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4D Magnetic Resonance Flow Imaging for Estimating Pulmonary Vascular Resistance in Pulmonary Hypertension

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Abstract

Purpose—To develop an estimate of pulmonary vascular resistance (PVR) using blood flow measurements from 3-dimensional velocity-encoded phase contrast magnetic resonance imaging (here termed 4D MRI).

Materials and Method—17 patients with pulmonary hypertension (PH) and 5 controls underwent right heart catheterization (RHC), 4D and 2D Cine MRI (1.5T) within 24 hours. MRI was used to compute maximum spatial peak systolic vorticity in the main pulmonary artery (MPA) and right pulmonary artery (RPA), cardiac output, and relative area change in the MPA. These parameters were combined in a 4-parameter multivariate linear regression model to arrive at an estimate of PVR. Agreement between model predicted and measured PVR was also evaluated using Bland-Altman plots. Finally, model accuracy was tested by randomly withholding a patient from regression analysis and using them to validate the multivariate equation.

Results—A decrease in vorticity in the MPA and RPA were correlated with an increase in PVR (MPA: $R^2 = 0.54$, $P < 0.05$; RPA: $R^2 = 0.75$, $P < 0.05$). Expanding on this finding, we identified a multivariate regression equation that accurately estimates PVR ($R^2 = 0.94$, $P < 0.05$) across severe PH and normotensive populations. Bland-Altman plots showed 95% of the differences between predicted and measured PVR to lie within 1.49 Wood units. Model accuracy testing revealed a prediction error of approximately 20%.

Conclusion—A multivariate model that includes MPA relative area change and flow characteristics, measured using 4D and 2D Cine MRI, offers a promising technique for non-invasively estimating PVR in PH patients.

Keywords

pulmonary hypertension; pulmonary vascular resistance; 4D MRI

INTRODUCTION

Pulmonary hypertension (PH) is characterized by a progressive increase in pulmonary vascular resistance (PVR) (1, 2). Pulmonary vascular resistance (PVR) has been shown to be a critical metric with both prognostic and diagnostic value (3). In clinical practice PVR is measured during right heart catheterization (RHC), a procedure that exposes the patient to risk of iatrogenic injury and occasionally requires sedation. While regularly measuring PVR to assess therapeutic efficacy and disease progression would be ideal, the invasive nature of RHC makes this impractical. Therefore, a non-invasive measurement of PVR would offer an invaluable clinical tool for regularly evaluating therapeutic response and proactively preserving healthy vascular function.

PVR is governed by the cross-sectional area of the distal pulmonary vascular bed, which is known to progressively decrease in PH due to vascular hypertrophy, vasoconstriction, and in-situ thrombosis (1). This increase in resistance inevitably impacts blood flow patterns in the proximal vessels (4) that are also partially governed by changes in vascular distensibility, morphology, and right ventricular (RV) ejection behavior.

Previous researchers have looked to flow measurements for a non-invasive estimate of PVR. These studies have mostly focused on echocardiography to measure flow characteristics (e.g. maximum regurgitated flow velocity across the tricuspid valve) that correlate with PVR, but results have been modest. Four dimensional flow cardiac MRI (4D MRI) allows for non-invasive measurement of velocity in the spatiotemporal manner, enabling the assessment of novel hemodynamic measurements such as vorticity and other interesting clinical markers (e.g. wall shear stress(5-7)). Previous studies have shown 4D MRI to be an extremely promising diagnostic/prognostic tool in PH (8-11), with multiple proposed flow characteristics (i.e. flow velocity, retrograde flow, vortex existence time, etc.) correlating with a myriad of cardio-pulmonary markers. However, the strength of these correlations have been relatively modest ($R^2 < 0.9$), without adequate attention paid to relationships between flow characteristics and afterload (8, 10). In other studies, good multivariate correlations were found in animal studies with a modest sample size (9), which provided proof-of-concept for similar multivariate modeling in humans. In this study, we combine previously used flow characteristics (e.g. volumetric flow) with measures of vorticity in the main and right pulmonary artery. Vorticity is a measure of spatial velocity gradients that may serve as a sensitive measure of complex hemodynamic phenomena in the pulmonary vasculature incompletely captured by traditional flow measurements. Because distal resistance, proximal compliance, and RV contraction are coupled and have a synergetic influence on velocity profiles in the proximal vessels, we postulate that flow vorticity correlates with bulk hemodynamics. Based on vorticity generation and the PA pressure-distensibility relationship, we further hypothesized that PVR would correlate with velocity gradients in the proximal pulmonary vasculature, total flow, and the relative changes to the pulmonary arterial cross-sectional area over the cardiac cycle, allowing for a non-invasive estimate of PVR using a vorticity-based equation. Thus the aim of the current study is to derive a statistical multi-variate equation that can predict RHC measured PVR from flow and tissue kinematics available from 4D MRI.

MATERIALS AND METHODS

Using a prospective XXX Institutional Review Board-approved study, 22 patients (mean age $\pm$ SD = 58.6 $\pm$ 9.9 years old; F:M = 15:8) were prospectively enrolled from the NJH Pulmonary Hypertension Center between 7/30/12-9/24/14. Upon enrolment, each subject received same day RHC, MRI, and echocardiography. Informed consent was obtained in all subjects to perform testing and offer data access to all researchers involved in the study. Study participants underwent clinically-indicated RHC for diagnosis of PH or as a single annual reassessment of hemodynamics on PH therapy. RHC was performed utilizing a 7 French Swan-Ganz catheter via right internal jugular access for measurement of mean pulmonary artery pressure (mPAP), systolic pulmonary arterial pressure (sPAP), pulmonary artery wedge pressure (PAWP), thermodilution (or Fick, depending on physicians judgement) cardiac output (CO), cardiac index (CI), stroke volume (SV), and calculation of PVR (see Eq. (1)).

$$PVR = \frac{mPAP - PAWP}{CO} = mmHg * \frac{min}{L} = Wood \text{ unit} \quad (1)$$

PH was defined by demonstration of a mPAP $\geq$ 25 mmHg during standard diagnostic RHC or a prior history of RHC-proven PH (mPAP $\geq$ 25 mmHg), which persisted on PH pharmacologic therapy at the time of protocol. Control subjects were defined by mPAP < 25 mmHg. Biometric data including age, gender, body mass index (BMI), and heart rate were collected on the day of protocol performance.

MRI Protocol

A cine steady-state free precession (SSFP) technique with retrospective gating was used to image from the base to apex during brief end-expiratory breath-holds using contiguous short-axis slices in 8 mm increments. Additional long-axis and short axis SSFP images were obtained at the level of the main pulmonary artery (MPA). Ventricular volumetric and functional analyses were performed off-line by a blinded reader (MS, 1 year of experience) using commercially available software (Argus, MR B17, Siemens AG Healthcare Sector, Erlangen, Germany). RV end-diastolic and end-systolic contours were manually traced in the axial view for each slice. RV ejection fraction (RVEF) was determined using the modified Simpson's rule (12).

The PA relative area change, $RAC = (A_{max} - A_{min}) / A_{max}$ was computed by manually segmenting the aforementioned PA SSFP images, where A_{max} and A_{min} are the maximum and minimum cross-sectional PA areas, respectively.

4D MRI was performed on a 1.5T system (Siemens, Erlangen, Germany) with interleaved 3-dimensional velocity encoding (voxel volume = 2.4-2.6 $\times$ 2.4-2.6 $\times$ 2.4-3.0 mm, α = 14-15°, TE/TR = 2.85/48.56 ms, VENC = 150 cm/s, temporal resolution = 42-48 ms). Images were acquired using an RF-spoiler gradient echo pulse sequence, prospective ECG gating, and respiratory navigators using bellows (13). Raw phase contrast MRI data sets were: (1) filtered for noise using a magnitude mask; (2) anti-aliased using a custom Matlab program

(Matlab, MathWorks Inc); and (3) converted to Enight (Apex, NC) flow velocity data format using the Velomap software (14). Velocity data was processed in Paraview (Kitware, Clifton, NY) for visualization and flow quantification in separate vascular compartments. SSFP scout images were used for spatial co-registered segmentation in order to delineate flow-tissue boundaries. Vascular regions for vorticity computation were defined and standardized using specific anatomical landmarks. The MPA luminal region of interest was defined as volume extending from the pulmonic valve to the distal end of the MPA bifurcation using the planes that define the ostia of the RPA and LPA as lateral boundaries. The RPA luminal region of interest was defined as the volume extending from the RPA ostial plane (MPA boundary) to planes that defined the ostia of the right middle and right lower lobar arteries. Eq. (2) was used to compute the magnitude of the maximum spatial peak systolic vorticity within the MPA ($\vec{\omega}_{MPA}$) and RPA ($\vec{\omega}_{RPA}$). In Eq. (2), u , v , and w represent the velocity in the x , y , and z directions, respectively.

$$\vec{\omega} = \vec{\nabla} \times \vec{v} = \left(\frac{\partial u}{\partial y} - \frac{\partial v}{\partial x} \right) \hat{i} + \left(\frac{\partial u}{\partial z} - \frac{\partial w}{\partial x} \right) \hat{j} + \left(\frac{\partial v}{\partial z} - \frac{\partial w}{\partial y} \right) \hat{k} \quad (2)$$

In addition to vorticity, the following standard 4D MRI flow parameters were sampled from each waveform together with the RV systolic performance markers as shown previously (5): maximum PA flow: Q_{max} ; maximum velocity in the MPA: V_{max} ; RV cardiac output: CO ; and stroke volume: SV . CO was measured by integrating the velocity profile at the cross-section shown in Fig. 2, located 1 cm downstream of the pulmonary valve. Flow (Q ; Eq. (3)) is found by integrating the velocity vectors normal to the plane within the flow domain. In Eq. (3), Q at any time point, t_i , is computed by integrating velocity, $\vec{v}(x, y, t_i)$, over the surface of the lumen intersecting the plane shown in Fig. 2 (S), where $\hat{n}$ is the unit vector normal to the plane. The 4D MRI time sequence offered between 7 and 12 points of measurement in a cardiac cycle. Therefore, a waveform of 1000 points was generated using cubic spline interpolation and integrated using the Trapezoidal rule. CO used in the multivariate regression (described below) was found by dividing the integrated flow waveform by the cardiac cycle period, obtained from MRI.

$$Q(t_i) = \iint_S \vec{v}(x, y, t_i) \cdot \hat{n} \, dS \quad (3)$$

All MRI data processing was performed a single time by two blinded observers (MS – 1 year of experience; CAP – 0.5 years of experience). The Shrout-Fleiss intra-class correlation coefficient was utilized to confirm acceptable inter-observer variability. The analysis protocol is semi-automated and uniformly applied across the entire study population.

Statistical Analysis

Multivariate linear regression analysis (Eq. (4)) was used to correlate PVR (Output Parameter = y) to predictors (Input parameter = x_1, x_2, x_3, x_4), with coefficients $\delta_0, \delta_1, \delta_2, \delta_3, \delta_4$, computed from 4D MRI (MatlabR2014a, MathWorks, Massachusetts, U.S.A.). A

large discrepancy between the R^2 and Adjusted- R^2 suggests redundancy in the input parameters, but discrepancy was not observed in the following correlations. When reporting statistical results, a p-value below 0.05 was considered statistically significant and interpreted as the probability that an outcome was not a result of chance (15).

$$y = \delta_0 + \delta_1 x_1 + \delta_2 x_2 + \delta_3 x_3 + \delta_4 x_4 \quad (4)$$

Bland-Altman plots are included as a graphic comparison between PVR directly measured from RHC (Eq. 1) and estimated from the multivariate statistical model (Eq. 4).

Due to the relatively small sample size that was available for this study, we implemented a validation protocol to test the accuracy of the multi-variate model. The multi-variate equation was generated using data for all but one patient. The error for the model's prediction of PVR for the excluded patient was computed as: $Error = |PVR \text{ from RHC} - PVR \text{ from multi-variate model}|$. This was repeated for all 22 patients to calculate the expected error of the multi-variate model, when it is generated from a 21 patient cohort. The validation results that were found using this method were also compared against a Monte Carlo simulation (16) that randomly chose to exclude 1 patient. The excluded patient was chosen at random over 1000 simulations.

RESULTS

Subject Characteristics

Etiologies for PH included idiopathic (N=8), connective-tissue disease (N=7), methamphetamine exposure (N=1), and pulmonary hemangiomatosis (N=1). Consequently, there were 17 subjects with PH per RHC, and 5 normotensives who did not reveal mPAP 25mmHg during RHC. One normotensive subject completed only the 4D flow portion of the MRI protocol and not the anatomic/functional imaging acquisition due to claustrophobia.

Standard RHC hemodynamic and 4D MRI indices are presented in Table 1. No significant differences existed in Q_{max} , CO , A_{max} , and SV between PAH and control groups. A significant difference among considered groups existed in heart rate and V_{max} . Most markers measured during RHC or from 4D MRI presented a skewed distribution. Fig. 1 shows that a logarithmic transformation normalizes the data set to a Gaussian distribution. For this reason, all skewed data was normalized prior to fitting.

Example velocity streamlines generated using 4D MRI are shown for a single normotensive and PH patient in Fig. 3, and were indicative of the measurements collected for both samples. A reference plane is shown 1 cm above the pulmonary valve for coordination. A visible large-scale recirculation began to form in PH subjects immediately downstream from the pulmonary valve, which was either not seen in normotensive controls or is notably smaller in scale (see Fig. 3). This recirculation appeared to travel across the plane during systole and possibly compromised flow distribution at the bifurcation.

MPA and RPA vorticity vs. PVR

As resistive afterload increased with advancing disease progression, the 4D MRI-computed vorticity was observed to decrease proportionally (see Fig. 4). The magnitude of vorticity also appeared to decrease in offspring vessels (i.e. RPA) relative to the parent (i.e. MPA). However, the rate of vorticity decrease in the parent vessels, relative to the rate of increase in PVR, was higher compared to the child vessels.

In this study, we chose to focus on resistive afterload as one gold standard for PH prognosis. However, it is worth noting that MPA and RPA vorticity are also highly correlated with mPAP ($mPAP = 8.45 - 0.39 * \omega_{MPA} - 0.32 * \omega_{RPA}$; $R^2 = 8.45$, $P_{2-tailed} = 2.0e-8$), which is currently the clinical criteria for PH diagnosis.

Multi-variate Regression to Relate PVR to Metrics from 4D MRI

Figure 5 shows a multi-variate regression between PVR measured using RHC and a function of 3 measurements available from 4D MRI (ω_{MPA} , ω_{RPA} , CO) and 2 measurements from cine SSFP scout images (A_{min} and A_{max}). The multi-variate equation predicts 94% of the variability in PVR. Table 2 shows the resulting statistics of the linear regression model:

Given the observed probability, number of predictors, R^2 , and samples size, the statistical power for this multi-variable regression is 0.99. Excluding MPA and RPA vorticity from the multi-variate model reduces R^2 to 0.48, with RAC no longer holding statistical significance.

Bland-Altman plots show minimal bias ($-1e-15$ Wood units) and that 95% of the differences between measured and estimated PVR will lie within 1.49 Wood units.

Model Validation

Fig. 6 shows Monte Carlo results of the relative error computed from randomly withholding a single patient from the cohort to test the regression accuracy against that patient. The mean error of the model is at approximately 20% (mean $\pm$ SD = 19.3 $\pm$ 16.8%). Another validation test, which simply tested the mean error after excluding each patient separately, revealed comparable results: (mean $\pm$ SD = 20.5 $\pm$ 17.4%).

Fig. 7 shows a Monte Carlo simulation that computed the mean relative error of the multi-variate model when withholding 5, 4, 3, 2, and 1 patients. The error computed in each simulation is the maximum error of all the withheld patients. For example, if 5 patients are withheld from generating the model, all 5 patients will be tested against the model and the largest error is chosen. This analysis shows that the mean relative error of the model is decreasing as more patients are included.

DISCUSSION

We present a technique for estimating PVR from flow vorticity measurements taken from velocity-encoded 4D MRI. This discussion will cover previous attempts to estimate PVR from imaging modalities, the physics of vorticity, the link between PVR and PA flow patterns, and conclude with future work. In this study, we focused on PVR as the gold diagnostic/prognostic standard for evaluating PH patients, but note that combining MPA and

RPA vorticity into a multivariate model can also be used to predict 85% of the variability in mPAP.

Given the overall objective of this study, to find a statistical model to predict PVR from 4D MRI measurement, we believe the heterogeneous PH population used in this study should be considered as a strength rather than a weakness. It shows that PA flow patterns are sensitive enough to vascular function to be used as non-invasive markers, and this relationship appears independent from underlying etiology.

Previous attempts have been made to estimate *PVR* using non-invasive modalities. Note that the results in the literature review presented occasionally switched between the Pearson's correlation (r) coefficient and R^2 when comparing estimated and measured phenotypes. Since all presented correlations were linear, for consistency, we present their results as $R^2 = r^2$.

In 1994, Durkin *et al.* (17) attempted to estimate *CO* using a Stroke index measurement with an inert gas rebreathing technique with moderate agreement ($R^2 = 0.88$) between estimate and measurement in both hypertensive and normotensive subjects. In 2009, Kouzu *et al.* (18) estimated PVR from echocardiography, relating PVR to a ratio of the tricuspid regurgitant pressure gradient over the tricuspid regurgitation time-velocity integral with relatively modest results ($R^2 = 0.67$). Variations on this echocardiographic based method have been tried with variable success. Rajagopalan *et al.* (19) improved the agreement to $R^2 = 0.88$ for patients with $PVR < 8$ Wood. Scappellato *et al.* (20) improved this estimate even further, with an equation combining Doppler echocardiographic variables with pulmonary flow, to show an agreement of $R^2 = 0.92$ under $PVR = 9$ Wood units. However, their measurement required two sets of Doppler recording: (1) during tricuspid regurgitation and (2) systolic pulmonary flow. In fact, all Doppler based methods have yielded similar results (21-26) with the same major limitation: the need to measure tricuspid regurgitation hemodynamics. Measurable tricuspid regurgitation Doppler envelopes may not be present in normotensive patients, PH patients with modestly elevated pressures, or in patients with poor acoustic windows due to body habitus. In 2013, Cevik *et al.* (27) attempted to estimate PVR with tricuspid regurgitant velocities in children. This attempt revealed poor results ($R^2 = 0.28$), but did show that flow patterns were sensitive enough to identify acute vascular reactivity, which offers invaluable proof-of-concept for future studies.

While previous studies have utilized MRI to non-invasively estimate diagnostic/prognostic markers (5, 8, 9), results have been modest and little attention has been paid to afterload. Garcia-Alvarez *et al.* (28) presented an equation including PA velocities and ejection fraction ($R^2 = 0.68$), available from MRI, to estimate PVR. This method overcame limitations of Doppler measurements, and we have expanded on their work to further improve the predictive capacity of MRI by considering flow metrics indicative of velocity profile shape. Kreitner *et al.* (29) used phase contrast MRI to arrive at a multi-variate estimate of mean pulmonary arterial pressure and PVR. The resulting correlation between measured and estimated PVR was: $R^2 = .79$, where the regression model overestimated RHC measurements. Bland-Altman plots showed significant variability in the difference between the two measurements, with 10/19 patients being outside the 95% confidence interval.

Nevertheless, this was a well done study that showed that using flow measurements by MRI can overcome several limitations of valve-regurgitation Doppler flow measurements.

Most recently, Roldan-Alzate *et al.* (9) estimated PVR using 4D MRI in 6 dogs before and after inducing acute PH by microbeads injection. The resulting multi-variate relationship was promising ($R^2 = .90$), and also utilized pulmonary flow, but required tricuspid valve regurgitation velocity, which is subject to the aforementioned limitation.

Vorticity is a pseudo-vector quantity that is a function of space and time in physiological blood flow. It can be intuitively understood as the axis about which a tennis ball would spin if hypothetically suspended at a point in space within a moving fluid. The rate of spinning would characterize the magnitude of vorticity. Once an element of fluid has acquired vorticity via shear at a wall, it retains that vorticity until viscous losses diffuse the vorticity to nearby fluid elements or convert the rotational energy to heat. Both of these dissipative processes are relatively slow compared to the time scales in PA flow, but could be sensitive to PA diameter, distensibility, and morphology. Interestingly, a measured vorticity does not necessarily propose the presence of a visible vortex as visualized by recirculating flow and streamlines that loop (30). It merely alludes to a high velocity gradients and ripe conditions for a vortex to form.

There is undoubtedly a coupling relationship between PVR (the outflow boundary condition) and flow pattern formations in the fluid domain. Based on computational modeling results, an increase in PVR has been shown to be proportional to a decrease in WSS, which is also a function of the velocity gradient (4). This is consistent with the fact that vorticity decreases concurrently with an increase in PVR in all generations of the vascular tree (31). In fact, vorticity appears to decrease towards the periphery, where outflow resistance can exponentially increase with every advancing generation of the vascular tree, providing further evidence of the outlet boundary condition impacts the local velocity profile.

From a fluid mechanics perspective, it is not immediately clear why vorticity is decreased in the hypertensive pulmonary vasculature. This could be due to a decrease in PA compliance, increased MPA diameter, decreased flow velocity, or a combination of all of these factors. Additional analyses of the current data set as well as ongoing computational studies are being performed to explain this phenomenon.

As a derivative quantity, we expect vorticity to be a more sensitive measure of vascular function than the presence of retrograde flow or vortex duration, which are both correlated with mPAP (8, 10). It is worth noting that even though we find the magnitude of vorticity to decrease in hypertensive conditions, that finding does not conflict with the finding of Reiter *et al.* (10, 11), who observed that the vortex existence time measured in the inferior aspect of the MPA is linearly correlated with mPAP. Vorticity is a measure of spatial velocity gradients within the flow. These gradients could be implicated in the formation and duration of visible vortices, but not necessarily. To that end, while the relative onset time of retrograde flow is also correlated with mPAP (8), the presence of retrograde recirculating flow does not necessarily constitute a vortex either (32). Note that the strict definition of a vortex is an

ongoing discussion among fluid dynamicists (33). A practical example is flow funneling down a drain, which reveals a clear visible vortex but has a very low vorticity outside of the core (34).

In addition to the image acquisition/processing error involved in estimating velocity from a DICOM image, the image voxel dimensions for the current cohort were between $2.4\text{-}2.6 \times 2.4\text{-}2.6 \times 2.4\text{-}3.0$ mm. This means that a cross-section along a typical MPA, with a diameter of 3 cm, would only contain approximately 12 evenly distributed points of measured velocity. Cubic spline interpolation was used to interpolate 1000 points from the available 12.

Maximum velocity gradients, generally appearing in the boundary layer, are computed using the interpolated data set. However, comparing a Womersley velocity profile that underwent the aforementioned interpolation process with a true analytical profile reveals a maximum relative error in velocity gradient estimate of up to 60%. We acknowledge that this is a concerning finding. However, flow pattern markers that include velocity gradient calculation are strongly correlated with RHC measurements, are statistically different between normotensive and PH patients, and are consistent with physiological norms and previous findings. Therefore, we acknowledge that more work is needed to minimize this discrepancy, but stress that the error is likely proportional across the entire population and does not significantly compromise the excellent correlation presented in this manuscript. However, the constants (β_j) from the multi-variate equation presented to estimate PVR would change for images acquired with a different spatial resolution and will be addressed in future work.

Finally, the Monte Carlo simulations revealed a mean estimation error of approximately 20% when generating the multi-variate model from 21 patients. However, we show that the model accuracy is drastically dependent on the number of patients used to generate it. This result is not surprising, but it offers convincing proof-of-concept for this technique to estimate PVR from 4D MRI and suggests that recruiting more patients would specifically improve model predictive accuracy. In fact, assuming a linear relationship between the numbers of subjects included into the multi-variate model and the mean relative error predicts that an error of 5% can be achieved with as little as 26 patients.

PVR is only the resistive component of the pulmonary vascular impedance (35). Nevertheless, particularly in moderate and manifest PH, the reactive component can account for up to 30% of the afterload (36). Future studies will attempt to correlate flow patterns with more comprehensive metrics of pulmonary vascular impedance, which would significantly improve their diagnostic and prognostic capability. Furthermore, a critical component of RHC measurements is the assessment of acute vascular reactivity to O₂ and nitric oxide. Future studies will assess the sensitivity of proximal PA flow patterns to acute changes in distal PA function.

We evaluated the inter-observability error of this data set in previous work (37). However, to make these results truly clinically applicable, future studies will assess repeatability across larger multicenter studies. These factors could necessitate slightly different multi-variate equation algorithms and reveal new considerations for performing this analysis.

Finally, the aforementioned analysis and conclusions were reached based on a relatively small sample size ($n = 22$). In the discussion, we show that the error of the multi-variate model is largely dependent on sample size, and could be significantly reduced by recruiting a few additional patients. Based on these promising preliminary results, we will continue to recruit normotensive subjects and PH patients to increase the sample size.

In conclusion, we presented an equation with metrics obtained from non-invasive velocity encoded MRI measurements to estimate PVR with excellent agreement ($R^2 = 0.94$). This method does not require the measurement of tricuspid regurgitation velocities, uses data obtained from a single patient scan, and is shown to identify normotensive patients and hypertensive patients with excessively large PVR. This provides a clear advantage over previous techniques and utilizes current standard of care modalities. However, limited spatiotemporal resolution introduces large errors in estimating velocity gradients and warrants further investigation. Also, increasing sample size is a priority for improving the multi-variate model's predictive capability.

Glossary of Abbreviations:

Abbreviation	Summary
<i>4D MRI</i>	Velocity-encoded Phase Contrast Magnetic Resonance
<i>RHC</i>	Right Heart Catheterization
<i>BSA</i>	Body Surface Area
<i>BMI</i>	Body Mass Index
<i>PH</i>	Pulmonary Hypertension
<i>PVR</i>	Pulmonary Vascular Resistance
<i>MPA</i>	Main Pulmonary Artery
<i>RPA</i>	Right Pulmonary Artery
<i>Wood unit</i>	mmHg-min/L
<i>RV</i>	Right Ventricle
<i>mPAP</i>	Mean Pulmonary Arterial Pressure
<i>sPAP</i>	Systolic Pulmonary Arterial Pressure
<i>PAWP</i>	Pulmonary Arterial Wedge Pressure
<i>CO</i>	Cardiac Output
<i>SV</i>	Stroke Volume
<i>CI</i>	Cardiac Index = CO/BSA
<i>RVEF</i>	Right Ventricular Ejection Fraction
<i>RAC</i>	Relative Area Change of the MPA = $(A_{max} - A_{min})/A_{max}$
<i>A_{max,min}</i>	Maximum/Minimum PA Area
<i>VENC</i>	Velocity Encoding in 4D CMR
<i>SSFP</i>	Steady State Free Precision
<i>sgu</i>	Peak Systolic Vorticity in the MPA
<i>sgu</i>	Peak Systolic Vorticity in the RPA
<i>V_{max}</i>	Maximum Velocity over space and time
<i>Q_{max}</i>	Maximum PA Flow

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Figure 1. Example of the natural log transformation normalizing the PVR distribution. (a) A highly positively skewed distribution across the entire cohort. (b) Normalization of measured PVR in the entire cohort.

Figure 2.
Streamline generation from the 4D-MRI velocity field. Flow evaluation plane was positioned 1 cm above the pulmonic valve.

Figure 3.

Example velocity streamlines generated using 4D MRI, for a sample Normotensive and PH patient, at 5 points in the cardiac cycle. The plane shown is located 1 cm downstream of the pulmonary valve. Time points t_1 - t_5 represent instances after the R-wave from EKG: $t_1 = 0.023$ ms, $t_2 = 0.071$ ms, $t_3 = 0.118$ ms, $t_4 = 0.165$ ms, $t_5 = 0.213$ ms.

Figure 4.

Vorticity in the MPA (left, orange) and RPA (right, blue) correlated against PVR ($P < 0.05$). In both cases, vorticity is decreased proportional with PVR increase, while the magnitude of vorticity decreases from the MPA to RPA.

Figure 5.

(a) Multi-variate regression between RHC measured PVR vs. a function of vorticity in the MPA (ω_{MPA}), RPA (ω_{RPA}), cardiac output (CO), and the relative area change in the MPA.

(b) Bland-Altman plot of the difference between RHC and the multi-variate model PVR, with the mean $\pm 2SD$ at 0 ± 0.4 .

Figure 6.

Monte Carlo results for the first 100 simulations of a validation study. Each point represents the relative error between the predicted PVR and measured PVR for a single randomly chosen subject that is excluded from the cohort at each simulation. The mean error for 1000 simulations is $19 \pm 17\%$ ($\pm$ SD). Where the mean is shown as a solid line while standard deviations as dashed lines.

Figure 7.

The mean relative error of 100 Monte Carlo simulations vs. the number of randomly selected patients used to generate the multi-variate model. This data proves that increasing the number of patients used for generating the multi-variate model decreased the error of the estimate.

Table 1

Patient characteristics and hemodynamic data.

	Normotensive (N = 5)	PH (N=17)	p Value
Age	54 ± 9	60 ± 10	NS
Gender (FM)	3:2	11:6	
BMI	29.3 ± 5.2	26.6 ± 9.4	NS
Systolic blood pressure	127 ± 8	127 ± 16	NS
Diastolic blood pressure	70 ± 11	79 ± 9	NS
mPAP (mmHg)	20.1 ± 3.1	37.1 ± 11.1	0.001
PVR (Wood's Units)	2.1 ± 0.9	7.4 ± 7.0	0.008
PAWP (mmHg)	10.4 ± 4.2	11.6 ± 4.5	NS
mRAP (mmHg)	6.4 ± 2.8	7.5 ± 3.2	NS
CO (L/minute)	5.7 ± 1.3	5.1 ± 1.5	NS
Q_{max} (L/min)	28.8 ± 9.4	23.0 ± 6.2	NS
V_{max} (m.s ⁻¹)	0.88 ± 0.14	0.60 ± 0.23	< 0.05
A_{max} (cm ²)	7.7 ± 1.9	10.0 ± 1.9	NS
SV (mL)	80.2 ± 21.4	57.8 ± 19.4	NS
Heart rate (bpm)	61 ± 10	75 ± 12	< 0.05
RVEF (%)	53.9 ± 8.4	41.2 ± 14.8	0.05

Data are expressed as a mean ± 1 standard deviation.

Table 2

Statistical details of the regression shown in Fig. 5.

		SE	t-statistic	p-value
Intercept ($i = 0$)	11.4890	1.0900	10.5400	7.1265e-9
$Ln(\omega_{MPA})$ ($i = 1$)	-0.7017	0.1484	-4.7298	1.9360e-4
$Ln(\omega_{RPA})$ ($i = 2$)	-0.67243	0.0980	-6.8598	2.7694e-6
$Ln(BSA)*Ln(CO)$ ($i = 3$)	-0.2539	0.0780	-3.2561	4.6499e-3
$(A_{max}-A_{min})/A_{max}$ ($i = 4$)	2.0704	0.6589	3.1423	5.94103e-3

Number of Observations: 22

Degrees of Freedom: 17

Fisher F-value: 65.3

Associated Probability (p-value): 4.32e-10