaction and vascular lesions as well as the alveolar pressure and gas tension (9, 30,
470 34, 43). Therefore, perhaps due to partial restoration of the pulmonary vasculature
471 following PEA, there was a marked decrease in the asymptotic pressure. It has been
472 suggested that the difference between the arterial P_∞ and venous P_∞ is related to
473 microcirculatory resistance (7). In support of this theory, we observed a ~41% decrease
474 in P_∞ and the decrease was strongly correlated to the decreased PAPm and PVR.
475
476 **Diastolic Pressure Decay**
477
478 The diastolic pressure decay time is a topic of special interest in the pulmonary
479 circulation; it is usually assumed to follow a mono-exponential function determined by
480 arterial compliance and resistance. The decay time represents the time necessary for the
481 pressure to decrease to $1/e$ of the difference between P_0 (i.e. pressure at the time of
482 closure of the pulmonary valve) and the zero-flow pressure (Figure 1). For simplicity,
483 the pressure decay time is often expressed as the RC-time, calculated as the product of
484 PVR or TPR and estimated total pulmonary arterial compliance. Total pulmonary
485 arterial compliance can be derived from a Windkessel model (27); although it is
486 commonly calculated as the stroke volume to pulse pressure ratio (26, 56). It has been

proposed that in the pulmonary circulation, resistance and compliance are coupled through an inverse hyperbolic relationship, resulting in a fixed RC-time in health and disease and during treatment (4, 26, 27). A fixed RC-time implies that knowledge of either resistance or compliance enables the derivation of the other parameter and that RV oscillatory power remains a constant fraction of total RV power (46). However, the concept of a fixed RC-time has repeatedly been challenged, as shortened RC-time has been shown in CTEPH patients (31), patients with elevated PAWP (56) and subjects with a PAPm < 25 mmHg (55)

In keeping with a previous study (31), we observed that RC_{PVR} reduced post-PEA, which could be interpreted as indicating that the decrease in PVR exceeds the increase in compliance. However, our observation is in direct contrast to other studies that showed similar RC_{PVR} immediately following PEA (14, 50) and one year post-surgery (50). We also observed that RC_{TPR} did not change significantly post-PEA, consistent with another recent study (10). Finally, we observed that τ increased following PEA consistent with a substantial improvement in arterial compliance. Using RC_{PVR} and RC_{TPR} as estimates of pressure decay time does not take the zero-flow pressure into account and assumes negligible outflow of the stroke volume during systole (47). Hence, resistance-compliance products may overestimate the true pressure decay time (9), especially in PH patients. Unlike RC_{PVR} and RC_{TPR}, τ does not make these assumptions and therefore may be a more accurate estimate of the pressure decay time. The findings of this study and previous studies (9, 19, 31, 53, 56), do not appear consistent with the hypothesis of a fixed RC relationship.

Study Limitations

The main limitation of this study is its small size and many of the statistical comparisons are probably underpowered. We pooled the data from the three pulmonary artery branches together under the assumption that there is no major admittance mismatch between the main, right and left pulmonary arteries as previously shown (52). The absence of a difference between different branches also supports this assumption. As wave power/energy is expressed per CSA of the artery, it follows that WIA is potentially sensitive to vessel diameter variations. By pooling data from the three pulmonary artery branches, we neglect the effect of the different diameters of main, right and left PAs. PA diameter may also decrease after surgery as PAPm decreases. However, a crude estimate of the main PA CSA based on cardiac output and mean flow velocity showed that the change in PA area/diameter (~1 mm) was small and statistically insignificant. Acquiring high quality velocity measurements was technically challenging and good quality velocity data were not obtainable from the left pulmonary artery from two of the patients. The pulmonary flow may be highly disturbed in PH patients (25), even after PEA, causing increased signal noise and artefacts on the Doppler flow tracings. Catheter whip as well as artefacts due to the vessel wall can also introduce errors. Thus, careful maneuvering of the catheter during the procedure, excellent quality control and meticulous data processing were necessary. Signal noises and motion artefacts are particularly problematic around valve closure; however as we have focused on events occurring during early and mid-systole, this was less of a problem in our study.

Conclusions

WIA provides novel insights into pulmonary arterial hemodynamics. Following PEA, reservoir, excess and asymptotic pressures decreased and these changes were associated with improved RV afterload, function and size. However, despite of substantial improvements in pulmonary pressures, PVR and wave speed, a measure of pulmonary arterial stiffness, there were only small reductions in arterial wave reflection 3 months post-PEA, even in patients with a PAPm below 25 mmHg. We interpret this as indicating a lack of improvement in vascular admittance mismatch despite PEA. The possibility that this contributes to persistent exercise intolerance and residual symptoms in some patients should be explored in future.

Glossary

BCW: backward compression wave

CTEPH: chronic thromboembolic pulmonary hypertension

FCW: forward compression wave

FDW: forward decompression wave

PAPm: mean pulmonary arterial pressure

PAWP: pulmonary arterial wedge pressure

PEA: pulmonary endarterectomy

PVR: pulmonary vascular resistance

RC: product of resistance and compliance

RV: right ventricle

TPR, total pulmonary resistance

WIA: wave intensity analysis

WRI: wave reflection index

561 τ: diastolic time constant

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Additional information

Competing interests

None.

Author contributions

The study was carried out at Hammersmith Hospital, Imperial College Healthcare NHS Trust, London and Aarhus University Hospital. J.S., A.D.H., U.S. and K.H.P. conceived and designed the experiment. J.S., J.E.N.K, L.S.H and S.M. collected the experimental data. J.S., A.D.H., K.H.P., L.S.H. and S.M. performed data analysis and interpretation. J.S. drafted the paper and all authors revised it critically for important intellectual content. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Figure 1: Schematic of the Diastolic Pressure Decay

P_0 is the pressure at time, t_0, corresponding to the end of ventricular ejection (pulmonary valve closes). This was assumed to correspond to the time of maximal negative dP/dt. The asymptotic pressure (P_∞) is the limit for the exponential decay of the pressure during diastole and corresponds to the pressure at which outflow through the microcirculation would be predicted to be zero assuming a mono-exponential decay. The pressure decay time, i.e. the time constant, τ, represents the time necessary for the pressure to decrease to $1/e$ of the difference between P_0 and P_∞.

Figure 2: Wave Intensity Analysis

Measured pressure and flow velocity profile in the main pulmonary artery and the corresponding wave intensity (WI) patterns are shown for a patient (**A**, **B**) before and (**C**, **D**) after pulmonary endarterectomy (PEA). For comparison, (**E**, **F**) a WI pattern from a representative control subject without pulmonary vascular disease from a previous study (52) is also shown. The contour of the net wave intensity is highlighted in red. Following PEA, pulmonary arterial pressure decreased (mean pulmonary artery pressure < 25 mmHg) and velocity increased (signal noises and motion artefacts can be seen in end-systole). The three dominant systolic waves observed are: forward compression wave (FCW) related to right ventricular contraction, forward decompression wave (FDW) related to ventricular relaxation and backward compression wave (BCW) due to wave reflection. Note that large BCW persisted after surgery. In contrast, the control subject displayed a negligible BCW.

Figure 3: Post-Surgery Wave Intensity Parameters

822 Wave intensity parameters, specifically (**A**) wave speed, (**B**) forward compression wave
823 (FCW) energy and (**C**) wave reflection index (WRI) of the patients after pulmonary
824 endarterectomy (PEA) and of control subjects without pulmonary vascular disease (N =
825 10) from a previous study (52) are presented here. Post-PEA patients are separated into
826 two groups: those with a mean pulmonary arterial pressure (PAPm) < 25 mmHg (N = 3)
827 and those with residual pulmonary hypertension (res. PH, N = 5). Note that patients
828 with PAPm < 25 mmHg remained to have substantially larger wave reflection compared
829 to controls. Data are presented as estimated marginal means (pooled data from the main
830 and branch pulmonary arteries) and SE and analyzed using mixed linear models.
831
832 **Figure 4: Reservoir-excess Pressure Analysis**
833 Separation of the measured pressure from the main pulmonary artery into a reservoir
834 pressure and an excess pressure and superimposition of the excess pressure waveform
835 on to the velocity waveform (scaled so that the peaks of the waveforms coincide) are
836 shown for a patient (**A, B**) before and (**C**, **D**) after pulmonary endarterectomy (PEA).
837 For comparison, (**E**, **F**) reservoir and excess pressure profiles for a representative
838 control subject without pulmonary vascular disease from a previous study (52) is also
839 shown. Both the reservoir and excess pressures decreased following surgery (note the
840 scale difference). The morphology of the flow velocity waveform deviated from the
841 excess pressure waveform in mid-systole, where there is a rapid initial decrease in the
842 velocity before the velocity plateaus. This is not matched in the excess pressure
843 waveform consistent with wave reflection. In contrast, the flow velocity waveform
844 resembled the excess pressure waveform of the control subject consistent with minimal
845 wave reflection. (Same patients as in figure 1).
846

Figure 5: Post-Surgery Reservoir Indices

Indices derived from reservoir-excess pressure analysis, specifically the (**A**) peak reservoir pressure, (**B**) peak excess pressure and (**C**) asymptotic pressure of the patients after pulmonary endarterectomy (PEA) and of control subjects without pulmonary vascular disease (N = 10) from a previous study (52) are presented here. Post-PEA patients are separated into two groups: those with a mean pulmonary arterial pressure (PAPm) < 25 mmHg (N = 3) and those with residual pulmonary hypertension (res. PH, N = 5). Data are presented as estimated marginal means (pooled data from the main and branch pulmonary arteries) and SE and analyzed using mixed linear models.

Figure 6: Relationship Between the Estimated Diastolic Time Constants τ, RC_{PVR} and RC_{TPR}

τ is the inverse of the diastolic rate constant, RC_{TPR} is product of total pulmonary vascular resistance and compliance and RC_{PVR} is the product of pulmonary vascular resistance and compliance. PEA: pulmonary endarterectomy

867 **Table 1**. Patient Symptoms and Hemodynamic Measurements

868

N = 8	†Pre-PEA	Post-PEA	Δ
WHO function class, I/ II/ III/ IV, N	0/ 1/ 7/ 0	3/ 3/ 2/ 0	--
Heart rate, min^{-1}	83 ± 14	80 ± 11	-3 [-16; 10]
Systolic BP, mmHg	129 ± 22	134 ± 17	5 [-11; 21]
Diastolic BP, mmHg	87 ± 19	86 ± 9	-6 [-15; 12]
Cardiac output, l/min	4.1 ± 1.8	5.4 ± 2.2	1.3 [0.4; 2.2]*
Right atrial pressure, mmHg	12 ± 5	8 ± 5	-5 [-11; 1]
Systolic PAP, mmHg	82 ± 14	55 ± 22	-27 [-47; -7]*
Diastolic PAP, mmHg	32 ± 9	21 ± 9	-11 [-23; 1]
Mean PAP, mmHg	49 ± 10	32 ± 13	-16 [-31; -2]*
PAWP, mmHg	9 ± 3	10 ± 3	1 [-3; 4]
PVR, Wood Units	11.1 ± 4.3	5.1 ± 4.4	-6.1 [-10.5; -1.6]*
Peak velocity in main PA, cm/s	38.7 ± 12.0	55.7 ± 22.4	17.1 [3.1; 30.9]*
Mean velocity in main PA, cm/s	21.0 ± 7.1	31.6 ± 11.9	10.6 [3.1; 18.1]*
Arterial compliance, ml/mmHg	1.0 ± 0.3	2.2 ± 0.9	1.2 [0.5; 2.0]*
RV stroke work, ml·mmHg	1895 ± 987	1714 ± 1291	-181 [-1246; 883]

869

870 Abbreviations: BP, blood pressure; PAP, pulmonary arterial pressure; PA: pulmonary
871 artery, PAWP, pulmonary artery wedge pressure; PEA, pulmonary endarterectomy;
872 PVR, pulmonary vascular resistance; RV, right ventricle; WHO, World Health
873 Organization

874 Data are presented as mean ± SD and the differences between pre- and post-PEA data
875 (post – pre) are presented with 95 % CI.

876 *$p < 0.05$ versus pre-PEA.

877 †Pre-PEA data from 6 of these patients have been included in a previous study (52).

878 **Table 2**. Wave Characteristics

	Pre-PEA	Post-PEA	Δ
Wave speed	16.5 [14.8; 18.2]	8.10 [6.33; 9.87]	-8.39 [-10.85; -5.93]*
Ln (FCW intensity, kW/m^2)	11.7 [11.4; 12.0]	11.7 [11.4; 11.9]	-0.04 [-0.31; 0.24]
Ln (FCW energy, kJ/m^2)	8.64 [8.40; 8.88]	8.67 [8.43; 8.91]	0.03 [-0.14; 0.21]
Ln (BCW intensity, kW/m^2)	10.4 [10.1; 10.7]	10.0 [9.7; 10.3]	-0.42 [-0.84; -0.01]*
Ln (BCW energy, kJ/m^2)	7.24 [6.93; 7.56]	6.93 [6.61; 7.26]	-0.31 [-0.72; 0.10]
Wave reflection index, %	27.6 [22.8; 32.4]	21.5 [16.5; 26.4]	-6.15 [-13.0; 0.7]
Ln (FCW to RV power density ratio)	4.89 [4.64; 5.14]	4.94 [4.68; 5.19]	0.05 [-0.31; 0.40]
Ln (FCW to RV energy density ratio)	5.19 [4.96; 5.42]	5.20 [4.96; 5.43]	0.01 [-0.32; 0.34]

879

880 Abbreviations: BCW, backward compression wave; FCW, forward compression wave;

881 PEA, pulmonary endarterectomy.

882 Data from the main, right and left pulmonary arteries were pooled together and

883 presented as estimated marginal means [95 % CI] derived from a mixed linear model.

884 Note that FCW intensity and energy exceeds RV power and energy (ratio > 1). This is

885 because wave intensity and energy were normalized to the length of the cardiac cycle

886 (Equation 5).

887 *$p < 0.05$ versus pre-PEA.

888 †Pre-PEA data from 6 of these patients have been included in a previous study (52).

889

890

891 **Table 3**. Reservoir Function

N = 8	Pre-PEA	Post-PEA	Δ
Reservoir-excess pressure analysis			
Asymptotic pressure, mmHg	31.5 [26.3; 36.8]	21.1 [15.8; 26.3]	-10.5 [-15.4; -5.6]*
Peak reservoir pressure, mmHg	32.6 [28.1; 37.2]	20.9 [16.4; 25.5]	-11.7 [-14.8; -8.6]*
Reservoir pressure integral, mmHg·s	9.85 [8.52; 11.19]	6.53 [5.19; 7.86]	-3.33 [-4.20; -2.45]*
Peak excess pressure, mmHg	23.0 [19.6; 26.5]	17.8 [14.3; 21.3]	-5.21 [-7.23; -3.20]*
Excess pressure integral, mmHg·s	4.78 [4.07; 5.49]	3.65 [2.94; 4.36]	-1.13 [-1.61; -0.65]*
Ln (Systolic rate constant, s^{-1})	2.64 [2.43; 2.85]	2.39 [2.18; 2.60]	-0.25 [-0.44; -0.07]*
Diastolic rate constant, s^{-1}	7.17 [5.58; 8.75]	5.07 [3.48; 6.65]	-2.10 [-3.11; -1.09]*
Diastolic pressure decay time			
τ, s	0.17 [0.13; 0.22]	0.23 [0.19; 0.28]	0.06 [0.02; 0.10]*
RC_{PVR}, s	0.60 ± 0.15	0.49 ± 0.13	0.11 [0.00; 0.22]
RC_{TPR}, s	0.75 ± 0.21	0.75 ± 0.18	0.00 [-0.16; 0.16]

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894 Abbreviations: PEA, pulmonary endarterectomy; RC_{PVR}, product of pulmonary vascular
895 resistance and compliance; RC_{TPR}, product of total pulmonary resistance and
896 compliance; τ, diastolic time constant.

897 Data from the main, right and left pulmonary arteries were pooled together and
898 presented as estimated marginal means [95 % CI] derived from a mixed linear model.

899 RC_{PVR} and RC_{TPR} are presented as mean ± SD.

900 *$p < 0.05$ versus pre-PEA.

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