

# Measuring Flow Hemodynamic Indices and Oxygen Consumption in Children with Pulmonary Hypertension: A Comparison of Catheterization and Phase-Contrast MRI

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**Abstract** We sought to compare pulmonary flow hemodynamic indices obtained by Fick and thermodilution catheterization techniques with phase-contrast MRI (PC-MRI) in children with diverse etiologies of pulmonary arterial hypertension (PAH). Calculation of pulmonary flow ( $\dot{Q}_p$ ) using the Fick principle in most catheter laboratories relies on an estimate of oxygen consumption which may limit its reliability. Flow hemodynamic indices acquired from thirty patients with PAH who underwent successful same-day PC-MRI and catheterization were evaluated for absolute and percent bias. Comparison of  $\dot{Q}_p$  between PC-MRI and Fick revealed poor agreement with an absolute bias of  $0.96 \pm 0.53$  L/min/m<sup>2</sup> and percent bias of  $27.7 \pm 19.6\%$ . Same analysis between PC-MRI and thermodilution revealed better agreement as demonstrated by absolute bias  $0.64 \pm 0.47$  L/min/m<sup>2</sup> and percent bias  $16.8 \pm 12.3\%$ . Retrospectively calculated  $\dot{V}_{O_2}$  from PC-MRI and LaFarge equations revealed poor agreement, with an absolute bias of  $33.4 \pm 21.6$  mL/min/m<sup>2</sup> and percent bias of  $25.8 \pm 12.6\%$ . We found that Fick-derived flow

hemodynamics dramatically differs from PC-MRI computed metrics in children with PAH. The non-invasive nature of PC-MRI and short acquisition time is ideal for pediatric flow evaluation and may offer a novel route of absolute flow and resistance assessment when combined with cardiac catheterization.

**Keywords** Phase-contrast MRI · Pulmonary hypertension · Pulmonary flow · Catheterization

## Introduction

Measurement of right ventricular cardiac index (CI) is required for the calculation of pulmonary vascular resistance (PVR), which is a principal diagnostic and quantitative variable in pediatric pulmonary arterial hypertension (PAH) [1, 2]. Flow hemodynamics are essential for categorical evaluation of PAH subtype, determination of disease severity, acute vasoreactivity testing, and assessment of therapeutic efficacy [3, 4]. Precise assessment of pulmonary and systemic flow ratio ( $\dot{Q}_p:\dot{Q}_s$ ) is especially critical for the calculation of the respective resistance ratios in congenital heart disease (CHD) or in persistent PAH of newborns with extra-pulmonary shunts [5, 6]. Additionally, CI has a strong predictive value in both adult and pediatric PAH populations [7]. Accurate measurement of flow hemodynamics is clearly very important for diagnostic evaluation and appropriate management of patients with PPH but there is clear evidence that there are discrepancies between directly measured oxygen consumption values and those estimated by predictive equations [8].

Conventionally, flow hemodynamic indices are directly derived from the use of the institutional catheterization

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protocol, either by thermodilution or by the Fick principle [9]. Unfortunately, the thermodilution (TD) technique in the pediatric PAH population is complicated by lesions associated with CHD, right-heart valve regurgitation, the presence of aortopulmonary collateral vessels, low cardiac output, and developmental comorbidities particularly of the respiratory system [10]. For these reasons the Fick principle is the most widely used method for CI calculation. There is increasing evidence indicating that current assumptions associated with the estimation of oxygen consumption ( $\dot{V}_{O_2}$ ) necessary for CI calculation using the Fick principle may not be suitable for the pediatric population [10–13]. To estimate  $\dot{V}_{O_2}$  consumption, catheterization laboratories frequently apply the LaFarge tables which were derived for children older than 3 years of age and do not account for the acute effects of anesthesia and ventilation on respiratory and metabolic status. Significant errors in CI computation have been previously described in single-ventricle patients and in a heterogeneous group of CHD patients [11, 14]. The reliability of catheterization-derived CI in pediatric PAH population is uncertain. Methods to directly quantify oxygen consumption are in use in some catheterization laboratories, but are not yet in routine use. Improved published  $\dot{V}_{O_2}$  estimation algorithms exist for children less than 3 years of age, but they also have yet to be widely accepted [10, 11].

Phase-contrast MRI (PC-MRI) is considered the gold-standard method for the evaluation of flow waveforms and has been suggested for hemodynamic assessment of the pulmonary circulation, especially in combination with catheterization [14–17]. Velocity data generated from PC-MRI further enables the evaluation of such key factors as negative regurgitant flow, assessment of regional vascular stiffness by means of compliance and pulse wave velocity, quantification of intra- and extracardiac shunts, and computation of hemodynamic shear stress [17–19]. The appeal of PC-MRI for measuring flow through proximal pulmonary conduit vessels in children lies in the ability of internal validation of flow calculation through the main pulmonary artery and its primary branches with good reproducibility [18, 20].

In this study we sought to compare pulmonary flow hemodynamic indices obtained by standard catheterization techniques with PC-MRI in children with diverse etiologies of PAH. Additionally, we retrospectively calculated  $\dot{V}_{O_2}$  and pulmonary vascular resistance index (PVRi) using CI derived from PC-MRI and compared these results with respective LaFarge and thermodilution techniques. We hypothesized that results of flow calculations would vary markedly between PC-MRI and catheterization-derived methods.

## Methods

With the approval of the Institutional Review Board at the Children's Hospital Colorado, all patients with previously diagnosed PAH, including PAH associated with congenital heart disease, who underwent an initial PC-MRI with same-day hemodynamic evaluation in the cardiac catheterization laboratory between December 2010 and August 2016 were identified. The initial diagnosis of PAH was established after evaluation by our Pulmonary Hypertension Program, which included echocardiography and a previous diagnostic cardiac catheterization (not used for comparative evaluation), according to accepted guidelines [1]. Anesthesia was required in patients younger  $\leq 7$  years of age during MRI acquisition and occasionally used in older patients based on anticipated cooperation in the MRI room.

### PC-MRI

The PC-MRI acquisition protocol was performed as previously described [21, 22]. A gradient echo ECG gated sequence was applied to obtain tissue intensity and phase velocity maps using a 1.5 or 3.0 Tesla magnet (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany; Ingenia, Philips Medical Systems, Best, The Netherlands). Through-plane flow evaluation in the main artery pulmonary plane was chosen to be 1 cm above the pulmonary valve. The ascending aortic plane for systemic flow computation was chosen to be 1 cm above the sinotubular junction. For purposes of internal validity, flow evaluation was also performed in the left and right pulmonary arteries. Acquisition planes for both branches were taken 2 cm from the bifurcation. A typical sequence for free breathing PC-MRI with Cartesian encoding and retrospective sorting had a temporal resolution of 14–28 ms with 30–40 phases, echo times of 2.2–3.5 ms, matrix:  $160 \times 256$ , flip angle of  $25^\circ$  with 100% of the k-space sampled. Depending on patient size and field of view ( $128\text{--}225 \times 210\text{--}360$  mm), the cross-sectional pixel resolution was  $0.82 \times 0.82\text{--}1.56 \times 1.56$  mm<sup>2</sup> with a slice thickness of 5 mm. Resulting acquisition time varied upon heart rate between 1 min 45 s to 3 min. Velocity encoding values were adjusted according to the maximum velocities encountered during scout sequences to avoid aliasing artifact (typical values ranged from 100 to 150 cm/s).

Pulmonary and systemic flows were analyzed from time frame-segmented respective magnitude and phase-contrast images as previously described (Matlab Program; Mathworks, Inc., Natick, MA, USA) [21, 22]. Specifically, each temporal phase was segmented using a semi-automatic level-set method (Segment, Medviso), where a constructed

algorithm applies an active contour model which tracks the edges of the vessel wall initialized by a manual delineation in one time frame [21].

### Catheterization

The cardiac catheterization protocol was performed as recommended by pediatric PAH consensus guidelines [1, 9]. Hemodynamic and saturation data were collected in all cases under room air conditions. All patients underwent flow evaluation using the Fick principle and patients without evidence of intracardiac shunting also underwent thermodilution measurement of cardiac output. Estimated  $\dot{V}_{O_2}$  was calculated from LaFarge equations as shown previously [10, 13]. The oxygen saturations and corresponding oxygen content values were obtained from blood samples collected in the superior vena cava, pulmonary artery, aorta, and pulmonary vein as anatomy allowed. Oxygen content was calculated using the standard formula:

$$C_{O_2} = 13.6 \cdot \text{Hb} \cdot S_{O_2} + 0.003 \cdot p_{O_2},$$

where Hb is hemoglobin concentration (gm/dL),  $S_{O_2}$  is oxygen saturation, and  $p_{O_2}$  is partial oxygen pressure obtained from collected blood samples. The final CI was derived from the conventional Fick method as the ratio of  $\dot{V}_{O_2}$  to the difference in oxygen contents for the pulmonary and systemic circulations. Additional hemodynamics recorded included mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), and computed PVRi. Retrospectively calculated oxygen consumption using the  $\dot{Q}_p^{\text{MRI}}$  was then computed using the following formula:

$$\dot{V}_{O_2}^{\text{MRI}} = \dot{Q}_p^{\text{MRI}} \cdot (C_{PV_{O_2}} - C_{PA_{O_2}}) \cdot 10,$$

where  $C_{PV_{O_2}}$  and  $C_{PA_{O_2}}$  are pulmonary venous and arterial oxygen contents. PVRi was calculated from PC-MRI as determined from the result of  $(\text{mPAP} - \text{PAWP}) / \dot{Q}_p^{\text{MRI}}$ .

### Statistical Analysis

Statistical analyses were performed in Statistical Analytical Solutions (SAS) (version 9.4 SAS Institute, Cary, NC). Variables were checked for the distributional assumption of normality using histogram plots and Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed variables were reported as mean  $\pm$  SD, and skewed variables as medians with inter-quantile ranges. Flow hemodynamic characteristics collected from different modalities were compared using student *t* test for normally distributed continuous variables. Bland–Altman analysis and

correlation coefficients were applied to assess the variability between two methods estimating the same quantity [23]. Correlation coefficients were obtained from generalized linear regression models and were reported as beta  $\pm$  standard error. Variation between two different methods was computed as the mean of differences reported as mean  $\pm$  2SD. Significance was based on an  $\alpha$ -level of 0.05.

### Results

Demographics of the study population are summarized in Table 1. Thirty patients with PAH (age:  $13.0 \pm 5.1$  years (mean  $\pm$  SD; range: [0.75, 20]); 2 children were  $< 3$  - years; 17 subjects were female) who underwent same-day PC-MRI and catheterization were identified. Fourteen patients had idiopathic PAH, 12 children had PAH associated with CHD, two patients had PAH associated with restrictive lung disease, one patient had PAH due to schistosomiasis, and one patient had hereditary PAH. CHD included atrial septal defect (8 patients; 3 were studied post repair), ventricular septal defect (3 patients; 1 post repair), and patent ductus arteriosus post repair (1 patient).

Catheterization hemodynamic values are summarized in Table 2. All patients received flow evaluation using the Fick method and 16 patients were additionally studied by thermodilution (TD). As reported above 7 PAH patients had an intracardiac shunt present at the time of evaluation. Table 3 compares flow hemodynamics between PC-MRI and catheterization techniques. Comparison of  $\dot{Q}_p$  between PC-MRI and Fick revealed poor agreement with an absolute bias of  $0.98 \pm 0.70$  L/min/m<sup>2</sup> and percent bias of  $23.0 \pm 15.6\%$ . The graphical representation of agreement analysis is portrayed in Fig. 1. Measurements between PC-

**Table 1** Patient characteristics

Age (years)	13.0 $\pm$ 5.1
Female	17 (57%)
BSA (m <sup>2</sup> )	1.37 $\pm$ 0.38
IPAH	14 (47%)
CHD-PAH	12 (40%)
ASD	8 (27%)
VSD	3 (10%)
PDA	1 (3%)
Others	4 (13%)

Data reported as mean  $\pm$  SD

IPAH idiopathic pulmonary arterial hypertension, CHD congenital heart disease, ASD atrial septal defect, VSD ventricular septal defect, PDA patent ductus arteriosus

**Table 2** Hemodynamics

mPAP (mmHg)	40 ± 17
PAWP (mmHg)	8 ± 3
PVRi (WU/m <sup>2</sup> )	9.4 ± 8.1
Hemoglobin (gm/dL)	12.9 ± 1.8
VO <sub>2</sub> (L/min/m <sup>2</sup> )	131 ± 13
Heart rate (bpm)	79 ± 17

Data reported as mean ± SD

mPAP mean pulmonary arterial pressure, PAWP pulmonary arterial wedge pressure, PVRi pulmonary vascular resistance index, VO<sub>2</sub> oxygen consumption

MRI and Fick techniques correlated significantly ( $0.46 \pm 0.14$ ,  $p = 0.0038$  and  $r = 0.512$ ). Analysis of PC-MRI and TD revealed better agreement as demonstrated by absolute bias  $0.61 \pm 0.82$  L/min/m<sup>2</sup> and percent bias  $13.8 \pm 15.3\%$ . Stronger correlation existed between both modalities ( $0.86 \pm 0.19$ ,  $p = 0.0006$  and  $r = 0.760$ ). Bland–Altman analysis revealed limits of agreement  $- 1.85$  to  $+ 2.66$  L/min/m<sup>2</sup> between PC-MRI and Fick and  $- 1.81$  to  $+ 2.18$  L/min/m<sup>2</sup> between PC-MRI and TD. Evaluation of  $\dot{Q}_p:\dot{Q}_s$  using PC-MRI and Fick indicated absolute bias  $0.26 \pm 0.36$  and percent bias  $11.3 \pm 9.5\%$ , and between PC-MRI and TD absolute bias  $0.17 \pm 0.25$  and percent bias  $10.7 \pm 10.1\%$ .

Additional analysis compared retrospectively calculated  $\dot{V}_{O_2}$  and PVRi values with standard methods. Comparison of retrospectively calculated  $\dot{V}_{O_2}$  from PC-MRI and LaFarge revealed poor agreement, with an absolute bias of  $33.4 \pm 21.6$  mL/min/m<sup>2</sup> and percent bias of  $25.8 \pm 12.6\%$ . There was no correlation between these two methods. Wide range between limits of agreement was  $- 72$  to  $+ 84$  mL/min/m<sup>2</sup> (Fig. 2a). PVRi as calculated by PC-MRI revealed poor agreement with conventional Fick-based flow measurements, with an absolute bias of  $2.5 \pm 3.4$  WU m<sup>2</sup> and percent bias of  $28.1 \pm 21.9\%$ . Corresponding Bland–Altman revealed limits of agreement between  $- 9.8$  and  $8.3$  WU m<sup>2</sup> (Fig. 2b). Smaller yet still

considerable bias existed between PC-MRI and TD-derived PVRi with absolute bias  $2.5 \pm 3.4$  and percent bias  $24.1 \pm 18.2\%$ .

To investigate the potential association between the measured differences and basic demographic parameters, we correlated absolute and percent bias from each comparison with age, BSA, and heart rate. We did not find any correlation between these parameters and bias observed between the catheter and MRI methods. Lastly, 10 patients had flow evaluation of PC-MRI in the main, right, and left pulmonary arteries. Internal validity of PC-MRI was performed by comparing  $\dot{Q}_p$  measured in the main pulmonary artery and combined  $\dot{Q}_p$  from right and left pulmonary arteries. We found excellent agreement with absolute bias of  $0.20 \pm 0.12$  L/min/m<sup>2</sup> and percent bias  $4.9 \pm 3.0\%$ . Both methods showed almost identical agreement with strong correlation ( $0.980 \pm 0.105$ ,  $p < 0.0001$ ,  $r = 0.957$ ) and limits of agreement  $- 0.52$  to  $+ 0.52$  L/min/m<sup>2</sup>.

### Discussion

This study demonstrates that significant variation exists between flow hemodynamic metrics using conventional catheterization methods and PC-MRI derivations in children with PAH. Consequently, retrospectively calculated  $\dot{V}_{O_2}$  and PVRi failed to present agreement with values estimated from LaFarge equations and Fick  $\dot{Q}_p$ , respectively. We found that a 23.0% bias exists between PC-MRI, flow evaluation method, and the conventionally applied Fick method, while a smaller bias of 13.8% was identified when compared with TD. Interestingly, the bias between PC-MRI and Fick-based hemodynamic values was not associated with the determinants of LaFarge table: age, BSA, and heart rate.

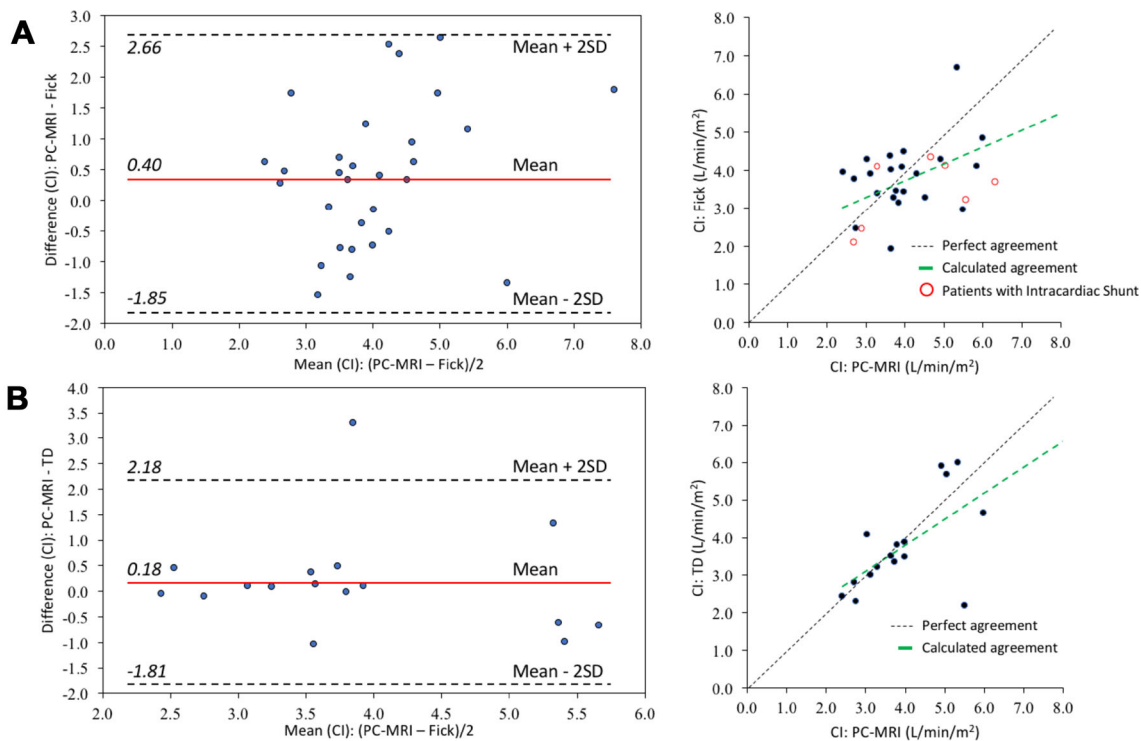
Our results are consistent with the conclusions from previously reported pediatric studies of the error associated with the Fick method, which supported a combination of MRI flow and catheterization pressure hemodynamic assessments [14, 15, 24, 25]. The PVRi value is critical in

**Table 3** Comparison of flow hemodynamic indices

	PC-MRI	Fick	Bias ± SD	% Bias ± SD	TD	Bias ± SD	% Bias ± SD
$\dot{Q}_p$ (L/min/m <sup>2</sup> )	3.8 ± 1.0	3.8 ± 1.2	0.96 ± 0.53	27.7 ± 19.6	3.7 ± 1.2	0.64 ± 0.47	16.8 ± 12.3
$\dot{Q}_p:\dot{Q}_s$	1.09 ± 0.42	1.02 ± 0.25	0.26 ± 0.36	11.3 ± 9.5	0.99 ± 0.10	0.17 ± 0.25	10.7 ± 10.1
$\dot{V}_{O_2}$ (mL/min/m <sup>2</sup> )	137 ± 37	131 ± 13	33.4 ± 21.6	25.8 ± 18.6	–	–	–
PVRi (WU m <sup>2</sup> )	8.7 ± 5.1	9.4 ± 8.1	2.9 ± 3.6	28.1 ± 21.9	9.6 ± 7.7	2.5 ± 3.4	24.1 ± 18.2

Data are reported as mean ± SD

$\dot{Q}_p$  pulmonary flow (RV CI),  $\dot{V}_{O_2}$  oxygen consumption, PVRi pulmonary vascular resistance index, TD thermodilution



**Fig. 1** Bland–Altman and scatter plots indicating the relationship between catheterization-derived flow methods and PC-MRI. **a** Relationship between Fick and PC-MRI measurement indicating poor agreement with equal distribution of overestimated and underestimated Fick  $\dot{Q}_p$  measurements. **b** Better agreement existed between

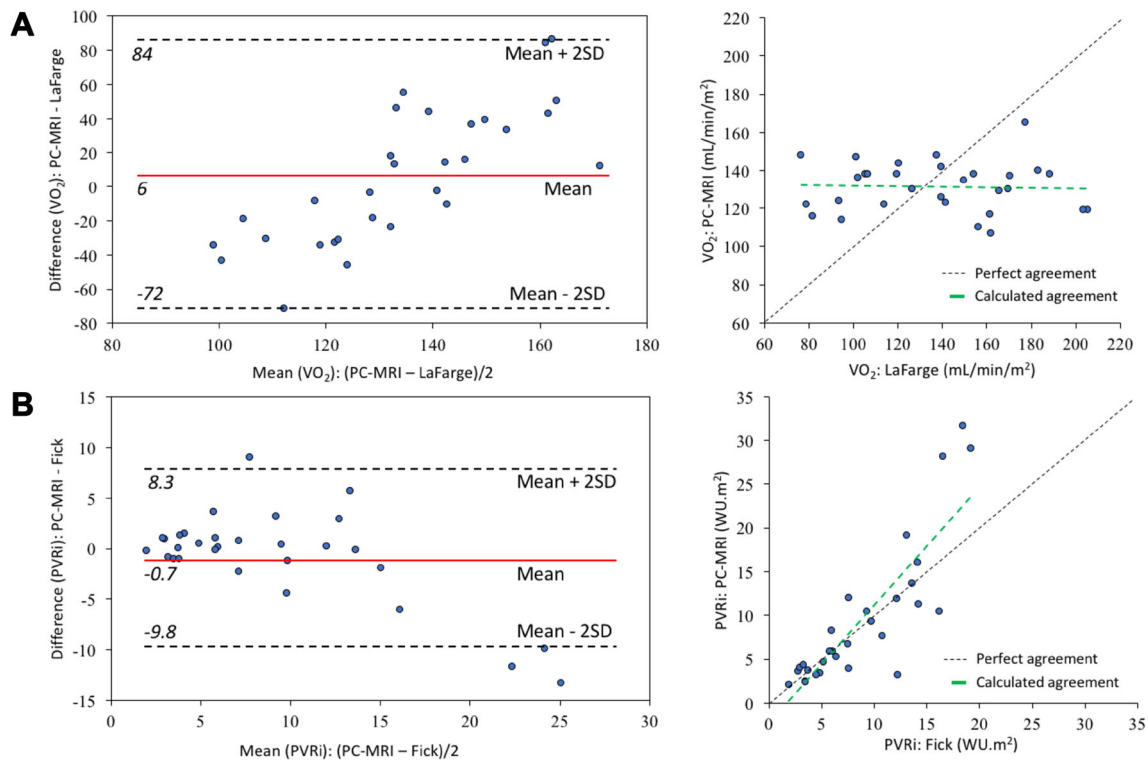
thermodilution and PC-MRI flow datasets with tendency for thermodilution method to underestimate  $\dot{Q}_p$ . In Bland–Altman plot, the red lines represent mean values and black-dashed lines represent  $\pm 2.0$  SD indicating limits of agreement

the evaluation of pediatric PAH and is mainly subjected to error from  $\dot{Q}_p$  calculation. Furthermore, PVRi and CI are important outcome predictors supported by a high level of evidence quoted in pediatric PAH outcome studies [7]. Accurate assessment of  $\dot{Q}_p$  can be confounded by the presence of persistent shunts in subjects with PAH and CHD [6]. PC-MRI is arguably considered to be the state-of-the-art method for flow evaluation with the capability of accurate quantification of shunt severity in single-ventricle patients. Most importantly internal validation is possible [14, 17, 25, 26]. In addition to comprehensive understanding of flow conditions, PC-MRI enables global and regional investigation of vascular stiffness along with computation of shear stress metrics, yet the acquisition requires more specific sequences and post-processing [22, 27]. Additionally, evaluation of flow prior to catheterization or in combination using hybrid MRI catheterization procedures may reduce radiation dose during catheterization and time of anesthesia/sedation. Lastly, the MRI-based vasoreactivity testing may offer novel set of parameters in addition to standard catheterization and provide more robust volumetric information crucial for the determination of ventricular–vascular coupling.

Rutledge et al. previously found significant disagreement between  $\dot{V}_{O_2}$  estimated by the LaFarge tables and respiratory mass spectroscopy indicating a 53% error in children less than 3 years of age and 11% in children older than 3 years [11]. In our study which included pediatric PAH patients with diverse etiology and a wider range of ages, we found an error of 25.8% between LaFarge and PC-MRI methods. Additionally, Seckeler et al. modified the LaFarge equation and defined an accuracy limit of 20% difference between these 2 methods in 42% of children < 3 years and 13% of children  $\geq 3$  years [10]. Age, anemia, and critical illness were found to be predictors of  $\dot{V}_{O_2}$  inaccuracy. In our study, the variability between LaFarge-based Fick measures and PC-MRI-derived  $\dot{Q}_p$  failed to reveal any correlation between standard demographic metrics and heart rate. However, the strict nature of our study design limited us to a smaller number of patients, and therefore, the exact relationship between these variables could not be more thoroughly investigated. Lastly, the type of sedation or anesthesia has significant effects on measured  $\dot{V}_{O_2}$ , and is not factored into the LaFarge equations [12].

There are several limitations to this study. Our patient cohort included few children < 3 years of age that would





**Fig. 2** Comparison of retrospectively derived  $\dot{V}O_2$  from PC-MRI and LaFarge-estimated values. Poor agreement exists between the 2 methods, as indicated by scatter plot (a) showing relatively equal distribution of overestimated and underestimated LaFarge values and corresponding Bland–Altman plot showing agreement between 2

methods. **b** Retrospectively calculated PVRi vs. Fick-based flow measures with Corresponding Bland–Altman plot of the difference in PVRi between 2 methods. In Bland–Altman plot, the red lines represent mean values and black-dashed lines represent  $\pm 2.0$  SD indicating limits of agreement

have allowed for more discrete evaluation of bias in both  $\dot{Q}_p$  and  $\dot{V}O_2$ . The error in LaFarge-estimated  $\dot{V}O_2$  and consequently Fick  $\dot{Q}_p$  has been shown to be much higher in younger children. Unfortunately, the same-day catheterization and PC-MRI acquisition is challenging in younger children due to prolonged anesthesia time. We did not correct for differences in heart rate between the 2 evaluations and this may have introduced an additional degree of error between the 2 measurements. As is standard at our institution, older children were under general anesthesia during the catheterization but were awake during the MRI acquisition. Lastly, our study included subjects who underwent PC-MRI acquisition with two different scanning systems. However, variable field strength has been shown previously not to alter flow hemodynamic measurements.

In conclusion, we found that Fick-derived  $\dot{Q}_p$  and PVRi significantly differs from PC-MRI-computed metrics in children with PAH. The non-invasive nature of PC-MRI and short acquisition time required for velocity encoding imaging is ideal for pediatric flow evaluation and may offer a novel route of comprehensive accurate hemodynamic assessment when combined with catheterization. Overall, our results support the ongoing advocacy for hybrid cardiac

MRI-guided catheterizations which would provide more accurate flow hemodynamic information along with precise anatomical mapping ability. Future investigation will focus on comparison of prognostic potential of same flow-based variables using two different methods.

**Compliance with Ethical Standards**

**Conflicts of interest** All authors report to have no conflict of interest.

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