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Non-invasive estimation of pulmonary hemodynamics from 2D-PC MRI with an arterial mechanics method

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A B S T R A C T

Pulmonary Hypertension (PH) is a challenging cardiopulmonary disease diagnosed when the mean pulmonary artery pressure (mPAP) is greater than 20 mmHg. Unfortunately, mPAP can only be measured through invasive right heart catheterization (RHC) motivating the development of novel non-invasive estimates. Pulmonary hypertension patients (n = 7) and control subjects (n = 8) had 2D phase contrast (PC) MRI of the main pulmonary artery during rest and moderate exercise. A novel method utilizing arterial mechanics was used to estimate mPAP and other pulmonary hemodynamics measures from the 2D PC images. mPAP estimated from MRI was greater in the PH group than the control group at both rest (24 ± 10 vs 12 ± 5 mmHg) and exercise (40 ± 8 vs 17 ± 9 mmHg). Area under the curve (AUC) calculated from receiver operator curve (ROC) analysis showed MRI estimated mPAP had excellent diagnostic ability to diagnose PH patients vs control subjects at rest and exercise (rest AUC = 0.91 [0.76 – 1.0], exercise AUC = 0.96 [0.88 – 1.0]). These are promising proof-of-concept results that pulmonary hemodynamics could be non-invasively estimated from an MRI and arterial mechanics approach. Future studies to determine the clinical utility of this method are needed.

1. Introduction

Pulmonary Hypertension (PH) is a common diagnostic challenge defined by a mean pulmonary artery pressure (mPAP) greater than 20 mmHg. Currently the gold-standard for mPAP measurements requires invasive right heart catheterization (RHC) which is a burden on individual patients and the healthcare system. Tricuspid regurgitation velocity (TRV) measured with transthoracic echocardiography can be used to non-invasively estimate peak PA pressure but nearly 50% of patients with PH do not have a measurable TR signal by echo (O'Leary et al., 2018). Moreover, PA pressure changes with physiological stress provide valuable clinical information but measuring TRV during stress is challenging. Improved non-invasive estimates of pulmonary hemodynamics are coveted. We present a novel method to non-invasively estimate PA hemodynamics from standard 2D phase contrast magnetic resonance imaging (PC-MRI) of the main PA (MPA).

2. Materials and methods

This project was approved by the UW-Madison IRB for secondary analysis (#2021-0016) of previously acquired data (Forouzan et al., 2019) (#2011-0369 and # 2011-0890) in a total of 7 patients with PH (6 females, 55 ± 16 years old, NYHA functional class II/III 6/1) and 8 healthy, asymptomatic control subjects (7 females, 56 ± 14 years old). Enrollment criteria and study protocol have previously been described (Forouzan et al., 2019).

MRI studies were performed on a clinical 1.5 T imaging system (GE Healthcare Optima MR450W, Waukesha, WI, United States) to acquire 2D-PC images of the MPA. MRI-exercise stress was conducted using a stepper device. After acquiring images at rest, subjects performed moderate exercise of 3–4 min duration each (PH: 30 ± 8 Watts, Control: 32 ± 7 Watts). MPA flow rates and cross-sectional area were calculated using the software "CV Flow version 3.3" (GE Healthcare, Milwaukee, WI). Pulse wave velocity (PWV) was calculated from the "QA" method using MPA flowrates (Q) and MPA cross-sectional areas (A) (Forouzan et al., 2019).

We propose that PA pressures can be non-invasively estimated using classical relationships from arterial biomechanics. The Moens-Kortweg equation for PWV

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$$PWV = \sqrt{\frac{Eh}{\rho D}} \tag{1}$$

where E is elastic modulus, h is wall thickness, ρ is density, and D is diameter, and the Law of Laplace for inflation of a linearly elastic cylindrical tube

$$P_s - P_d = \frac{Eh}{(1-\nu^2)R_d}\left(1 - \sqrt{\frac{A_d}{A_s}}\right) \tag{2}$$

where P is pressure, ν is Poisson's ratio (1/2), R is radius, and A_d and A_s are luminal cross-section area at diastole and systole, respectively, can be rearranged to calculate pulmonary artery pulse pressure (PAPP) from PWV and cross-sectional MPA areas at diastole and systole (Pewowaruk and Roldán-Alzate, 2019).

$$PAPP = \frac{8}{3}\rho PWV^2\left(1 - \sqrt{\frac{A_d}{A_s}}\right) \tag{3}$$

where ρ is the density of blood (1050 kg/m^3).

The remaining PA hemodynamic metrics (mean PA pressure [mPAP], systolic [sPAP], and diastolic [dPAP]) can be calculated using strong linear relationships ($r^2 > 0.95$) for both PH and control subjects (Saouti et al., 2010) because the pulmonary circulation remodels to maintain a fixed product of resistance and compliance.

$$mPAP = \frac{PAPP - 4.5}{0.88} \tag{4}$$

$$sPAP = 1.54^{*}mPAP + 2.7$$

$$dPAP = 0.66^{*}mPAP - 1.8$$

Total pulmonary resistance (TPR = mPAP / Cardiac Output) and PA compliance (PAC = Stroke Volume / PAPP) can also be calculated from the non-invasively estimated PA pressures.

We also evaluated the effect on non-linear arterial mechanics on our estimation of PA pressure from a linear mechanics approximation in a simulated population of 10,000 control individuals and 10,000 individuals with PH. This number was chosen because it produced smooth receiver-operator-characteristic curves. Based on the model proposed by Fung for soft tissue in elongation (Fung, 1967), an exponential model of arterial mechanics was created

$$P = \left(P_d + \frac{\alpha}{\gamma}\right)e^{\gamma\left(\frac{A}{A_d}-1\right)} - \frac{\alpha}{\gamma}$$

that has both non-linear (γ) and linear (α) contributions to arterial stiffness

$$A_d\frac{dP}{dA} = \gamma P + \alpha. \tag{6}$$

The simulated populations were created through normal distributions that matched the measured distributions of mPAP, PA area, relative area change, and PWV from our clinical study (Forouzan et al., 2019). PWV was calculated with the Bramwell-Hill equation evaluated at diastolic pressure

$$PWV = \sqrt{\frac{A_d}{\rho}\frac{dP}{dA}}$$

and mPAP was then estimated from Equations (3) and (4). mPAP estimation was repeated after introducing random error to PWV with standard deviations of up to 1 m/s.

Table 1
Non-Invasively Estimated Pulmonary Hemodynamics.

	Control (n = 7)		Pulmonary Hypertension (n = 8)	
	Rest	Exercise	Rest	Exercise
Mean PA Pressure (mmHg)	12 ± 5	17 ± 9	24 ± 10	40 ± 8
Systolic PA Pressure (mmHg)	21 ± 8	29 ± 14	39 ± 15	64 ± 12
Diastolic PA Pressure (mmHg)	6 ± 4	9 ± 6	14 ± 6	25 ± 5
PA Pulse Pressure (mmHg)	15 ± 5	20 ± 8	25 ± 9	40 ± 7
Total Pulmonary Resistance (Wood Units)	1.9 ± 0.8	1.9 ± 0.9	4.7 ± 2.7	4.5 ± 0.9
PA Compliance (mL/mmHg)	6.8 ± 2.7	5.7 ± 2.3	3.4 ± 1.1	2.0 ± 0.2

PA – Pulmonary artery.

3. Results

mPAP estimated from MRI was greater in the PH group than the control group at both rest (24 ± 10 vs 12 ± 5 mmHg) and exercise (40 ± 8 vs 17 ± 9 mmHg, Table 1). TPR estimated from MRI was also greater in the PH group than the control group at both rest (4.7 ± 2.7 vs 1.9 ± 0.8 Wood units) and exercise (4.5 ± 0.9 vs 1.9 ± 0.9 Wood units). Similar results were found for sPAP, dPAP, and PA compliance (Table 1). In the 5 individuals with PH who had invasive RHC measurements as a part of the study protocol, mPAP was underestimated at rest (27 ± 10 vs 33 ± 6 mmHg) and during exercise (42 ± 8 vs 45 ± 10 mmHg). The amount of underestimation was smaller during exercise.

The diagnostic capability of non-invasively estimated mPAP and TPR to differentiate control subjects from PH patients were assessed using receiver - operator characteristic (ROC) curve analysis to calculate area under the curve (AUC) (Fig. 1). Note that the healthy, asymptomatic control subjects did not undergo invasive RHC to confirm normal PA pressures. Non-invasively estimated mPAP had excellent diagnostic ability to differentiate control subjects from PH patients at rest and with exercise (rest AUC = 0.91 [0.76 – 1.0], exercise AUC = 0.96 [0.88 – 1.0]). Non-invasively estimated TPR also had excellent diagnostic ability to differentiate control subjects from PH patients (rest AUC = 0.98 [0.93 – 1.0], exercise AUC = 0.96 [0.88 – 1.0]).

In the simulated population (Fig. 2), a strong association was observed between actual and estimated mPAP. Similar to 5 individuals with RHC measurements, estimated mPAP was consistently lower than actual mPAP. Introducing PWV error decreased AUC (Fig. 2). For the anticipated PWV error standard deviation of 0.6 m/s (Forouzan et al., 2015), AUC was 0.81 compared to 0.99 without PWV error.

4. Discussion

This proof-of-concept study demonstrates that it may be feasible to non-invasively estimate mean PA pressures from MRI of the MPA using an arterial mechanics approach. Results from ROC curve analysis were promising and suggest the proposed method could be a useful non-invasive tool to estimate pulmonary hemodynamics at rest or under physiological stress. PA pressures physically depend on PWV squared, so the accuracy of this method depends heavily on precise quantification of PA PWV, which can be challenging due to the short length of the MPA. Non-invasive estimation of mPAP using standard 2D echo could potentially be implemented from Doppler using the diameter-velocity method for PWV (Feng and Khir, 2010).

Study limitations include small sample sizes and that control subjects did not have RHC. Tracking changes in PA pressures over time in patients with PH is another capability that a non-invasive tool should possess but was not assessed in this cross-sectional study.

In conclusion, we show promising proof-of-concept results that pulmonary hemodynamics could be non-invasively estimated from an MRI and arterial mechanics approach. Future studies to determine the clinical utility of this method are needed and should include both larger

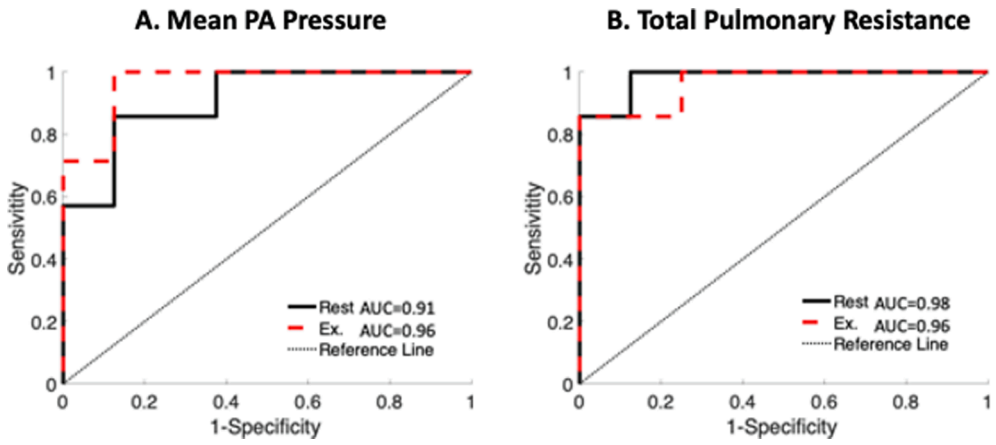

Fig. 1. A. ROC curve analysis showed non-invasively estimated mPAP had excellent diagnostic ability to differentiate PH patients from control subjects. B. ROC curve analysis showed non-invasively estimated TPR had excellent diagnostic ability to differentiate PH patients from control subjects.

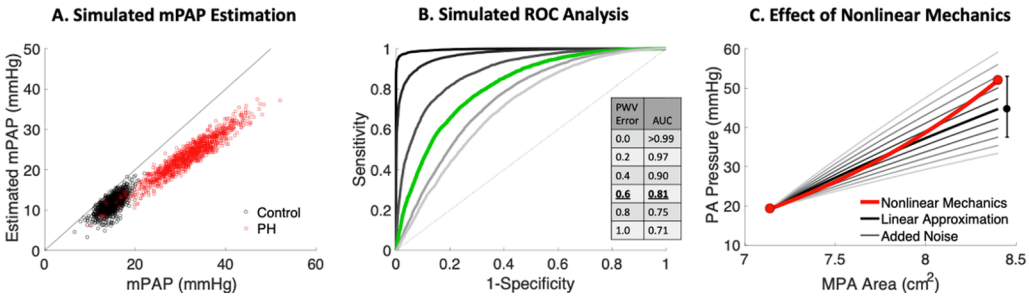

Fig. 2. A. Estimation of mPAP in a simulated population of 10,000 control individuals (black) and 10,000 individuals with PH (red) (only 1-in-10 data points shown). A strong association between actual and estimated mPAP was observed. B. Simulated mPAP estimation was repeated with 0-to-1 m/s error added to PWV. Increasing PWV error decreased AUC. The expected PWV error (0.6 m/s) is highlighted in green. C. Illustration of how a linear approximation of arterial mechanics based on diastolic stiffness (PWV) will underestimate pressure. Adding 0-to-1 m/s error to PWV increases estimate variability. Error bars show the anticipated PWV error of 0.6 m/s. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sample sizes and longitudinal follow-up.

CRediT authorship contribution statement

Ryan Pewowaruk: Wrote manuscript, analyzed data. **Omid Forouzan:** Edited and revised manuscript, acquired data. **Farhan Raza:** Edited and revised manuscript. **Adam Gepner:** Edited and revised manuscript. **Naomi Chesler:** Edited and revised manuscript, acquired data, designed clinical study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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