Diastolic Dysfunction With Preserved Ejection Fraction After the Fontan Procedure

Shahryar M. Chowdhury, MD, MSCR; Eric M. Graham, MD; Carolyn L. Taylor, MD; Andrew Savage, MD; Kimberly E. McHugh, MD; Stephanie Gaydos, MD; Arni C. Nutting, MD; Michael R. Zile, MD; Andrew M. Atz, MD

BACKGROUND: Heart failure phenotyping in single-ventricle Fontan patients is challenging, particularly in patients with normal ejection fraction (EF). The objective of this study was to identify Fontan patients with abnormal diastolic function, who are high risk for heart failure with preserved ejection fraction (HFpEF), and characterize their cardiac mechanics, exercise function, and functional health status.

METHODS AND RESULTS: Data were obtained from the Pediatric Heart Network Fontan Cross-sectional Study database. EF was considered abnormal if <50%. Diastolic function was defined as abnormal if the diastolic pressure:volume quotient (lateral E:e'/end-diastolic volume) was >90th percentile (≥0.26 mL). Patients were divided into: controls=normal EF and diastolic function; systolic dysfunction (SD) = abnormal EF with normal diastolic function; diastolic dysfunction (DD) = normal EF with abnormal diastolic pressure:volume quotient. Exercise function was quantified as percent predicted peak VO₂. Physical Functioning Summary Score (FSS) was reported from the Child Health Questionnaire. A total of 239 patients were included, 177 (74%) control, 36 (15%) SD, and 26 (11%) DD. Median age was 12.2 (5.4) years. Arterial elastance, a measure of arterial stiffness, was higher in DD (3.6±1.1 mm Hg/mL) compared with controls (2.5±0.8 mm Hg/mL), P<0.01. DD patients had lower predicted peak VO₂ compared with controls (52% [20] versus 67% [23], P<0.01). Physical FSS was lower in DD (45±13) and SD (44±13) compared with controls (50±7), P<0.01.

CONCLUSIONS: Fontan patients with abnormal diastolic function and normal EF have decreased exercise tolerance, decreased functional health status, and elevated arterial stiffness. Identification of patients at high risk for HFpEF is feasible and should be considered when evaluating Fontan patients.

Key Words: diastolic function ■ Fontan ■ heart failure ■ single ventricle
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stiffness in adults and children.7,8 The objective of this study was to utilize these measures to identify Fontan patients with abnormal diastolic function and normal ejection fraction (EF), and, to evaluate their cardiac mechanics, exercise function, and functional health status. We hypothesized that Fontan patients with abnormal diastolic function and normal EF would display a clinical status placing them at high risk for HFpEF, that is, they would have exercise function and functional health status worse than controls and comparable to Fontan patients with systolic dysfunction.

METHODS

We performed a secondary analysis of data was obtained from the NIH/NHLBI Pediatric Heart Network (PHN) Fontan Cross-sectional Study public use database (available at http://www.pediatricheartnetwork.org/ForResearchers/PHNPublicUseDatasets.aspx). The design of the PHN Fontan Cross-sectional Study has been previously described.9,10 Briefly, this was a multicenter, prospective, cross-sectional assessment of children with Fontan physiology. Subjects were recruited if they were 6–18 years old and had undergone Fontan procedure at least 6 months before initial study testing. Exclusion criteria included the presence of a noncardiac medical or psychiatric disorder that would prevent successful/valid completion of study testing. The study was approved at each center’s institutional review committee and patients or their parents/guardians gave informed consent. Medical history, standardized echocardiography, exercise testing, serum testing, and parental assessment of functional health status were performed. For the current study, patients in the data set were excluded if an echocardiographic assessment of diastolic function (as described below) could not be performed, or, if maximal exercise was not achieved.

Echocardiographic Assessment of Ejection Fraction and Diastolic Function

Doppler inflow E velocities from the dominant atrioventricular valve and tissue Doppler e’ velocities from the lateral aspect of the base of the dominant ventricle were included. End-diastolic volume (EDV), end-systolic volume (ESV), mass, and EF were calculated using a biplane-modified Simpson’s rule; these echocardiographic measures showed good agreement with volumes obtained from cardiac magnetic resonance imaging in a subset of this cohort.11 An EF<50% was considered abnormal. Patients with missing Doppler E, tissue Doppler e’, ventricular volumes, or fused Doppler E and A waves were excluded from the analysis. All volumes and masses were indexed to body surface area.

Conceptually, patients with abnormal active ventricular relaxation and small end-diastolic ventricular volumes are at risk for having abnormal passive ventricular stiffness—a hallmark of HFpEF. Therefore, was used to assess diastolic function in these patients. This measure correlates well with the reference standard measure of ventricular stiffness, β, obtained via pressure-volume loop analysis in adults and children.7,8 Due to the fact that there are not yet normal values for this measure in children, patients with an arbitrary cutoff of lateral Ee'/EDV:the 90th percentile (0.26 1/mL per m² in this cohort) were considered to have abnormal diastolic function. This cutoff value was used as it allowed an adequate sample size in the abnormal diastolic function group while still representing those patients with the most severe diastolic dysfunction.

Patient Classification

Fontan patients were divided into 3 groups: (1) those with normal EF and normal diastolic function—controls, (2) those with abnormal EF and normal diastolic function and normal diastolic function with preserved ejection fraction.

Nonstandard Abbreviations and Acronyms

| EA       | arterial elastance |
| EDV      | end-diastolic volume |
| Ees      | end-systolic elastance |
| ESV      | end-systolic volume |
| HFpEF    | heart failure with preserved ejection fraction |
| HFrEF    | heart failure with reduced ejection fraction |
| PHN      | Pediatric Heart Network |

CLINICAL PERSPECTIVE

What Is New?

• This is the first study to utilize quantitative imaging data to identify a subset of single ventricle patients post Fontan operation who display a heart failure phenotype consisting of diastolic dysfunction with preserved ejection fraction.

• These patients have impaired exercise tolerance compared with Fontan patients with normal cardiac function and similar reported heart failure symptoms to patients with systolic dysfunction.

What Are the Clinical Implications?

• Clinicians who encounter Fontan patients with heart failure symptoms and normal ejection fraction can utilize echocardiography to identify diastolic dysfunction in these patients.
function = systolic dysfunction (SD), (3) and those with normal EF and abnormal diastolic function = diastolic dysfunction (DD). There were too few patients with both abnormal EF and abnormal diastolic function (n=4) to be included in the analysis.

**Evaluation of Cardiac Mechanics**

Ventricular end-systolic elastance (Ees) is a component of systolic ventricular performance and is estimated using the ratio (0.9×systolic blood pressure)/ESV. Arterial elastance (Ea) is a measure of arterial stiffness and is estimated using the ratio (0.9×systolic blood pressure)/stroke volume. Blood pressures were taken by cuff at the time of echocardiography. Ventriculo-arterial coupling was assessed using the ratio Ea/Ees. These echocardiographic estimates of cardiac mechanics have been validated against pressure-volume loop analysis in children.12

**Assessment of Exercise Function**

Data from a maximal ramp exercise test were used in the analysis. Percent predicted maximum oxygen consumption (VO2) was used as a measure of overall cardiopulmonary health. Percent predicted O2 pulse was used as a surrogate for stroke volume augmentation.13

**Functional Health Status Assessment**

Functional health status was assessed using the parent report version of the Child Health Questionnaire (CHQ-PF50).14 A Physical and a Psychosocial Functioning Summary Score (FSS) were reported. The physical FSS assesses a subjective assessment of overall health and illness, presence, and extent of physical limitations due to health-related problems: self-care, mobility, and activities varying in strenuousness, limitations in school-related activities and friends due to physical health problems, and intensity and frequency of general pain and discomfort. The psychosocial FSS assesses limitations in the kind, amount and performance of school work and activities with friends due to emotional or behavioral difficulties, frequency of behavior problems and ability to get along with others, frequency of both positive and negative states: anxiety, depression, and positive affect, and satisfaction with school and athletic ability, looks/appearance, ability to get along with others, and life overall.15

**Statistical Analysis**

The evaluation of data as normal or non-normally distributed was assessed using the Shapiro-Wilk test. Sensitivity analysis was performed to assess for differences in percent predicted peak VO2 when the cutoff value for lateral E:e'/EDV defining diastolic function was changed to 75th, 80th, and 85th percentile to ensure 90th percentile was the most optimal cutoff value. Differences between patient groups were assessed using ANOVA or Kruskal Wallis tests, as appropriate, for continuous variables and Chi-square test or Fisher’s Exact test for categorical variables. Between-group post hoc comparisons using the Bonferroni correction were then performed in those variables which showed a statistically significant association. The relationship between lateral E:e'/EDV and percent predicted peak VO2 max was plotted and appropriate regression methods were used to assess their association based on the spread of the data. Univariable and multivariable linear regression were performed to assess the association between percent predicted VO2 max and patient group (control, SD, or DD), age, dominant ventricle, and atroventricular valve regurgitation. Independent variables were included in the multivariable regression if P<0.20 on univariable regression. Correlations between exercise measures and echocardiographic measures within patient groups were performed using Spearman’s correlation analysis. A P<0.05 was considered statistically significant. Statistics were performed using SPSS v. 25 (IBM, Armonk, NY).

**RESULTS**

Of the 546 patients in the PHN Fontan Cross-sectional Study, 239 had complete data sets for analysis and were included in the current study. Of these, 177 (74%) were in the control group, 36 (15%) were in the SD group, and 26 (11%) were in the DD group. Sensitivity analysis showed no differences in percent predicted peak VO2 between the DD group and the control or SD groups when cutoff values of 75th percentile (P=0.60), 80th percentile (P=0.25), or 85th percentile (P=0.13) of lateral E:e'/EDV were used, therefore, 90th percentile was used as the cutoff to define DD. Patient characteristics are found in Table 1. Notable findings include DD patients were more likely to be right ventricle dominant compared with controls and had a higher mass:volume ratio compared with SD patients and controls. Brain natriuretic peptide levels were not different between groups. Differences in clinical and echocardiographic measures between control, SD, and DD groups separated by ventricular dominance are presented in Table S1.

**Cardiac Mechanics**

Patients with SD displayed lower Ees than control patients. In contrast, DD patients had higher Ees than both SD and control patients (Figure 1A). Both SD and DD groups showed higher Ea than control patients; there were no differences in Ea between patients with SD and DD (Figure 1B). Ea/Ees was higher in SD patients compared with control and DD patients (Figure 1C).
Exercise Function

Results from exercise testing between the 3 groups are reported in Table 2. There were no differences in percent predicted peak VO\textsubscript{2} or percent predicted max O\textsubscript{2} pulse between SD and controls. DD patients had lower percent predicted peak VO\textsubscript{2} and trended toward lower percent predicted max O\textsubscript{2} pulse (ppO\textsubscript{2}P-max) compared with controls.

Association Between Cardiac Mechanics and Exercise Function

In all patients, the relationship between lateral E\textsubscript{e}/EDV and percent predicted peak VO\textsubscript{2} was best fit to a quadratic equation (F=4.76, P=0.009) (Figure 2). Due to this relationship, lateral E\textsubscript{e}/EDV was not a candidate for entry into linear multivariable regression analysis to identify independent associations with percent predicted peak VO\textsubscript{2}. Instead, regression modeling model included patient group (control, SD, or DD). Univariable linear regression modeling showed that age (β=−0.19, P=0.01) and patient group (β=−0.18, P=0.01) had an association with percent predicted peak VO\textsubscript{2}. Dominant ventricle (P=0.56) and atrioventricular valve (P=0.60) regurgitation showed no association with percent predicted peak VO\textsubscript{2} and were not included in the multivariable model. The multivariable model included age and patient group and the results are reported in Table 3. Patient group and age were both independent predictors of percent predicted peak VO\textsubscript{2}.

Functional Health Status

Patients with SD (45±13) and DD (44±13) had lower physical FSS compared with control patients (50±7), P<0.01. There were no differences in psychosocial FSS between control (48±11), SD (46±13), and DD (44±14) patients, P=0.18.

DISCUSSION

The existence of HFpEF in Fontan patients has long been speculated by congenital cardiology clinicians...
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However, identification of this population has been challenging. The main finding of this study was that Fontan patients with abnormal diastolic function and normal EF displayed decreased exercise tolerance and functional health status compared with controls—consistent with a subset of patients being high risk for HFpEF. Other important findings included that DD patients had elevated arterial stiffness, comparable to patients with SD, and were more likely to have a dominant right ventricle compared with controls. To our knowledge, this is the first study to detect and characterize DD in a relatively large multicenter sample of Fontan patients using validated non-invasive quantitative measures.

Pathophysiologic mechanisms that contribute to the development of HFpEF in patients with biventricular circulation include diastolic dysfunction, chronically increased afterload, reduced cardiac output reserve (subclinical systolic dysfunction, chronotropic incompetence), ventilatory dysfunction, activation of the autonomic nervous system, and renal dysfunction. Data from previous studies show that these conditions exist in Fontan patients from an early age. Therefore, the rationale that Fontan patients are at risk for developing HFpEF appears valid. This is supported by data from the current study showing patients with abnormal diastolic function, elevated mass to volume ratio, and normal EF displayed clinical signs of heart failure, including exercise intolerance and low reported functional health status. In the clinical setting, differentiation of this group from other forms of Fontan failure may be important in order to guide appropriate treatment strategies, analogous to differing treatment strategies between biventricular HFrEF and HFpEF. Likewise, it may be prudent for future clinical trials to account for differing Fontan heart failure phenotypes in their design to ensure appropriate patient selection.

Table 2. Exercise Testing Results in Control, Systolic Dysfunction, and Diastolic Dysfunction Patients

|                  | Control (n=177) | SD (n=36) | DD (n=26) | P value |
|------------------|----------------|-----------|-----------|---------|
| Resting heart rate, bpm | 77 (22) | 84 (28) | 72 (23) | 0.10    |
| Resting SpO₂ (%)  | 95 (4)   | 95 (6)   | 96 (7)   | 0.50    |
| % predicted max heart rate | 77 (13) | 77 (21) | 73 (15) | 0.42    |
| Maximum SpO₂ (%)  | 92 (8)   | 91 (17)  | 92 (7)   | 0.54    |
| % predicted peak VO₂ | 67 (23) | 63 (29) | 52 (20) | 0.02    |
| % predicted max O₂ pulse | 93 (29) | 87 (26) | 75 (43) | 0.06    |

Results reported as median (interquartile range). DD indicates diastolic dysfunction; and SD, systolic dysfunction.

*P<0.05, Control vs DD.

Multiple characteristics of DD Fontan patients in this study parallel adults with biventricular HFpEF. Biventricular patients with HFpEF display both elevated Ees and elevated Ea resulting in their relatively normal ventriculo-arterial coupling that contributes to a preserved EF. This is in contrast to biventricular patients with HFrEF that demonstrate elevated Ea and decreased Ees, leading to abnormal ventriculo-arterial coupling and decreased EF. This pattern was mirrored in Fontan patients in the current study. Ventriculo-arterial coupling has been shown to be related to outcomes in Fontan patients, future studies should assess this association between Fontan patients with SD versus DD. In addition, biventricular HFpEF patients exhibit impaired peak VO₂ and decreased quality of life indicators compared with controls, similar to our DD

Figure 1. Differences in cardiac mechanics between controls, systolic dysfunction, and diastolic dysfunction.

A, Differences in Ees (contractility) between controls, SD, and DD. B, Differences in Ea (afterload) between controls, SD, and DD. C, Differences in Ea/Ees (ventriculo-arterial coupling) between controls, SD, and DD. Over a bracket represents P<0.01 between the groups. DD indicates diastolic dysfunction; Ea, arterial elastance; Ees, end-systolic elastance; and SD, systolic dysfunction.
Fontan cohort.28,29 Interestingly, similar to biventricular HFpEF patients, Fontan DD patients trended toward having impaired augmentation of stroke volume on exercise testing. This is thought to be due to impaired filling in diastole in biventricular HFpEF.30 This impairment in ventricular relaxation may be especially important in the single ventricle—with passive flow through the pulmonary arterial system, the pressure gradient created during ventricular relaxation becomes the major contributor to the maintenance of low right and left sided filling pressures required for adequate cardiac output. The importance of diastolic function to Fontan exercise function may explain why SD patients displayed comparable exercise function to controls as they had relatively normal diastolic function. These clinical parallels between biventricular HFpEF and Fontan DD support future investigations into the molecular/cellular pathologic parallels between the groups.

Fontan patients with DD were more likely to have a dominant right ventricle in this study. The right ventricle appears to be less suited to operate under systemic conditions than the left ventricle which may predispose it to the development of DD. Studies in adults with systemic right ventricles have shown higher levels of myocardial fibrosis compared with control patients with systemic left ventricles.31 A similar relationship has been demonstrated in single ventricle patients, with single right ventricle patients showing evidence of greater fibrotic burden than single left ventricles.32 Higher fibrotic burden may explain the higher incidence of DD in the single right ventricle group. In a follow-up study involving the current study cohort, ventricular morphology was not associated with clinical outcomes.33 However, ventricular morphology’s role in predicting outcomes in clinical subsets of Fontan failure, such as HFpEF, warrants further study.

Diastolic dysfunction is conventionally assessed by evaluating atrial pressures and ventricular end-diastolic pressures invasively. However, in Fontan physiology, patients with elevated filling pressures are often at the end-stage of their disease with few effective treatment options other than mechanical support or transplantation. The non-invasive identification of Fontan patients with diastolic dysfunction prior to development of elevated filling pressures may allow for more medical or surgical treatment options in the

Table 3. Multivariable Analysis for Predictors of Percent Predicted Peak VO₂ max

|          | B     | SE    | \(\beta\) | t     | \(P\) value |
|----------|-------|-------|-----------|-------|-------------|
| Constant | 83.720| 5.407 |           | 15.483| <0.001      |
| Age      | −0.919| 0.395 | −0.168    | −2.326| 0.021       |
| Patient group | −4.505 | 1.916 | −0.169    | −2.352| 0.020       |

Patient group included patients who were controls, systolic dysfunction, or diastolic dysfunction.

Figure 2. Relationship between lateral E:e'/EDV and percent predicted peak VO₂. Scatterplot of lateral E:e'/EDV and percent predicted peak VO₂. Patient groups are separated by color coding. Quadratic fit line shown (\(F=4.76, P=0.009\)). EDV indicates end-diastolic volume.
future as treatments for diastolic dysfunction are developed. It may also allow investigators to evaluate the contribution of diastolic dysfunction to other Fontan pathologies, such as pulmonary vascular disease and liver fibrosis. Unfortunately, DD was previously difficult to assess non-invasively in the single ventricle population. Even invasively, detecting occult DD prior to an elevation in EDP is challenging, requiring the use of microconductance catheters to produce pressure-volume loops and/or load alteration strategies. The current study shows that identification of DD in Fontan patients using a simple validated non-invasive measurement, lateral E:e'/EDV, is feasible and can be used to detect patients at high risk of clinical heart failure in the setting of a normal EF. Currently, it appears using a lateral E:e'/EDV cutoff value of 0.26 mL⁻¹ is reasonable to identify Fontan patients at high risk for HFpEF recognizing that cutoff values are likely to change as longitudinal studies are performed and as larger studies allow us to refine cutoff values based on ventricular morphology. Investigation into further clinical uses of this measure and its ability to predict longitudinal outcomes are warranted.

**Limitations**

While this is the largest multicenter cohort of Fontan patients studied, there was a relatively small sample size. A number of patients were excluded due to missing echocardiographic data, specifically, missing spectral and tissue Doppler data. Though not explicitly stated in the public data set, we suspect a number of patients were lost due to E and A wave fusion, potential due to prolongation of their systolic time due to systolic dysfunction; it is important to further investigate these patients as they may be high risk for combined systolic and diastolic heart failure. These missing data, and data not included in the data set, such as lack of invasive hemodynamic data and information on aorto-pulmonary collaterals, may limit the applicability of these data to a broad group of patients. Two-dimensional echocardiography was used to evaluate ventricular volumes in this study which is limited by suboptimal reproducibility and accuracy compared with cardiac magnetic resonance imaging in single ventricle patients, especially those who are right ventricular dominant. Unfortunately, only 25% of the patients studied had cardiac magnetic resonance imaging data available in the data set, therefore, echocardiography was used. Even though there was acceptable reproducibility and accuracy of ventricular volumes compared with cardiac magnetic resonance imaging in this cohort, error within the measurements may have affected our results. However, when these patients’ longitudinal data are released for public use, our utilization of these echocardiographic measures will allow us to perform follow-up studies in this cohort, as the same methods were used to evaluate their ventricular volumes longitudinally. Few patients with DD were identified due to the nature of our definition of DD being lateral E:e'/EDV >90th percentile. In addition, in HFpEF, diastolic dysfunction is not necessarily a rule. We suspect a subset of patients in the control group who exhibited normal EF and normal diastolic function by our definition in fact had HFpEF and were not detected using the current methods. This was a cross-sectional study, future studies should investigate differences in outcomes between the control, SD, and DD groups. There is opportunity to do this using this cohort and other Fontan cohorts the PHN is currently studying.

**CONCLUSIONS**

We identified a subset of Fontan patients with abnormal diastolic function and normal EF who displayed decreased exercise tolerance and abnormal functional health status, similar to Fontan patients with systolic dysfunction. These patients displayed elevated arterial stiffness and were more likely to be right ventricular dominant. Fontan clinicians and investigators should consider heart failure phenotypes, such as DD, when providing care and designing studies.

**ARTICLE INFORMATION**

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**Affiliations**

Division of Cardiology, Department of Pediatrics (S.M.C., E.M.G., C.L.T., A.S., K.E.M., A.C.N., A.M.A.) and Division of Cardiology, Department of Medicine (S.G., M.R.Z.), Medical University of South Carolina, Charleston, SC (S.G., M.R.Z.).

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**Disclosures**

None.

**Supplemental Material**

Table S1

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**Disclosures**

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Table S1. Demographic and clinical data in control, systolic dysfunction, and diastolic dysfunction patients stratified by ventricular morphology.

|                      | Dominant Left Ventricle | Dominant Right Ventricle | Mixed |
|----------------------|-------------------------|--------------------------|-------|
|                      | Control (n = 108)       | SD (n = 15)              | DD (n = 9) |
|                      | Control (n = 48)        | SD (n = 17)              | DD (n = 14) |
|                      | Control (n = 21)        | SD (n = 4)               | DD (n = 3) |
| Age (years)          | 11.6 (4.9)              | 13.5 (8.1)               | 12.5 (6.9) |
|                      | 10.2 (4.8)              | 11.0 (3.9)               | 10.6 (3.6) |
|                      | 9.7 (2.8)               | 14.4 (6.1)               | 11.1 (n/a) |
| Height (cm)          | 146 (28)                | 149 (30)                 | 156 (41) |
|                      | 137 (32)                | 145 (25)                 | 139 (25) |
|                      | 135 (28)                | 145 (28)                 | 140 (n/a) |
| Weight (kg)          | 38.5 (26.6)             | 42.0 (23.5)              | 55.5 (41.6) |
|                      | 29.6 (20.0)             | 32.0 (20.2)              | 34.9 (20.7) |
|                      | 30.1 (18.3)             | 36.2 (31.9)              | 30.7 (n/a) |
| SBP (mm Hg)          | 99 (15)                 | 100 (13)                 | 109 (14) |
|                      | 99 (19)                 | 99 (17)                  | 101 (16) |
|                      | 103 (28)                | 110 (23)                 | 97 (n/a) |
| DBP (mm Hg)          | 55 (13)                 | 53 (12)                  | 55 (19) |
|                      | 57 (13)                 | 53 (17)                  | 57 (17) |
|                      | 58 (14)                 | 69 (9)                   | 50 (n/a) |
| AV valve regurgitation, n (%) | | | |
| None-mild            | 95 (88%)                | 14 (93%)                 | 8 (89%) |
|                      | 43 (90%)                | 11 (65%)                 | 12 (86%) |
|                      | 14 (67%)                | 2 (50%)                  | 2 (67%) |
| Moderate-severe      | 13 (12%)                | 1 (7%)                   | 1 (11%) |
|                      | 5 (10%)                 | 6 (35%)                  | 2 (14%) |
|                      | 7 (33%)                 | 2 (50%)                  | 1 (33%) |
| EF (%)               | 63 (10)                 | 44 (5)                   | 63 (16) |
|                      | 59 (14)                 | 44 (7)                   | 66 (16) |
|                      | 64 (10)                 | 40 (16)                  | 72 (n/a) |
| EDV (mL/m²)          | 54 (22)                 | 56 (18)                  | 33 (6) |
|                      | 64 (23)                 | 64 (29)                  | 46 (17) |
|                      | 51 (23)                 | 49 (44)                  | 33 (n/a) |
| ESV (mL/m²)          | 21 (9)                  | 32 (12)                  | 12 (7) |
|                      | 25 (15)                 | 36 (21)                  | 15 (7) |
|                      | 18 (8)                  | 28 (29)                  | 11 (n/a) |
| Lateral e' (cm/s)    | 10.0 (4.2)              | 9.1 (3.1)                | 7.7 (2.0) |
|                      | 7.9 (3.0)               | 8.6 (3.2)                | 5.9 (2.3) |
|                      | 10.1 (4.3)              | 9.7 (3.1)                | 8.2 (n/a) |
| Lateral E:e'         | 6.9 (3.0)               | 7.2 (3.5)                | 10.1 (1.5) |
|                      | 10.0 (3.5)              | 7.3 (2.4)                | 19.1 (7.5) |
|                      | 6.4 (3.9)               | 7.2 (2.5)                | 10.3 (n/a) |
| Lateral E:e'/EDV (1/mL/m²) | 0.12 (0.08)            | 0.11 (0.07)              | 0.27 (0.04) |
|                      | 0.14 (0.08)             | 0.12 (0.06)              | 0.38 (0.18) |
|                      | 0.14 (0.07)             | 0.12 (0.06)              | 0.28 (n/a) |
| Ventricle mass (g/m²) | 62 (21)                | 69 (31)                  | 50 (17) |
|                      | 66 (27)                 | 63 (20)                  | 64 (36) |
|                      | 84 (26)                 | 65 (34)                  | 88 (n/a) |
| Mass:Volume (g/mL)   | 1.1 (0.4)               | 1.2 (0.2)                | 1.5 (0.7) |
|                      | 1.1 (0.4)               | 1.1 (0.3)                | 1.3 (0.4) |
|                      | 1.5 (0.6)               | 1.3 (0.2)                | 2.3 (n/a) |
| BNP                  | 18 (28)                 | 20 (30)                  | 17 (39) |
|                      | 15 (14)                 | 17 (20)                  | 15 (16) |
|                      | 22 (18)                 | 18 (30)                  | 27 (n/a) |

Results reported as median (interquartile range) or count (percentage). BNP = brain natriuretic peptide; DBP = diastolic blood pressure; DD = diastolic dysfunction; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; SBP = systolic blood pressure; SD = systolic dysfunction.