Dobutamine stress testing for the evaluation of atrial and diastolic ventricular function in Fontan patients

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INTRODUCTION

The Fontan strategy is the preferred treatment for univentricular heart defects.1 In the Fontan circulation, blood is ejected by the single ventricle into the aorta and systemic vasculature. Through the Fontan connection blood flows passively over the pulmonary vasculature, without the presence of a subpulmonary pump. Although this palliation results in (near) normal aortic oxygen saturation and eliminates single ventricular volume overload, the unique physiology of a Fontan circulation can result in a myriad of complications in the long term, including arrhythmia, thromboembolism, protein losing enteropathy and plastic bronchitis.1

In the common concept of the Fontan circulation the ‘bottle-necks’ in this circulation include (1) potentially suboptimal flow in the baffle connecting the inferior caval vein to the pulmonary arteries, (2) limited pulmonary venous return to the single ventricle because of passive pulmonary flow with abnormal pulsatility, (3) inflow impairment into the single ventricle related to diastolic dysfunction and (4) systolic single ventricular dysfunction.2 3 Many patients have normal systolic function yet impaired circulatory function. Ventricular inflow impairment relates to several factors.
including, among others, ventricular diastolic properties and atrial function. Remarkably the contribution of the atria in the Fontan circulation has been poorly studied.

Previously we demonstrated that atrial and ventricular diastolic function at rest—measured by cardiac MRI (CMR)—are not related to outcomes in Fontan patients. Patients with a Fontan circulation have an abnormal diastolic function response to dobutamine stress, compared with age-related controls. This results in a decrease of single ventricle end diastolic volume (EDV) during the dobutamine stress. Imaging during dobutamine stress can be used to unmask occult dysfunction and has been linked to clinical outcomes.

In this study, we aimed to assess atrial and ventricular diastolic function during rest and dobutamine stress CMR in Fontan patients and relate the dobutamine stress response to exercise capacity and events during the follow-up. We hypothesise the atrial and ventricular response to dobutamine stress allows for a better characterisation of single ventricular inflow impairment than measurements obtained during a resting state and relates to clinical outcome.

METHODS

Study design

We performed a secondary analysis of a Dutch multicentre cross-sectional study. Inclusion criteria for this previous study were: (1) Fontan patients aged ≥8 years; (2) having undergone a staged total cavopulmonary connection (TCPC) with either intra-atrial lateral tunnel (ILT) or extracardiac conduit (ECC); (3) TCPC completion before 7 years of age; (4) at least 3 years of follow-up since completion TCPC. Exclusion criteria were severe intellectual impairment or contraindications for CMR. All subjects or their legal guardians provided written informed consent. Patients or the public were not involved in the design or execution of the study. For the current study, all subjects who successfully underwent dobutamine stress CMR with complete imaging of the atria and cardiopulmonary exercise testing were included for analysis.

CMR study

All patients underwent steady state free precession (SSFP) CMR on a 1.5T whole-body scanner. Images were obtained in either the short axis or axial orientation including complete imaging of the atria. An extended CMR protocol has been published previously. After CMR acquisition during resting conditions, the CMR study was repeated with the same imaging protocol during low-dose (7.5 µg/kg/min) intravenous dobutamine infusion. Vital parameters were monitored continually during dobutamine infusion. Imaging protocol was resumed once a new steady state in vital parameters was achieved. Dobutamine infusion was reduced to 5 µg/kg/min in case of adverse events (ie, an increase in heart rate, systolic or diastolic blood pressure of ≥20% compared with baseline or a decrease in heart rate, systolic or diastolic blood pressure of ≥20%, or if the subject experienced discomfort). If adverse events persisted, dobutamine infusion was halted.

CMR postprocessing

Segmentation was performed on a Windows workstation using Medis Suite 3.2 (Medis Medical Imaging Systems, Leiden, the Netherlands). Epicardial contours of the single ventricle were manually segmented in all phases and slices. All ventricular structures that eject in the aorta were segmented as a functional single ventricle. Endocardial segmentation of the ventricle was performed automatically by a threshold-based method (MassK, Medis Medical Imaging Systems, Leiden, the Netherlands) and manually adjusted where needed. All atrial structures that drain pulmonary venous return and unload in the single ventricle were manually segmented, considering them as a functional mono-atrium. Examples of segmentation are provided in online supplemental files. Atrioventricular connections are classified according to the

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**Table 1** Ventricular and atrial functional parameters

| Parameter                  | Definition                                                                 |
|----------------------------|---------------------------------------------------------------------------|
| **Ventricle**              |                                                                           |
| Early filling volume (mL/m²) | Ventricular filling volume during the first 1/3 of diastole                |
| Late filling volume (mL/m²)  | Ventricular filling volume during atrial contraction                      |
| Deceleration time (ms)      | Time from early peak filling rate to zero-velocity baseline, based on the linear segment of the downward slope |
| Early peak filling rate (mL/s)  | Peak filling rate during early diastole                                   |
| Late peak filling rate (mL/s)  | Peak filling rate during late diastole                                   |
| E/A ratio                   | Early peak filling rate/late peak filling rate                            |
| **Atria**                  |                                                                           |
| Maximal volume (mL/m²)      |                                                                           |
| Minimal volume (mL/m²)      |                                                                           |
| Cyclic volume change (mL/m²) | Maximal volume—minimal volume                                             |
| Early emptying volume (mL/m²) | Atrial emptying volume during early diastole, considered to reflect atrial reservoir function. |
| Late emptying volume (mL/m²) | Atrial emptying volume during late diastole, considered to reflect atrial contractile—or booster pump—function. |
| Conduit volume (mL/m²)      | Ventricular filling can occur without atrial volume change, that is, when venous return equals atriocentral flow. This conduit volume is calculated using the following formula: Ventricular stroke volume (atrial early emptying volume-atrial late emptying volume). |

All volumes are indexed for body surface area.
Congenital heart disease

sequential segmental analysis categorisation by Anderson and Shirali. Functional parameters were derived from atrial and ventricular volume-time curves, as previously described. The reserve of a functional parameter is defined as ‘dobutamine stress value minus resting value’. Functional parameters are summarised in table 1.

Volumes are indexed for body surface area, derived using the Haycock et al formula.

Outcomes

Exercise capacity and events during the follow-up were assessed. All subjects underwent cardiopulmonary exercise testing on the same day as CMR examination, as previously described. Peak oxygen uptake (averaged over the final 30 s of testing) was assessed for patients with maximal exercise capacity (defined as respiratory exchange ratio (RER) ≥1.05). Ventilatory efficiency (VE/CO2) slope during submaximal exercise was assessed for all patients.

Patient records were abstracted for events during the follow-up. The day of study visit was considered day 0 for follow-up. Events were assessed as a composite endpoint, consisting of: death; listing for heart transplant; arrhythmia (defined as any arrhythmia requiring medication or intervention); and reintervention (both surgical and catheter-based reinterventions).

Statistical analysis

Continuous data are presented as median (IQR). Continuous data were compared using the non-parametric Wilcoxon test. Paired tests were used for the comparison of rest and stress measurements. Categorical data are

### Table 2

| Study population | ECC | ILT | P value |
|------------------|-----|-----|---------|
| N                | 57  | 26  | 31      |
| Sex (male)       | 37  | 15  | 22      | 0.296 |
| Age at study (years) | 12.8 | 11.9 | 13.6 | 0.228 |
| Age at Fontan (years) | 2.9 | 3.1 | 2.9  | 0.594 |
| BSA (m²)         | 1.34 | 1.37 | 1.28  | 0.867 |
| Dominant ventricle |    |     | 0.174  |
| Left             | 39  | 20  | 19      |
| Right            | 17  | 5   | 12      |
| Undetermined     | 1   | 1   | 0       |
| Cardiac diagnosis |    |     |         |
| TA               | 13  | 9   | 4       | 0.052 |
| DILV             | 10  | 3   | 7       | 0.275 |
| DORV             | 10  | 2   | 8       | 0.073 |
| PA+IVS           | 7   | 4   | 3       | 0.513 |
| HLHS             | 7   | 3   | 4       | 0.876 |
| Other            | 10  | 5   | 5       | 0.759 |
| Heterotaxy syndrome | 7   | 3   | 4       | 0.876 |
| AV valve regurgitation |     |     |         |
| None to trivial  | 40  | 18  | 22      | 0.882 |
| Moderate to severe | 17  | 8   | 9       |
| VE/VCO₂ slope (%) | 108.7 (101.3–118.7) | 106.0 (101.5–112.3) | 112.2 (101.5–148.6) | 0.042 |
| RER≥1.05 (n)     | 37  | 20  | 17      | 0.082 |
| Peak oxygen uptake (% predicted) | 81.5 (66.2–93.7) | 82.7 (67.6–88.4) | 78.1 (65.4–96.0) | 0.918 |

Characteristics are shown for the study population and for both surgical modifications. Exercise capacity is shown as percentage of predicted value. P values reflect the difference between surgical modifications.

AV, atrioventricular; DILV, double inlet left ventricle; DORV, double outlet right ventricle; ECC, extracardiac conduit; HLHS, hypoplastic left heart syndrome; ILT, intra-atrial lateral tunnel; MA, mitral atresia; PA+IVS, pulmonary atresia with intact ventricular septum; RER, respiratory exchange ratio; TA, tricuspid atresia; VE/VCO₂, ventilatory efficiency.
presented as count (percentage) and compared using the \( \chi^2 \) test or Fisher's exact test for tests including counts of zero. Correlations were assessed by the non-parametric Spearman's \( \rho \).

Events during follow-up were assessed by Cox proportional hazards models. A \( p<0.05 \) was considered statistically significant. All statistical tests with regard to outcome were adjusted for multiple testing using the Benjamini-Hochberg procedure. All analyses were performed using R V.3.6.1 (R Core Team, 2019, Vienna, Austria).

**RESULTS**

**Patient characteristics**

We identified 57 unique patients with complete examinations. Patient characteristics are shown in table 2. Twenty-six patients with an ECC Fontan modification and 31 patients with an ILT Fontan modification were included. Median age was 12.8 years (range 8.4–26.3).

Thirty-nine patients had a dominant left ventricle (LV), 17 had a dominant right ventricle (RV) and 1 patient had a single ventricle of undetermined morphology. Patients with an LV and RV had similar age (13.2 (10.5–15.6) for LV vs 12.8 (10.3–15.5) for RV, \( p=0.737 \)) and body surface area (BSA) (\( p=0.215 \)).

Moderate-to-severe AV regurgitation was present in 17 (30%) of patients. The presence of AV regurgitation did not differ between surgical modifications (\( p=0.882 \)).

Exercise capacity in the study population was relatively well preserved. Maximal exercise effort (RER \( \geq 1.05 \)) was achieved in 37 patients. For these patients peak oxygen uptake was 82% (66 – 94) of the predicted value for age.

**Atrial response to dobutamine stress**

Atrial cyclic volume change increased from 9.7 (7.5–12.7) to 13.5 (10.1–17.0) mL/m\(^2\) during dobutamine stress (\( p<0.001 \)). Atrial early emptying volume increased by 1.9 (−1.6 to 3.6) mL/m\(^2\), \( p=0.001 \). Atrial late emptying volume increase by 2.2 (0.2–4.4) mL/m\(^2\) (\( p<0.001 \)). Conduit volume did not change during dobutamine stress (\( p=0.092 \)). For ECC patients atrial maximal volume decreased during dobutamine stress (difference −3.3 (−11 to 1.5) mL/m\(^2\)), whereas ILT patients increased maximal volume by 2.7 (−0.6 to 6.9) mL/m\(^2\) (\( p=0.001 \) for difference between ILT and ECC). Similarly, atrial conduit volume increased for ECC patients during dobutamine stress and decreased for ILT (2.7 (−2.7 to 6.5) vs −4.7 (−9.2 to −0.5) mL/m\(^2\) change, \( p=0.003 \)).

No parameter of atrial function reserve correlated with heart rate increase. Atrial response to dobutamine stress did not differ between patients with a dominant LV versus RV. Resting atrial minimal volume was higher in patients with moderate-to-severe AV regurgitation compared with those without. No differences in atrial function (reserve) was seen between patients with and without significant AV regurgitation or across groups of AV connections.

**Ventricular response to dobutamine stress**

Parameters of atrial and ventricular parameters during rest and dobutamine stress are shown in table 3. During

| Parameters                          | Rest         | Dobutamine   | Reserve     | p value |
|-------------------------------------|--------------|--------------|-------------|---------|
| **Ventricle**                       |              |              |             |         |
| Heart rate (\( /\text{min} \))      | 71.4 (62.1–87.1) | 97.1 (77.4–112.1) | 20.0 (6.0–30.7) | \(<0.001\) |
| End-diastolic volume (mL/m\(^2\))   | 96.8 (80.0–130.0) | 88.4 (72.6–111.8) | −7.5 (−15.5–1.9) | \(<0.001\) |
| End-systolic volume (mL/m\(^2\))    | 49.3 (37.8–67.1) | 38.1 (30.6–47.7) | −8.9 (−19.5–4.6) | \(<0.001\) |
| Stroke volume (mL/m\(^2\))         | 49.1 (38.6–62.2) | 53.5 (39.2–61.8) | 2.1 (−2.1–5.8) | 0.060 |
| Ejection fraction (%)               | 49.3 (42.5–55.6) | 57.6 (48.5–62.9) | 6.8 (3.6–14.2) | \(<0.001\) |
| Deceleration time (ms)              | 177 (134–240) | 176 (131–241) | −7 (−77–73) | 0.664 |
| Early filling volume (mL/m\(^2\))  | 13.6 (8.8–18.9) | 10.1 (6.6–16.1) | −1.6 (−5.7–0.7) | 0.046 |
| Atrial filling volume (mL/m\(^2\)) | 9.8 (7.6–13.0) | 10.9 (9.4–13.8) | 1.0 (−0.4–3.4) | \(<0.001\) |
| Early peak filling rate (mL/s)      | 194 (142–254) | 221 (170–272) | 30 (−1–62) | \(<0.001\) |
| Late peak filling rate (mL/s)       | 134 (99–172) | 192 (136–251) | 39 (17–106) | \(<0.001\) |
| E/A ratio                           | 1.5 (1.2–1.8) | 1.2 (0.9–1.6) | −0.2 (−0.5–0.1) | 0.001 |
| **Atria**                           |              |              |             |         |
| Maximal volume (mL/m\(^2\))        | 34.9 (28–48.3) | 37.1 (28.1–46.1) | 1.4 (−5.4–4.7) | 0.949 |
| Minimal volume (mL/m\(^2\))        | 25.6 (18.8–32.8) | 22.0 (18.0–30.3) | −2.8 (−8.5–2.4) | 0.018 |
| Cyclic volume change (mL/m\(^2\))  | 9.7 (7.5–12.7) | 13.5 (10.1–17.0) | 3.0 (0.4–5.9) | \(<0.001\) |
| Early emptying volume (mL/m\(^2\)) | 6.9 (5.3–9.1) | 8.4 (7.2–10.9) | 1.9 (−1.6–3.6) | 0.001 |
| Late emptying volume (mL/m\(^2\))  | 6.5 (4.6–8.8) | 8.9 (7.1–12.4) | 2.2 (0.2–4.4) | \(<0.001\) |
| Conduit volume (mL/m\(^2\))        | 21 (15.7–27.1) | 17.9 (12–24.7) | −2.5 (−7.6–3.6) | 0.092 |

All volumes are indexed for body surface area.
the dobutamine infusion, ventricular EDV and end-stroke volume (ESV) both decreased. Stroke index remained similar and cardiac output increased as a result of higher heart rates with dobutamine infusion (as previously reported). During the dobutamine stress, ventricular early filling volume slightly decreased and atrial contraction related (late) ventricular filling volume increased. E/A ratio decreased from 1.5 (1.2–1.8) to 1.2 (0.9–1.6). Deceleration time did not change with dobutamine stress.

DISCUSSION
We assessed atrial function and diastolic ventricular function at rest and during dobutamine stress in a cohort of young staged TCPC patients. We noted that atrial early and late emptying increased during the dobutamine stress CMR, rather than conduit volume. For ECC patients atrial early emptying volume reserve related to peak oxygen uptake. This has not been demonstrated at rest. We could not demonstrate a relationship between the type of morphology of the atria and atrioventricular connection with atrial, diastolic ventricular function or clinical outcome. No other parameters of ventricular or atrial function related to either exercise capacity or clinical events during the follow-up.

The atria are important to provide adequate drainage of pulmonary venous blood in the, often preload impaired, single ventricle in the Fontan circulation. As different complex congenital heart diseases can necessitate a Fontan palliation, the morphology and connections of the atria is highly variable in this patient population. Atrial isomerism, double inlet or absent AV connections and one or two AV valves, including hypoplastic AV annuli

| Table 4 | Correlations between functional reserve parameters and exercise capacity |
|---------|---------------------------------------------------------------|
|        | Peak oxygen uptake | VE/VCO₂ |
| Ventricle | r | P value | r | P value |
| End-diastolic volume reserve | 0.34 | 0.039 | −0.20 | 0.143 |
| End-systolic volume reserve | 0.10 | 0.560 | −0.02 | 0.879 |
| Stroke volume reserve | 0.25 | 0.139 | −0.21 | 0.115 |
| Ejection fraction (%) | 0.01 | 0.959 | −0.20 | 0.137 |
| Early filling volume reserve | 0.06 | 0.706 | −0.16 | 0.243 |
| Atrial filling volume reserve | 0.11 | 0.501 | −0.18 | 0.172 |
| Deceleration time (ms) | −0.01 | 0.943 | 0.19 | 0.176 |
| E/A ratio | 0.06 | 0.743 | −0.04 | 0.775 |
| Atria | Maximal volume reserve | 0.05 | 0.756 | 0.14 | 0.315 |
| Minimal volume reserve | −0.08 | 0.626 | 0.11 | 0.407 |
| Cyclic volume change reserve | 0.25 | 0.134 | 0.01 | 0.969 |
| Early emptying volume reserve | 0.37 | 0.026 | 0.05 | 0.719 |
| Late emptying volume reserve | 0.10 | 0.551 | −0.09 | 0.517 |
| Conduit volume reserve | −0.08 | 0.648 | −0.18 | 0.184 |

Reserve is defined as the difference between measurements during dobutamine stress and resting values. All volumes are presented as mL/m², indexed for body surface area. P values are shown unadjusted for multiple testing. No P values were considered statistically significant after adjusting for multiple testing.

Predictors of exercise capacity
Predictors of peak oxygen uptake and VE/VCO₂ slope are shown in table 4. Higher atrial early emptying volume reserve correlated with higher peak oxygen uptake (r=0.37, p=0.026), but this correlation was not considered statistically significant after adjusting for multiple testing. Stratified by Fontan modifications, only for ECC patients higher atrial early emptying volume reserve correlated with higher peak oxygen uptake (r=0.66, p=0.002). This association remained statistically significant after adjusting for multiple testing. No other functional parameter predicted peak oxygen uptake. No functional parameter predicted VE slope. Peak heart rate during exercise testing weakly correlated with heart rate during (low-dose) dobutamine stress (r=0.30, p=0.023), but also with heart rate during rest (r=0.32, p=0.014).

Predictors of events during follow-up
During a 7.1 (6.0–8.2) years follow-up 22 patients (39%) experienced a clinical event. Two patients died during the follow-up. Five patients underwent reoperation and an additional seven patients underwent interventional procedures. Thirteen patients experienced arrhythmia (12 supraventricular tachycardia; 1 third-degree AV block). One-year event-free survival estimate was 91% (84%–99%). Five years event-free survival estimate was 75% (95% CI 64% to 87%). Predictors of events during the follow-up are shown in table 5. No parameter of atrial or ventricular diastolic function predicted events during the follow-up.
are all part of the morphological spectrum of univentricular hearts. This might affect the haemodynamic relationship between the atria and both the pulmonary venous drainage and inflow into the single ventricle. In this study and with current methodology, we could not demonstrate an effect of dominant ventricular morphology or type of AV connection.

Different surgical modifications of TCPC manipulate the atria in different ways. Atrial scarring as a result of surgery might disturb the compliance and pump function of the atrium. The ECC bypasses the atria completely, whereas the ILT modification creates a baffle in the right atrium using either prosthetic or tissue material. This excludes part of the atrial volume to create a connection between the inferior caval vein and the pulmonary artery. Previously, we demonstrated ILT patients have preserved atrial volumes of the pulmonary venous atrium, despite having part of the atrial volume used to create the intra-atrial tunnel. In the current study, atrial maximal volume increased during dobutamine stress for ILT patients, while it decreased for ECC patients. This might be related to the effects of dobutamine on the part of the (contractile) atrial wall forming the intra-atrial tunnel.

Little is known about the normal atrial response to dobutamine stress. During exercise atrial, early and late emptying increase. Trained athletes have a higher increase of atrial late emptying following exercise compared with sedentary controls.

Power loss in the Fontan circuit has been studied extensively, but the pulmonary venous atrium has received little attention in this respect. Future studies that would assess flow dynamics and power loss in the pulmonary venous atrium would be of great interest. Energetically favourable flow patterns through the atria are probably necessary for a good early ventricular filling phase in the context of diminished pulmonary venous return. A better understanding of atrial (dys)function could be used to guide treatment strategies for patients with functionally univentricular congenital heart disease.

In long-standing diastolic dysfunction in structurally normal hearts, atrial pressure increases to maintain early ventricular filling. This is reflected in atrial size and function. Patients with heart failure with preserved ejection fraction have diminished atrial early and late emptying compared with healthy controls. Fontan patients, in contrast, generally have increased atrial pump function compared with health controls. We found dobutamine stress CMR reveals signs of (limited) impairment of diastolic single ventricular function, confirming earlier observations. Diastolic dysfunction of the single ventricle following Fontan palliation has previously been demonstrated using invasive measurements. 

At rest the isovolumetric relaxation constant (τ) is prolonged in Fontan patients compared with controls. During dobutamine stress, EDV decreases and end diastolic pressure remains similar. Isovolumetric relaxation shortens (as in healthy controls). In our present study, early peak filling rate and deceleration time, which are non-invasive estimates of isovolumetric relaxation, showed only a minor improvement during dobutamine stress. The ventricular stiffness constant β fails to decrease during dobutamine stress. In young Fontan patients, signs of impaired relaxation have been observed at rest. Dobutamine stress has been used to reveal diastolic dysfunction. Our present study provides non-invasive measures of diastolic function for Fontan patients during rest and dobutamine stress.

In previous research we demonstrated that the single ventricular reserve during low-dose dobutamine stress, a measure of systolic function, relates to clinical events during long-term follow-up. Despite the negative results of our current study, evaluating occult atrial and ventricular diastolic function, dobutamine stress for the evaluation of occult systolic dysfunction may be a useful tool in the clinical evaluation of (asymptomatic) Fontan patients in adolescence and early adulthood. Stressors other than dobutamine, such as physiological exercise or inotropic agents, could be considered for the evaluation of occult diastolic dysfunction in future research.

Limitations

Several limitations of our present study should be considered. The lower temporal resolution of SSFP CMR,
compared with echocardiography, can lead to underestimation or overestimation of parameters of diastolic function.22 We assessed the response to dobutamine stress using the same CMR protocol for both measurements to reduce the effect of temporal undersampling on stress reserve parameters.

Invasive measurements of atrial and ventricular pressure were not assessed due to the retrospective and non-invasive nature of our study. Non-invasive estimates of ventricular filling pressures, such as echocardiographic E/e' were well within the normal range in a previous study including similar patients.9

Dobutamine stress is considered to mimic exercise physiology. However, exercise-induced changes in respiration and activity of the lower extremities muscles could affect ventricular filling in the Fontan circulation. As respiration has a considerable effect on ventricular filling, imaging was obtained during free breathing. The contribution of respiration to ventricular filling is not exacerbated during the exercise.25 During supine exercise CMR EDV and ESV fail to increase, similar to our results, implying a limited role of these factors in augmenting preload.26-28

We assessed a large number of both atrial and ventricular parameters for multiple clinical outcomes. To minimise the probability of type 1 errors (‘false positive findings’) corrections for multiple testing were applied. Despite the relatively large sample size, the penalty for multiple testing with a large number of parameters hampered statistical power. Future research replicating our results could confirm associations which were considered statistically significant before applying this penalty.

CONCLUSIONS

We assessed the function of the pulmonary venous atrium and diastolic function of the single ventricle during resting conditions and dobutamine stress for Fontan patients of contemporary surgical modifications. Dobutamine stress increases atrial early and late emptying, rather than conduit volume. Atrial early emptying volume reserve relates to exercise capacity for patients with an ECC Fontan modification. No other parameters of atrial or ventricular diastolic function predicted outcomes. Atrial stress testing might demonstrate occult dysfunction and increase insight in ventricular inflow impairment seen in these patients.

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