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RESEARCH ARTICLE

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Quantifying 4D flow cardiovascular magnetic resonance vortices in patients with pulmonary hypertension: A pilot study

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Abstract

In this 4D flow cardiovascular magnetic resonance (CMR) study, vortical blood flow in the main pulmonary artery (MPA) is quantified using circulation (Γ), a metric used in fluid dynamics to quantify the rotational components of flow. Circulation (Γ) is a 4D flow CMR metric that quantifies the vortical blood flow pattern in the MPA of patients with pulmonary hypertension (PH), distinguishes them from healthy controls, and shows high correlation with invasive markers of PH severity.

KEYWORDS
4D flow cardiovascular magnetic resonance, cardiovascular imaging, pulmonary hypertension, vortical flow

BACKGROUND

Pulmonary hypertension (PH) describes a heterogeneous group of conditions (WHO Groups 1–5) characterized by high pulmonary artery pressures (mean pulmonary artery pressure [mPAP] ≥ 20 mmHg),[1,2] including highly morbid conditions leading to right heart failure and death as well as milder elevations in PAP associated with respiratory and cardiac disease.

Right heart catheterization (RHC) is the gold standard for assessing the presence and severity of PH, but is invasive; therefore, more limited, noninvasive measures are needed. Echocardiography, the most common noninvasive test, is limited by acoustic window and observer dependence.[3]

Abbreviations: 6MWD, nonencouraged 6-min walk distance; CMR, cardiovascular magnetic resonance; LV, left ventricle; MPA, main pulmonary artery; MPAD, main pulmonary artery diameter; mPAP, mean pulmonary arterial pressure; PH, pulmonary hypertension; RHC, right heart catheterization; RV, right ventricle.

2D Echocardiography is also limited in its evaluation of the complex anatomy of the right ventricle (RV) and in its estimation of functional parameters, both important measures in PH. Response to treatment is also evaluated with the nonencouraged 6-min walk distance (6MWD), which is a noninvasive submaximal exercise test that correlates with cardiopulmonary performance, but does not directly measure PAP.[1] Additionally the 6MWD is a multifactorial measure influenced by patients' overall physicalfitness and does not directly reflect outcomes in patients with PH.[4]

Cardiovascular magnetic resonance (CMR) has become a widely used noninvasive imaging method to assess a wide range of cardiovascular diseases including PH.[5,6] Time-resolved, three-directional MR phase contrast (4D flow) CMR is a relatively recent magnetic resonance imaging (MRI) technology that offers a qualitative and quantitative evaluation of PH.[7] In normal individuals, laminar and unaltered stream lines are seen in the main pulmonary artery (MPA) in 4D flow imaging.[8] Whereas, studies using 4D Flow CMR have identified a blood flow vortex in the MPA of patients with PH. Assessment of vortical flow characteristics allows for the diagnosis of PH and estimation of mPAP that can be useful in patient follow-up and treatment monitoring.[9,10] A quantifiable metric of vortex formation maximizes reproducibility and facilitates accurate objective evaluation of disease severity and prediction of patient outcome. Circulation (Γ) is a metric used in fluid dynamics to quantify the rotational component of flow. It has been previously validated as a means of quantitating rotational flow in the ascending aorta.[11] Circulation (Γ) is the line integral of the tangential component of velocity (v) around a closed contour with length (l).

$$\Gamma = \oint v \bullet dl.$$

Circulation is related to vorticity using Stokes theorem, with vorticity at a point being the circulation per unit area, or the combined strength of the total vortex lines within a defined area. We hypothesized that measurement of circulation would allow identification of patients with PH and correlate with invasive markers of PH severity. The purpose of this study was to evaluate pulmonary arterial rotational flow characteristics, quantified by circulation (Γ), in patients with PH.

MATERIALS AND METHODS

Subject demographics

Seventeen patients with established PH (mean age 61.9 ± 8.9 years, range from 48.5 to 75.3 years old, 2 male and 15 female) were prospectively enrolled. Other than an underlying clinically proven diagnosis of PH, there was no selection criteria applied to the study population. All patients underwent same-day standard of care RHC as well as 4D Flow CMR. PAH was defined by a pulmonary artery pressure of 20 mmHg or higher during a state of rest, accompanied by a pulmonary capillary wedge pressure of 15 mmHg or lower in RHC. Seven healthy controls, mean age 54.3 ± 14.6 years, range from 28.1 to 63.0 years old, six male and one female, underwent 4D Flow CMR. Exclusion criteria for healthy volunteers included any history of systemic or PH, diabetes mellitus, ischemic or nonischemic heart disease, and renal disease. Exclusion criteria for both PH patients and healthy volunteers were contra-indication to CMR studies (e.g., presence of metallic implants and inability to follow instructions for breath holding). Our institutional review board approved the study protocol and all participants gave written informed consent.

Data acquisition

All PH patients underwent clinical RHC. Parameters obtained included mPAP, systolic and diastolic PAP, pulmonary arterial wedge pressure, and pulmonary vascular resistance with cardiac output measured by thermodilution.

Magnetic resonance (MR) examinations were performed at 1.5T (Magnetom Avanto, Siemens) using a 6-channel thoracic coil combined with 6-channel spine coil. Cardiac MRI protocol for the PH patients contained cine steady-state free precession sequences in standard cardiac planes as well as the 4D phase contrast imaging. 4D Flow CMR data were acquired in a 3D volume to include the MPA.[12] Measurements were synchronized to heart rate and respiration using prospective electrocardiographic gating and adaptive diaphragm navigator gating. Imaging parameters were as follows: velocity sensitivity encoding gradient = 130 cm/s, TE = 2.58, TR = 40.8, matrix = 192 × 142, field of view = 320 × 320 mm, spatial resolution = 2.5 mm, temporal resolution ~50 ms, flip angle = 15°; generalized auto calibrating partially parallel acquisitions [GRAPPA], $R = 2$, readout bandwidth = 440 Hz/pixel, lines/segment = 2, and with average imaging time ~12–15 min. CMR 4D flow parameters that were measured included: circulation (mm^2/s), MPA diameter (MPAD), right ventricular ejection fraction (RVEF), RV stroke volume index (mL/m^2/beat), RV end diastolic mass, left ventricular ejection fraction (LVEF, %), LV stroke volume Index (mL/m^2/beat), LV end diastolic mass (g).

Data analysis

MR data preprocessing, including noise reduction and correction for velocity aliasing, was performed using previously published techniques.[12–14] 4D flow CMR was analyzed in EnSight (CEI) to calculate velocity maps. A blood flow vortex in the MPA has been defined as velocity vectors forming concentric ring-shaped curves parallel to the RV outflow tract orientation.[15,16] Therefore, a plane parallel to the RV outflow tract, including only the blood pool in the MPA, was exported as a flatfile. The plane was placed superior to any valvular turbulent blood flow and proximal to the branch pulmonary arteries. The length of the vortex was calculated manually by visually locating the vortex, defining the boundaries of the vortex on the chosen plane, and measuring its length by calculating the distance between the defined starting and ending points. The flatfile was exported to Matlab (Natick) and circulation was calculated with respect to that plane as the line integral of the tangential component of velocity.

Quantification of ventricular function in PH patients was performed using commercially available software (Qmass® version 7.4) with manual contouring of the left ventricular (LV) and RV epicardial and endocardial borders in end-systole and end-diastole.

For the purpose of assessing intraobserver agreement and reproducibility of results, all 4D Flow CMR data were anonymized, randomized, and reanalyzed by the same reader, blinded to the result of the initial assessment, following a minimum 2-week interval after the first analysis.

Statistical analysis

All continuous data are expressed as mean ± standard error. Following tests of normality (Shapiro-Wilk and Lilliefors) that did not reject the null hypothesis, differences between PH patients and controls were assessed using two-sample unequal variance two-tailed Student's *t*-test. Correlation between continuous variables including RHC measures and circulation were evaluated using the Pearson product moment correlation. Data were analyzed in Matlab (Natick) and $p < 0.05$ was considered statistically significant.

RESULTS

One PH patient's RHC data could not be used as the examination was aborted for coughing and the data was of poor quality. Thus, the final study cohort was 16 patients (Table 1, demographics). The average mPAP for 16 PH patients was 32.7 ± 10.8 mmHg. Qualitatively, increased vortical blood flow was seen in patients with PH (Figure 1a, *see also online supplemental animation*), compared to the laminar blood flow in the healthy controls, (Figure 1b). This vortical blood flow was quantified with circulation (mm^2/s), which was greater in the MPA of patients with PH compared to controls across the cardiac cycle (average 1.21 ± 1.42 vs. 0.39 ± 0.70, respectively, Figure 2). Circulation integrated across the cardiac cycle was greater in PH patients than control subjects (979 ± 608 vs. 364 ± 262 mm^2/s^2, respectively, $p = 0.002$, Figure 3). Similar to previous two-dimensional studies,[17] the MPA diameter (MPAD) as measured with 2D MR was significantly correlated with mPAP ($R = 0.879$, $p < 0.01$); however, there was no significant correlation between MPAD and circulation ($R = 0.237$, $p = 0.377$), suggesting that vortical blood flow is not simply a manifestation of increased MPA size.

Circulation in patients with PH was correlated with RHC measures of disease severity (Table 2, $N = 16$): mPAP ($R = 0.564$, $p = 0.023$), peak systolic pressure ($R = 0.634$, $p = 0.008$), PVRI ($R = 0.518$, $p = 0.040$), and pulmonary pulse pressure ($R = 0.526$, $p = 0.036$). There was a negative correlation between increased circulation and pulmonary artery compliance as measured by the ratio between stroke volume and pulse pressure (SV/PP) during RHC, although this correlation did not reach significance ($R = -0.486$, $p = 0.056$). To test whether differences in circulation reflect differences in forward flow (i.e., circulation is a reflection of volume of flow, rather than a phenomenon created by increased afterload in PH), we evaluated the association of circulation with cardiac output obtained by RHC in PH patients. There was no correlation of circulation with cardiac output ($R = 0.07$, $p = 0.80$). Similarly, circulation was not correlated with functional parameters, including: RV ejection fraction (RVEF, $R = 0.22$, $p = 0.41$), RV stroke volume index ($R = 0.21$, $p = 0.44$), or RV end diastolic mass ($R = 0.20$, $p = 0.46$). Of note, in PH patients, there was no correlation between mPAP and RVEF ($R = -0.29$, $p = 0.26$). Similarly, circulation was not correlated with LV ejection fraction ($R = 0.41$, $p = 0.12$), LV stroke volume index ($R = 0.13$, $p = 0.64$), or LV end diastolic mass ($R = -0.34$, $p = 0.21$). A *t*-test comparison of circulation was conducted between PH patients and healthy controls, circulation was significantly higher ($p = 0.002$) in PH patients (1.13 ± 0.87) in comparison with healthy controls (0.43 ± 0.38).

Intraobserver reproducibility of circulation in PH patients and healthy controls was excellent with an intraclass correlation coefficient (ICC) of 0.802. A ROC curve analysis was conducted using data from 20

TABLE 1 Study population.

Characteristic	pH patients ($n = 16$)	Healthy controls ($n = 7$)
Sex (female/male)	11/2	1/6
Age (years)	63 ± 9	54 ± 15
Circulation (r)	1.21 ± 1.42	0.39 ± 0.70
Systolic blood pressure (mmHg)	124.8 ± 21.7	118 ± 7.6
Diastolic blood pressure (mmHg)	69.08 ± 7.8	76 ± 6.4
RHC parameters		
Right atrial pressure (mmHg)	7.44 ± 3.01	***
Pulmonary artery systolic pressure (mmHg)	53.7 ± 16.9	***
Pulmonary artery diastolic pressure (mmHg)	20.1 ± 6.3	***
Pulmonary capillary wedge pressure (mmHg)	9.4 ± 4.4	***
Mean pulmonary artery pressure (mmHg)	32 ± 11	***
Pulmonary vascular resistance index ($dyn \times s/cm^5 \times m^2$)	946 ± 619	***
Cardiac index ($L/min/m^2$)	2.36 ± 0.51	***
CMR parameters		
Main pulmonary artery diameter (mm)	34.1 ± 5.1	31 ± 4.1
RV end diastolic volume (mL)	154.0 ± 64.4	131.5 ± 51.5
RV end systolic volume (mL)	74.9 ± 40.9	70.9 ± 34.3
RV ejection fraction (%)	51.4 ± 11.4	57.8 ± 7.6
RV end diastolic mass (g)	25.4 ± 7.97	44 ± 8.4
LV ejection fraction (%)	61.9 ± 5.4	60.2 ± 6.3
LV end systolic volume (mL)	46.1 ± 12.7	58.3 ± 15.6
LV end diastolic volume (mL)	120.6 ± 26.6	109.3 ± 45.6
LV end diastolic mass (g)	81.7 ± 21.1	67 ± 18.3

Note: Values are given as mean ± SD.

Abbreviations: CMR, cardiac magnetic resonance; LV, left ventricle; RHC, right heart catheterization; RV, right ventricle.

***Right heart catheterization was not performed in healthy controls.

individuals, 10 of whom were classified as having PH and 10 as healthy controls. The analysis revealed a moderate diagnostic accuracy, with an area under the ROC curve (AUC) of 0.740. At a fixed sensitivity of 70%, the specificity was also 70%, indicating the ability of the test to correctly identify individuals with PH. The Youden index was 0.400, suggesting a potential optimal cutoff point for distinguishing between PH and healthy controls (Figure 4).

DISCUSSION

This pilot study describes a 4D flow CMR derived metric, circulation, which is a novel method for noninvasive direct quantification of pulmonary arterial vortical flow. We have shown that circulation (r) (1) quantifies the rotational blood flow pattern in patients with PH, (2) is well correlated with hemodynamic markers of PH severity, such as mPAP and peak systolic pressure, and (3) is a robust measure with high intraobserver reproducibility.

Multiple recent studies have investigated quantification of vortical flow in patients with PH using 4D flow MRI. Early investigations by Kamada et al. found that quantification of the backward flow component of the vortical flow in the main pulmonary artery yields significant results that correlate with PH severity. Authors observed significant decreases in the full width at half maximum and volume flow rate of the backward flow after balloon pulmonary angioplasty.[18] Subsequent authors used 4D flow MRI to identify these vortical flow patterns. There have been two main approaches to vortical quantification to date: vortex time duration and vortex volume. Krauter et al. introduced an automated method to

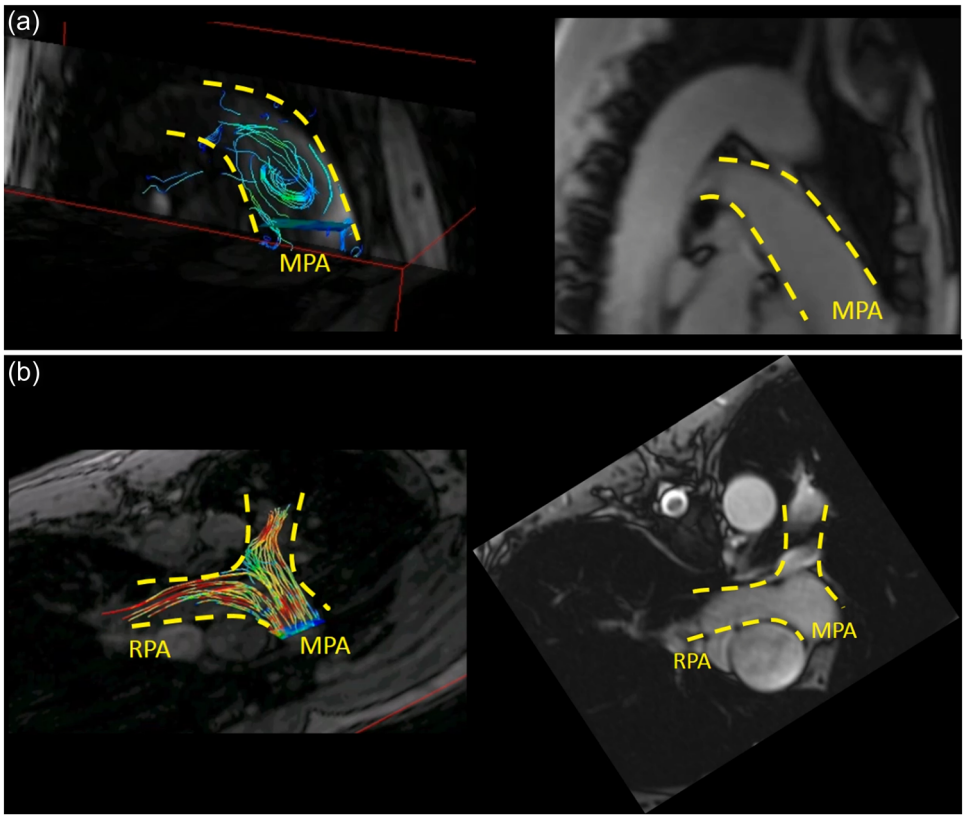

FIGURE 1 (a) Vortical blood flow in the main pulmonary artery of a patient with pulmonary hypertension (PH). 4D Flow cardiovascular magnetic resonance (CMR) streamlines demonstrate vortical blood flow in the main pulmonary artery (MPA) of a patient with PH. (b) Laminar blood flow in the main pulmonary artery of a healthy control. 4D Flow CMR streamlines demonstrate laminar blood flow in the MPA of a healthy control (See also online supplemental animation).

track and detect vortices from 4D flow MRI data and used vortex duration (t_{vortex}) to estimate mPAP. They showed strong correlation between t_{vortex} values and visual analysis as well as capability of t_{vortex} values to accurately estimate mPAP.[19] T_{vortex} as an objective 4D flow CMR parameter for quantification of vortical flow has been also used in a couple of other recent studies.[20,21] These studies found that T_{vortex} could noninvasively quantify and predict mPAP changes in patients with PH. One potential shortcoming of vortex duration measurements is dependence on 4D MR temporal resolution, which may vary from scan to scan. Analysis of vortex size at peak systole using the Lambda2 ($\lambda 2$) method is another approach for quantification of vortical flow.[22] Hong et al. used this method of vortex quantification and observed that mean vortex volume was increased in all selected regions in main pulmonary artery and its branches but maximum vortex volume was only increased in the main pulmonary artery.[23] It is unknown, however, whether vortical volume at peak systole can be used as a surrogate of changes that are known to occur throughout the entire cardiac cycle and further investigations are needed.

We believe that circulation has advantages that may make it preferable to measurements of vortex volume or duration in regard to quantification of PH. Circulation is a macro measurement that captures vortical flow within a volume, while vorticity is a point in space measurement.[24] Since we intended to assess the overall flow of blood in the pulmonary arteries and resultant pressure, we chose the composite metric, circulation, as it captures information that is more complete. Our data show that the vortical blood flow can be quantified using circulation throughout the entire cardiac cycle and that circulation is highest during late systole, just after the period of maximal forward blood flow. Previous 2D MR phase contrast studies have shown similar late systolic retrograde flow along the posterior MPA,[25] which is likely a 2D representation of the same process.

It is not known what causes vortical blood flow in patients with PH and whether vortical flow precedes or follows enlargement of the MPA. It is likely a cascade process akin to aneurysm formation whereby altered hemodynamics generate physical forces that compromise the integrity of the vascular wall leading to dilatation, increasingly disordered hemodynamics and reduced wall shear stress, and an enlarging MPA.[26–29] Authors have suspected that vortical blood flow in the MPA arises from

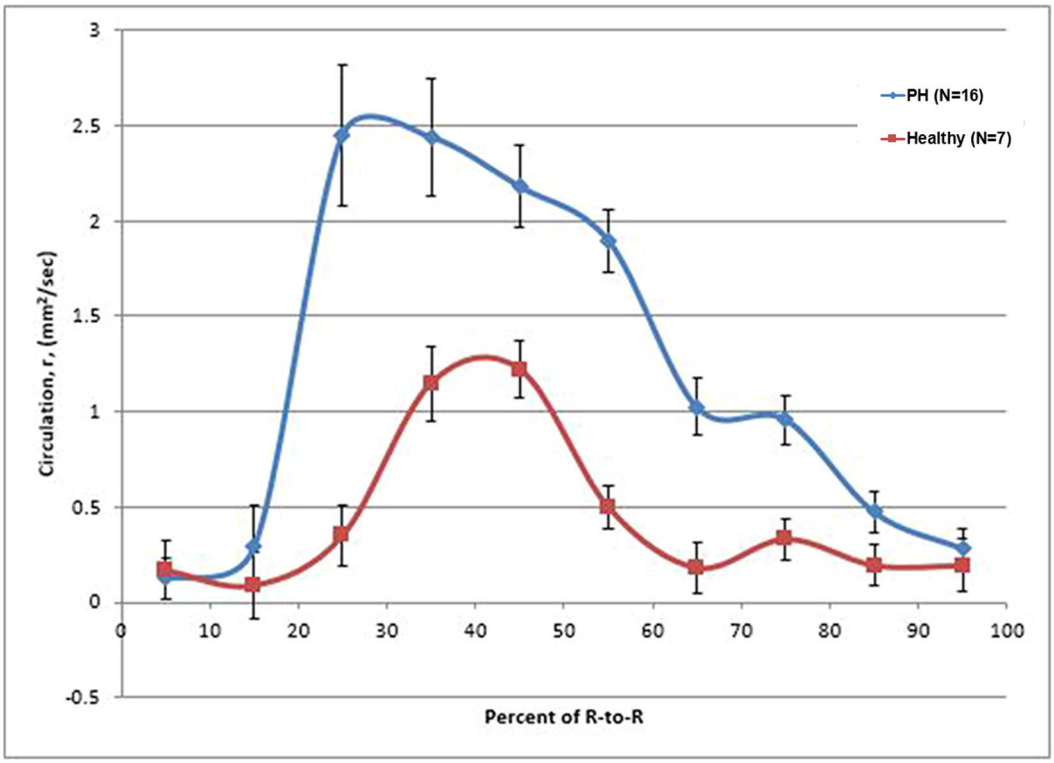

FIGURE 2 Circulation in the main pulmonary artery is increased in patients with pulmonary hypertension (PH) compared to healthy controls across the cardiac cycle. Mean circulation in the main pulmonary artery (MPA) in patients with PH ($N = 16$) and healthy controls (HC, $N = 7$) as a percent of R–R interval. Error bars are standard errors.

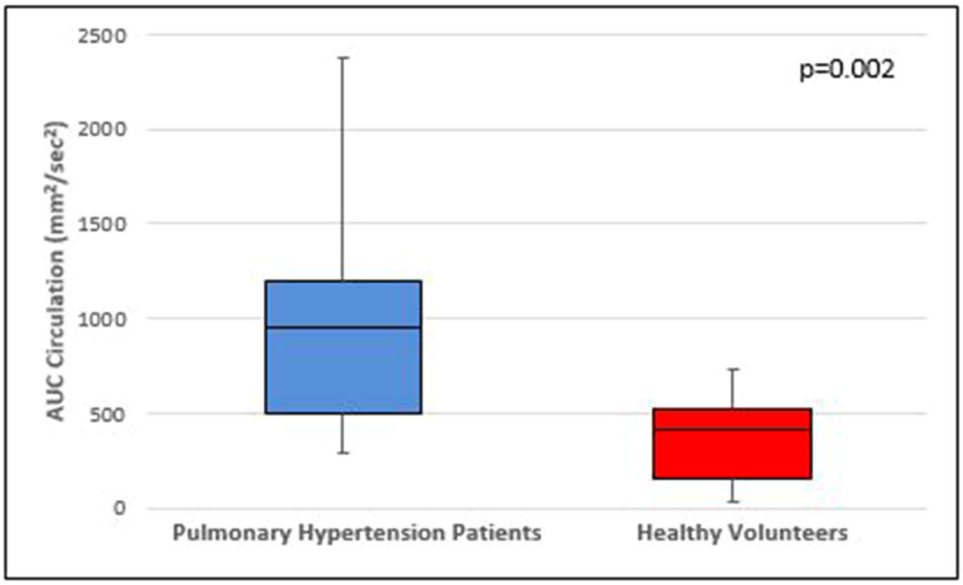

FIGURE 3 Increased circulation in the main pulmonary artery distinguishes patients with pulmonary hypertension from healthy controls. Circulation integrated across the cardiac cycle in patients with PH (mean 978.9 mm^2/s^2) and HC (mean 363.6 mm^2/s^2), $p = 0.002$. Box plot with first quartile, median, and third quartile with the ends of the whiskers represents the maximum and minimum of all of the data.

TABLE 2 Circulation integrated across the cardiac cycle correlates with invasive RHC measures ($N = 16$), but does not correlate with CMR measures of function.

	R	*p*-Value
RHC parameter		
Mean pulmonary artery pressure (mPAP) (mmHg)	0.564	**0.023**
Peak systolic pressure (mmHg)	0.634	**0.008**
Pulmonary vascular resistance index (PVRI), dyn × s/cm^5 × m^2	0.518	**0.040**
Pulmonary pulse pressure (mmHg)	0.526	**0.036**
Pulmonary compliance (SV/PP, mL/mmHg)	−0.485	0.056
Cardiac output (L/min)	0.069	0.800
CMR parameter		
Right ventricular ejection fraction (RVEF, %)	0.222	0.407
RV stroke volume index (mL/m^2/beat)	0.207	0.442
RV end diastolic mass (g)	0.199	0.460
Left ventricular ejection fraction (LVEF, %)	0.410	0.115
LV stroke volume index (mL/m^2/beat)	0.129	0.635
LV end diastolic mass (g)	−0.335	0.205

Note: Pearson correlation with *p*-values < 0.05 considered statistically significant. Bold values are statistically significant $p < 0.05$.

Abbreviations: CMR, cardiac magnetic resonance; LV, left ventricle; RHC, right heart catheterization; RV, right ventricle.

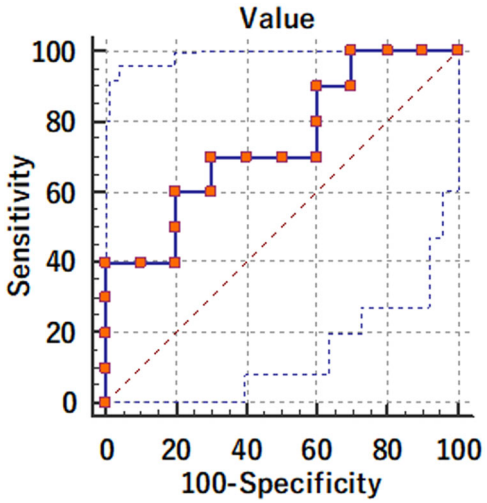

FIGURE 4 Receiver operating characteristic (ROC) curve depicting the diagnostic accuracy of the circulation (r) for discriminating between pulmonary hypertension (PH) and healthy controls. The plot illustrates the trade-off between sensitivity and specificity, with a cut-off value of >0.40.

increased afterload caused by elevated pulmonary vascular resistance and decreased compliance of the pulmonary vasculature. Perhaps the vortex allows for preservation of the kinetic energy of blood in the setting of reduced vascular wall compliance.[15] Although we found no correlation between circulation (r) with cardiac output or RV function on CMR, recent studies has shown that proximal PA remodeling is worse in intermediate-risk than in low-risk PAH patients.[30–32] Since, we showed that circulation (r) is related to the PA diameter and mean PA pressure, we believe this metric can be employed for risk stratification in PAH patients.

Our study is limited by a small sample size of Group 1 established PH patients who were under treatment prior and during the study. Future evaluations will focus on increasing the spectrum of disease severity and evaluating different PH subtypes. In addition, pre- and posttreatment imaging would help determine whether 4D flow CMR can be used for noninvasive assessment of treatment effect. The latest definition of PH as of 2019 is mPAP greater than 20 mmHg.[2] However, we had to use the definition at the time (mPAP greater than 25 mmHg) when this study was performed. The narrow range of PH severity in our patients may explain why a correlation between circulation and RVEF was not seen; our pilot cohort did not include patients who had severely decompensated PH who couldn't tolerate supine position for the amount of time needed for the CMR imaging. Another potential limitation of our study is sex differences between our PH patients and healthy controls, with the majority of PH patients being female and the majority of control subjects being male. Previous studies showed vortical blood flow in the MPA in both male and female PH patients and laminar flow in healthy controls of both sexes[15,16]; therefore, we do not expect the sex of the participants to significantly impact the results However, considering the sample sizes of patients ($N = 16$) and healthy controls ($N = 7$), there was a limited opportunity to perform a matched comparison for factors such as age, sex, ethnicity, and other confounders. It is crucial to acknowledge that this study serves as a pilot investigation, with its primary purpose being to establish the foundation for future research in this field, including inter and intra-reader reproducibility of these metrics based on the encouraging results of the current study. While interobserver data was not collected, mPAP and circulation measurements were calculated by separate individuals. Moreover the reader measuring velocity on 4D flow CMR was blind to the mPAP values at the time of assessment and our data is largely consistent with prior reports.

The time to acquire and analyze 4D Flow CMR data sets is limiting; however, optimization of scanning parameters continues to reduce scanning acquisition times. In recent studies whole-heart 4D Flow CMR was acquired

with preserved quality without respiratory gating, reducing scanning time by 70% and facilitating clinical use.[33] Semiautomated postprocessing of 4D Flow CMR data exists and one of these shared tools was used for this project[13,14]; however, the development of more automated methods for flow visualization and quantification would make 4D Flow CMR more relevant in the clinical setting.

CONCLUSIONS

The 4D flow CMR derived metric, Circulation (Γ), allows quantification of pulmonary arterial vortical flow in the main pulmonary artery of patients with PH, distinguishes them from healthy controls, and shows high correlation with invasive markers of PH severity. Circulation (Γ) represents a promising, nonionizing, noninvasive metric for diagnosing and following patients with or suspected of having PH.

AUTHOR CONTRIBUTIONS

Ali Borhani: Writing—original draft preparation; reviewing and editing. **Kristin K. Porter**: Conceptualization; methodology; data curation; writing; original draft preparation. **Muhammad Umair**: Visualization; investigation; reviewing and editing. **Linda C. Chu**: Supervision. **Stephen C. Mathai**: Software; validation. **Todd M. Kolb**: Software; validation. **Rachel L. Damico**: Reviewing and editing. **Paul M. Hassoun**: Supervision; reviewing and editing. **Ihab R. Kamel**: Reviewing and editing. **Stefan L. Zimmerman**: Supervision; conceptualization; methodology; reviewing and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This Health Insurance Portability and Accountability Act (HIPAA) approved study was conducted at Johns Hopkins University School of Medicine. The Johns Hopkins University Institutional Review Board approved this study, and written informed consent was obtained for all patients. This material is the authors' original work, which has not been published elsewhere or is currently being considered for publication elsewhere. The article reflects the authors' own research and analysis in a truthful and complete manner. The authors give consent for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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