



Echo-Doppler assessment of ventricular filling pressures in adult Fontan patients



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ABSTRACT

Background: Diastolic dysfunction is felt to be part of the natural history of patients with prior Fontan operation. Despite that, data on noninvasive assessment of diastolic function and ventricular filling pressures in Fontan patients are limited.

Methods: We included 45 adult Fontan patients who underwent right heart catheterization with pulmonary artery wedge pressure (PAWP) measurement and transthoracic echo-Doppler assessment within 7 days. Offline measurement of systemic atrioventricular valve pulsed-wave (PW) and medial/lateral atrioventricular annular tissue Doppler velocities was performed and correlated to PAWP.

Results: Median age was 31.4 years (IQR 24.8–37); 51% of patients were females. Median ventricular ejection fraction was 55% (IQR 50.3–57.5) and median PAWP was 10 mm Hg (IQR 8–11). PW Doppler E velocity ($r = 0.64$, $p \leq 0.0001$), deceleration time ($r = -0.40$, $p = 0.008$), and E/A ratio ($r = 0.33$, $p = 0.03$) correlated with PAWP. Median medial and lateral E/e' ratios also correlated to PAWP ($r = 0.71$, $p = 0.002$ and $r = 0.75$, $p < 0.0001$; respectively). An E velocity >75 cm/s had 88% sensitivity and 86% specificity [97% negative predictive value (NPV); 58% positive predictive value (PPV)], E/A ratio >1.7 had 100% sensitivity and 61% specificity (100% NPV; 26% PPV), and deceleration time <135 ms had 88% sensitivity and 83% specificity (97% NPV; 58% PPV) for predicting PAWP >12 mm Hg.

Conclusion: Our data suggest that PW Doppler atrioventricular E velocity, E/A ratio, and deceleration time could be used to identify adult Fontan patients with normal filling pressures. However, PPVs for PAWP >12 mm Hg were poor. Further studies, particularly prospective, simultaneous echo-catheterization correlation, are critically needed.

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1. Introduction

Over the past three decades, noninvasive determination of diastolic function and estimation of ventricular filling pressures have become a standard component of transthoracic echocardiography-Doppler assessment. Diastolic dysfunction is part of the natural history of Fontan patients, either due to chronic volume overload pre-Fontan or to ventricular under filling that occurs following the operation [1]. The determination of ventricular filling pressures is particularly crucial in the failing Fontan patient since it will guide management and potential interventions. Despite that, data on the echo-Doppler evaluation of

diastolic function and filling pressures in Fontan patients are scarce and mostly limited to pediatric populations [2–6].

Our aim was to correlate atrioventricular pulsed-wave (PW) and annular tissue Doppler to pulmonary artery wedge pressure (PAWP) in adult Fontan patients and assess the performance of echo-Doppler in the estimation of ventricular filling pressures.

2. Methods

This study included 45 Fontan patients seen in our Adult Congenital Heart Disease clinic who underwent transthoracic echocardiography and PAWP measurement within 7 days. The study was approved by the Institutional Board Review and only patients who provided research authorization were selected.

Using an electronic search tool, we identified 54 adult Fontan patients (age ≥ 18 years) who underwent right heart catheterization between January 2000 and February 2017 and had echo-Doppler assessment within a week of catheterization. Two patients were excluded due to atrioventricular valve (AVV) prosthesis/stenosis, 3 patients did not have PAWP measured at time of the procedure, and in one patient right heart pressures were not properly calibrated (as noted by the operator). We also excluded 3 patients with ectopic atrial rhythm/atrial tachycardia and short PR interval, due to the potential influence

Abbreviations: AVV, atrioventricular valve; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; IVRT, isovolumic relaxation time; PAWP, pulmonary artery wedge pressure; PW, pulsed-wave; ROC, receiver-operator curve; SVRI, systemic vascular resistance index; VEDP, ventricular end-diastolic pressure.

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on Doppler variables (particularly E/A ratio). The final cohort included 45 patients. Cardiac catheterization was performed in a fasting state under mild sedation and during spontaneous breathing. When multiple procedures were available, the most recent one was chosen.

PW Doppler of the systemic AVV was performed at the level of the leaflets tips [7]; when two valves were present, the one originally connected to the pulmonary veins was sampled unless this valve was atretic. Lateral annular tissue Doppler was measured at the lateral/free wall insertion site of the annulus whereas medial annular velocity was measured at the ventricular septum insertion point. Similar to atrioventricular PW Doppler, if two valves were present, this measurement was performed at the medial aspect of the annulus originally connected to the atrium attached to the pulmonary veins. Doppler measurements were performed offline by one of the investigators (W.R.M.); modified isovolumic relaxation time (IVRT) was measured as previously described [5]. When atrial fibrillation was present, data from 3 to 5 beats were averaged. Ejection fraction and AVV regurgitation data were obtained from the echocardiographic reports. Cardiac catheterization data were abstracted from the procedure notes; when both right and left PAWP were measured, the highest one was selected. One patient with an atriopulmonary Fontan was found to have extrinsic right upper pulmonary vein compression on right atrial angiography, so the left PAWP was used; no other patients had pulmonary vein stenosis/compression. A mean PAWP >12 mm Hg was defined as elevated filling pressures [8].

Continuous variables are presented as medians and interquartile range (25th–75th percentiles); categorical variables are presented as counts. Chi-square and rank sum tests were used to compare categorical and continuous variables between groups. Correlations between variables were performed using Pearson's correlation. Logistic regression was used in the construction of receiver-operator characteristics (ROC) curves for the prediction of elevated filling pressures. Data were analyzed using JMP for SAS (Cary, NC) version 13.0. *p*-Values <0.05 were considered statistically significant.

3. Results

Median age was 31.4 years (24.8–37) and 51% of patients were females. Median time interval between cardiac catheterization and echocardiogram was 2 days (1–3.5). Atrial fibrillation was present in 4 patients (9%). Underlying congenital lesions were: tricuspid atresia in 18 patients (40%); double-inlet left ventricle in 12 patients (27%), pulmonary atresia/intact ventricular septum in 7 (16%), double-outlet right ventricle in 2 (4%), and other in 6 (13%). Fontan connections were atriopulmonary in 25 patients (56%), lateral-tunnel/intra-atrial type in 14 (31%), and extracardiac in 6 (13%). Mild subaortic was present in 2 patients; none of patients had >mild subaortic obstruction.

Indications for cardiac catheterization were: atrial arrhythmias in 13 (29%), decreased functional capacity in 12 patients (27%), fluid overload in 7 (16%), cardiac transplantation evaluation in 4 (9%), decreased ventricular ejection fraction in 3 (7%), fatigue in 2 (4%), Fontan obstruction in 2 (4%), cirrhosis and protein-losing enteropathy in one each (2%). Twenty-six patients (58%) were on diuretics and 28 (62%) were on angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker (ACEi/ARB) therapy. Twenty (44%) patients had undergone pacemaker implantation [13 (29%) showing atrial and 7 (16%) ventricular pacing at the time of most recent electrocardiogram prior to catheterization].

3.1. Cardiac catheterization and echocardiographic data

Cardiac catheterization and echo-Doppler data for the overall cohort are presented in Table 1. Median PAWP was 10 mm Hg (8–11) and median cardiac index 2.3 l/min·m² (2.0–2.6). At the time of the echocardiographic evaluation, median systolic blood pressure was 100 mm Hg (95.5–111.3) and diastolic blood pressure 61 mm Hg (54.3–70); median heart rate was 70 bpm (60.5–78.5). Median ventricular ejection fraction by transthoracic echocardiography was 55% (50.3–57.5).

Atrioventricular median E velocity was 63 cm/s (50–76) and median E/A ratio 1.6 (1.2–2.2). Median deceleration time was 150 ms (133–182) and median IVRT 79 ms (63–95). PW Doppler E velocity ($r = 0.64$, $p \leq 0.0001$), E/A ratio ($r = 0.33$, $p = 0.03$), deceleration time ($r = -0.40$, $p = 0.008$), and IVRT ($r = -0.40$, $p = 0.008$) correlated with PAWP (Fig. 1). Median medial annular e' velocity was 5.9 cm/s (4.7–7.5), whereas lateral e' velocity was 11.2 cm/s (7.5–13.8). Sixteen patients had both medial and lateral e' velocities measured; their correlation was 0.68 ($p = 0.003$). There was no relationship between annular velocities and PAWP. Median medial E/ e' was 9.7 (8.3–13.9) and lateral

E/ e' 5.6 (4–7.6); both were directly correlated to PAWP ($r = 0.71$; $p = 0.002$ and $r = 0.75$, $p < 0.0001$; respectively) (Fig. 2).

AVV regurgitation \geq moderate was present in 7 patients. There were no differences in E velocity (58 [50; 74.5] versus 72 [65.5; 94.5], $p = 0.11$); E/A ratio (1.6 [1.2; 2.2] versus 1.7 [1.2; 2.5], $p = 0.86$); deceleration time (159 [134; 188.5] versus 131 ms [104.8; 158.1], $p = 0.08$), or IVRT (79 [63; 95.5] versus 78 ms [65.8; 91.8], $p = 0.96$) between patients without and with \geq moderate AVV regurgitation, respectively. Similarly, there were no differences in PAWP (9 [7.8; 11] versus 10 [9; 14], $p = 0.18$) between these two groups.

Eight patients had a ventricular ejection fraction <50%. Among patients with an ejection fraction \geq 50%, correlations between PAWP and Doppler variables were: E velocity 0.61 ($p < 0.001$), deceleration time -0.31 ($p = 0.06$), IVRT -0.39 ($p = 0.02$), E/A 0.31 ($p = 0.07$), medial E/ e' 0.79 ($p = 0.001$), and lateral E/ e' 0.67 ($p = 0.003$). Among patients with ejection fraction <50%, correlations were: E velocity 0.81 ($p = 0.01$), deceleration time -0.77 ($p = 0.08$), IVRT -0.92 ($p = 0.01$), E/A 0.80 ($p = 0.03$), medial E/ e' 0.65 ($p = 0.35$), and lateral E/ e' 0.94 ($p = 0.05$).

Eight patients had elevated ventricular filling pressures at the time of catheterization (median PAWP 16.5 mm Hg [14.3–18.9]). Invasive hemodynamics and echo-Doppler for patients with normal and elevated filling pressures are presented in Table 1. As expected, patients with elevated filling pressures showed higher median PAWP, ventricular end-diastolic pressure (VEDP), and Fontan pressures compared to those with normal filling pressures ($p \leq 0.0001$ for all); median cardiac index was also higher in the elevated filling pressure group (2.7 l/min·m² [2.1–4.1] versus 2.3 l/min·m² [1.9–2.6], $p = 0.04$). Systemic vascular resistance index (SVRI) was lower in the elevated filling pressure group (2720 [1565–3917] versus 3444 dynes·m²/l·min [3067–4643], $p = 0.02$). There were no differences in ACEi/ARB therapy use between patients with elevated and normal filling pressures (62% versus 62%, respectively; $p = 0.99$). Diuretics were more frequently used among patients with elevated filling pressures (100% versus 48%, $p = 0.02$).

There were no differences in vital signs at the time of echocardiography between groups. Compared to the normal filling pressure group, patients with elevated filling pressures had higher median E velocities (99.5 cm/s [76.8–132.3] versus 55 cm/s [49–69], $p = 0.0002$) and E/A ratios (2.5 [1.7–3.4] versus 1.5 [1.1–2], $p = 0.02$) as well as shorter median deceleration time (119 [100.5–134] versus 162 ms [141–193], $p = 0.0002$). Due to the small sample size, differences in tissue Doppler variables could not be assessed.

ROC curves for prediction of elevated filling pressures were constructed using E velocity, E/A ratio, and deceleration time. The areas under the curve for E velocity and E/A ratio were 0.92 and 0.83, respectively, whereas the area under the curve for deceleration time was 0.86. An E velocity >75 cm/s had a sensitivity of 88% and specificity 86% for predicting a PAWP >12 mm Hg (97% negative predictive value; 58% positive predictive value) and an E/A ratio >1.7 had sensitivity of 100% and a specificity of 61% (100% negative predictive value; 26% positive predictive value), whereas a deceleration <135 ms had sensitivity of 88% and a specificity of 83% (97% negative predictive value; 58% positive predictive value) for predicting elevated filling pressures.

4. Discussion

To our knowledge, this is the largest study assessing the estimation of ventricular filling pressures in adult Fontan patients using echo-Doppler parameters. Although the correlations between echo-Doppler variables and PAWP were modest, our results suggest that atrioventricular early diastolic velocity, E/A ratio, and deceleration time might allow us to exclude high filling pressures in adult Fontan patients. However, their positive predictive value for elevated filling pressures was poor.

Over the past three decades, intense effort has been dedicated to the echo-Doppler evaluation of diastolic function and ventricular filling

Table 1
Cardiac catheterization and echo-Doppler data.

| | n | Overall group (n = 45) | n | Normal filling pressures (n = 37) | n | High filling pressures (n = 8) | p-Value |
|-------------------------------------|----|---------------------------|----|--------------------------------------|---|-----------------------------------|---------|
| Cardiac catheterization data | | | | | | | |
| Fontan pressure, mm Hg | 45 | 15 (12.5–17.5) | 37 | 14 (12–16) | 8 | 23 (18–26.5) | 0.0001 |
| PAWP, mm Hg | 45 | 10 (8–11) | 37 | 9 (7.5–10) | 8 | 16.5 (14.3–18.9) | <0.0001 |
| VEDP, mm Hg | 42 | 10 (9–13.3) | 34 | 10 (9–11) | 8 | 16.5 (16–21.8) | <0.0001 |
| Cardiac index, l/min·m ² | 45 | 2.3 (2.0–2.6) | 37 | 2.3 (1.9–2.6) | 8 | 2.7 (2.1–4.1) | 0.04 |
| SVRi, dynes·m ² /l·min | 43 | 3400 (2754–4584) | 35 | 3444 (3067–4643) | 8 | 2720 (1565–3917) | 0.02 |
| Echo-Doppler data | | | | | | | |
| Ventricular ejection fraction, % | 45 | 55 (50.3–57.5) | 37 | 55 (50;57.5) | 8 | 55 (40.9;56.9) | 0.72 |
| Ventricular ejection fraction <50% | 45 | 7 (16%) | 37 | 6 (16%) | 8 | 2 (25%) | 0.62 |
| AVV regurgitation ≥moderate | 45 | 7 (15%) | 37 | 5 (14%) | 8 | 2 (25%) | 0.59 |
| E velocity, cm/s | 45 | 63 (50–76) | 37 | 55 (49–69) | 8 | 99.5 (76.8–132.3) | 0.0002 |
| A velocity, cm/s | 41 | 39 (28.5–50) | 36 | 39 (28.5–50.5) | 5 | 44 (28–51) | 0.99 |
| E/A | 41 | 1.6 (1.2–2.2) | 36 | 1.5 (1.1–2) | 5 | 2.5 (1.7;3.4) | 0.02 |
| Deceleration time, ms | 43 | 150 (133–182) | 35 | 162 (141–193) | 8 | 119 (100.5–134) | 0.0002 |
| Isovolumic relaxation time | 43 | 79 (63–95) | 36 | 83.5 (63.3–99) | 7 | 67 (46.5–82) | 0.06 |
| Medial annular e' velocity, cm/s | 17 | 5.9 (4.7–7.5) | 14 | 6.1 (5.2–7.3) | 3 | 2.7 (1.7–8.9) | NP |
| Lateral annular e' velocity, cm/s | 21 | 11.2 (7.5–13.8) | 19 | 11.6 (8–13.9) | 2 | 4.3 (3.9–4.7) | NP |
| Medial E/e' | 17 | 9.7 (8.3–13.9) | 14 | 9.1 (7.7–10.8) | 3 | 28.1 (13–55.3) | NP |
| Lateral E/e' | 21 | 5.6 (4–7.6) | 19 | 5.5 (4–6.8) | 2 | 20.1 (16.2–24.1) | NP |

Variables are presented as median and interquartile range. AVV – atrioventricular valve; VEDP – ventricular end-diastolic pressure; PAWP – pulmonary artery wedge pressure; NP – not performed due to small sample size; SVRi – systemic vascular resistance index.

pressures in patients with acquired cardiac disease [7,9]. Echocardiography allows for easy access, noninvasive, longitudinal assessment of ventricular hemodynamics. Mitral valve and pulmonary vein PW and mitral annular tissue Doppler provide valuable insight into diastology and have been shown to predict increased left VEDP and PAWP with good accuracy [9]. Moreover, diastolic dysfunction diagnosed by echo-Doppler has been found to be of prognostic value in essentially every cardiac disorder [10].

Diastolic dysfunction is part of the natural history of patients with Fontan circulation, either due to chronic volume overload pre-Fontan or ventricular under filling following the operation [1]. Given the absence of pulsatile flow, post-capillary pressures play a central role in Fontan physiology, directly affecting systemic venous pressure and cardiac output. It is paramount that ventricular filling pressures and overall hemodynamics are well delineated in patients with failing Fontan since these will guide management and potential interventions. Therefore,

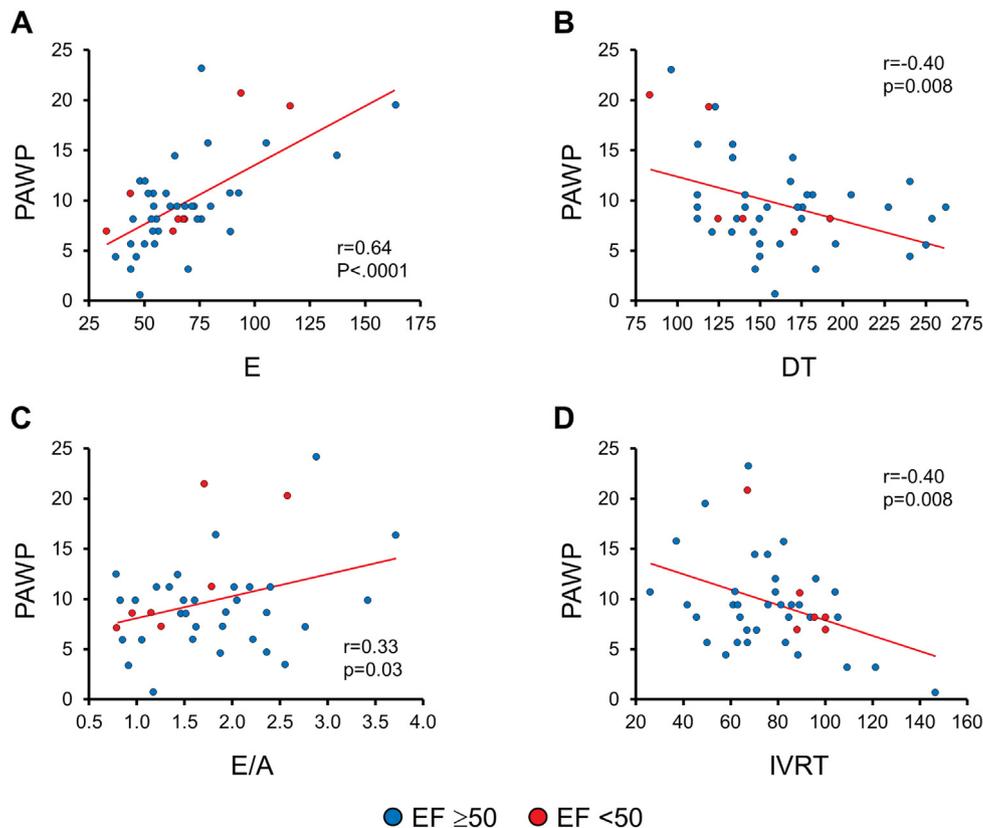


Fig. 1. Correlation between pulsed-wave Doppler variables and pulmonary artery wedge pressures. Correlations between pulsed-wave atrioventricular E velocity (Panel A), deceleration time (DT) (Panel B), E/A ratio (Panel C), and isovolumic relaxation time (IVRT) (Panel D) and pulmonary artery wedge pressures. (EF – ejection fraction).

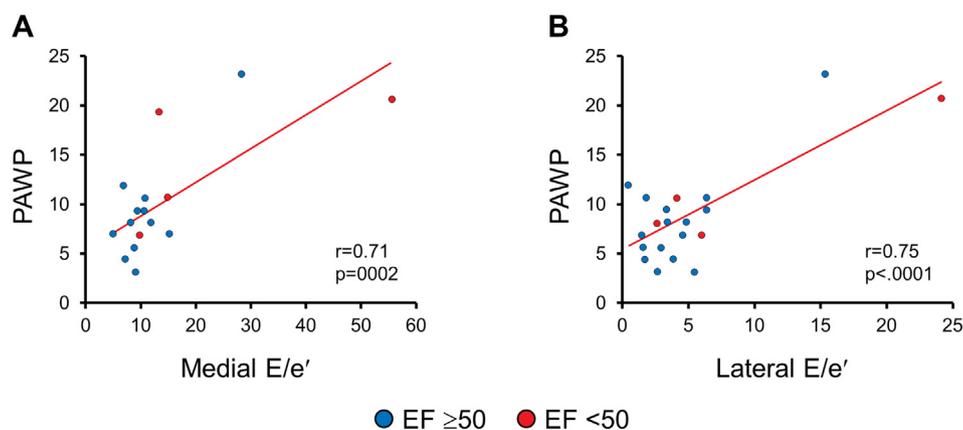


Fig. 2. Correlation between atrioventricular tissue Doppler and pulmonary artery wedge pressures. Correlations between medial (Panel A) and lateral (Panel B) atrioventricular E/e' velocities and pulmonary artery wedge pressures. (EF – ejection fraction).

almost invariably these patients undergo cardiac catheterization. Surprisingly, despite the major role of diastolic dysfunction in Fontan circulation, data on echo-Doppler assessment are scarce and mostly limited to pediatric populations [3–5]. Cordina et al. have recently proposed atrioventricular systolic-to-diastolic duration ratio using continuous-wave Doppler as predictor of VEDP pressure in 15 adult Fontan patients. In their study, the only conventional echo-Doppler parameter to correlate with ventricular filling pressures was pulmonary vein A to atrioventricular A wave duration difference [6].

In our cohort, atrioventricular E velocities correlated with ventricular filling pressures and an E velocity >75 cm/s identified patients with abnormal filling pressures with good sensitivity. Early transmitral flow measurement by PW Doppler was one of the first parameters studied in noninvasive assessment of diastology [11,12], as it is proportional to left atrial-ventricular gradient. In our cohort, E velocities were lower than predicted in acquired cardiac diseases or even normal individuals, which is in agreement with previous observations [3]. As transmitral flow is influenced by cardiac output, these results are not unexpected given the low flow state seen in Fontan physiology. A short deceleration time (<135 ms) and E/A ratio >1.7 also identified patients with elevated filling pressures in our Fontan cohort. This deceleration time is shorter than the deceleration time typically used to predict elevated filling pressures in patients with acquired cardiac disease (160 ms) [7,9] and this difference may be related to the lower associated peak E velocities noted in Fontan patients. Similarly, the optimal E/A ratio cut-off for prediction of elevated PAWP derived from our data differs from the recommended cut-off to for patients with acquired cardiac disorders [7]. Our observations underscore that cut-offs typically used in patients with two-ventricle circulation should not be extrapolated to Fontan patients, given the complex interaction between cardiac output, left atrial pressure, atrial mechanical function, and ventricular relaxation seen in the heterogeneous population of single ventricle patients. Noteworthy, despite the small proportion of patients with reduced ventricular ejection fraction in our cohort, correlations between echo-Doppler variables and filling pressures appear to be better in this group, which is keeping with observations in individuals with acquired cardiac disease [13,14].

Several studies have reported mitral E/e' ratio to be a better marker of elevated filling pressures [7,13,15], with some authors reporting lateral E/e' or the average between lateral and medial E/e' to be superior to medial E/e' alone [14]. In a two-ventricle circulation, medial mitral tissue Doppler might be affected by right ventricular diseases, such as in severe tricuspid regurgitation, pulmonary hypertension, and right ventricular dysfunction [16]. In Fontan patients, this could be a potential concern, for example, in patients with pulmonary atresia/intact ventricular septum or atriopulmonary connections and markedly enlarged right atria. In our cohort, the correlation between medial and lateral e' velocities was only modest. Menon et al. [4] also observed free wall

(lateral) e' velocities to be lower in single ventricle patients with morphologic right ventricles compared to left ventricular morphology. The lack of tissue Doppler data for some of the patients can be explained by our current inability to interpret these findings when acquired. In order for us to critically analyze these measurements and use them in clinical practice, it is crucial that we define “expected” tissue Doppler velocities in adults in relationship to the underlying anatomy and Fontan connection. Although we found a correlation between PAWP and E/e' ratios, we were unable to analyze their performance in predicting elevated filling pressures. It is noteworthy, however, that lateral E/e' had the best correlation with PAWP among all variables analyzed. This finding deserves further investigation.

We acknowledge the limitations of the study including its retrospective nature and inherent biases. Most of our patients were symptomatic and the performance of echo-Doppler in predicting PAWP among asymptomatic patients might differ. In addition, the fasting state might have influenced the invasively measured hemodynamics. It should also be highlighted that echocardiographic and catheterization data were not obtained simultaneously. We chose to include PAWP in our correlations since PAWP is a better surrogate for left atrial pressures than VEDP [17]; thus, our results should not be extrapolated to estimations of VEDP. Tissue Doppler data were only available for a small proportion of patients, preventing the assessment of E/e' as a predictor of filling pressures. Similarly, a very small proportion of patients had good quality pulmonary vein Doppler so those variables were not included. Despite the relatively large sample for an adult Fontan study, the number of patients with elevated filling pressures corresponded to only approximately a fifth of the cohort, limiting our statistical analyses. This was also the case for comparisons between right/left ventricular morphologies, absence or presence of \geq moderate AVV regurgitation or ventricular pacing, and preserved/reduced ventricular ejection fraction. Lastly, the large number of atriopulmonary Fontan patients in our cohort should be acknowledged, as hemodynamics might be different in those with other types of Fontan connections (particularly, cardiac output).

In summary, our observations suggest that PW Doppler atrioventricular E velocity, E/A ratio, and deceleration time could be used to exclude elevated filling pressures in adult Fontan patients referred for cardiac catheterization. However, their correlation with PAWP and positive predictive values were modest. Our results also highlight the importance of defining “normal, expected” Doppler values in adult patients with Fontan physiology and that cut-offs and ranges used in noninvasive assessment of diastology in two-ventricle circulation might not apply to Fontan patients. Given the central role of ventricular diastolic function in Fontan circulation and the growing adult Fontan population, further studies (particularly prospective, simultaneous echo-catheterization correlation) are critically needed.

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Contributors

Drs. Connolly, Warnes, Taggart, O'Leary, and Oh were involved in the conception/design of the study as well revising the manuscript critically. Drs. Miranda and Egbe were involved in the above mentioned steps, but were also responsible for data analysis and drafting the manuscript. All authors have provided approval of final version of the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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