CONGENITAL HEART DISEASE

Cardiac Involvement in Mulibrey Nanism: Characterization with Magnetic Resonance Imaging

Sari Kivistö,[1,]* Marita Lipsanen-Nyman,[2] Markku Kupari,[3] Pauli Hekali,[1] and Kirsi Lauerma[1]

[1]Helsinki Medical Imaging Center, [2]Department of Pediatrics, and [3]Cardiovascular Laboratory, Helsinki University Central Hospital, Helsinki, Finland

ABSTRACT

Mulibrey nanism (MUL) is an autosomal recessive disorder that is enriched in the Finnish population. Variable degrees of pericardial and myocardial involvement can lead to heart failure and premature death. The purpose of this study was using magnetic resonance imaging (MRI) to assess structural and functional abnormalities of the MUL cardiopathy in all four cardiac chambers as well as in the pericardium. Thirty-one patients with MUL (mean age 27, range 15–50 years) and 16 controls (mean age 31, range 19–45 years) were examined with a Siemens Vision 1.5-T imager. Ten patients had undergone pericardiectomies to relieve symptoms of constrictive pericarditis. In surgery performed 0.5–25 years before MRI, the removed pericardium was found to be thickened and consisting of scarlike fibrosis. Turbo spin echo images were obtained for assessment of pericardial thickness, and breath hold left ventricular (LV) short axis and four-chamber cine images were obtained for the volumetric data. In MRI, pericardial thickness was normal (under 3.4 mm) in all patients with MUL. In the 10 pericardiectomized patients, the remnants of the pericardium were of normal thickness as well. The LV septum ($p = 0.01$) and posterior wall ($p < 0.001$) were hypertrophied and end-diastolic volumes of both ventricles ($p < 0.05$) were reduced in all patients. The LV systolic function was preserved. The volume chance during the first third of diastole ($p = 0.030$), the absolute peak filling rate ($p = 0.047$), and the time to peak rate of LV diastolic filling

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*Correspondence: Sari Kivistö, M.D., Helsinki Medical Imaging Center, Helsinki University Central Hospital, Box 340, Fin 00029 Helsinki, Finland; Fax: +358-9-471-74404; E-mail: sari.kivisto@hus.fi.

($p = 0.030$) indicated restrictive LV diastolic filling. The right ventricular ejection fraction and contraction of both atria were reduced.

Key Words: Cardiac MRI; Pericardial diseases; Constrictive pericarditis; Restrictive cardiomyopathy; Diastolic dysfunction.

INTRODUCTION

Mulibrey nanism (MUL) is a genetic disorder that is enriched in the Finnish population. Only sporadic cases have been reported outside of Finland (Voorhess et al., 1976). Recently, causative mutations for this condition have been found in chromosome 17q (Avela et al., 1997, 2000). Multiple organ systems are affected in MUL (Perheentupa et al., 1973). Cardiac failure is a common and important prognostic finding. Constrictive pericarditis has been regarded as the main mechanism of heart failure, but pericardiectomy has not always been helpful. Autopsy findings suggest that myocardial fibrosis may play a role in these cases (Tuuteri et al., 1974).

Lipsanen-Nyman et al. (2003) recently described a 25-year follow-up study of MUL cardiopathy consisting of echochardiography, cardiac catheterization, and autopsy reports. Using echocardiography, they found 34 patients with left ventricular (LV) hypertrophy, left atrial dilatation, and impaired LV filling. In our present study, we have assessed characteristic features of MUL cardiopathy with magnetic resonance imaging (MRI). In addition to conventional analysis of LV mass and volume changes during the cardiac cycle, we have also analyzed pericardium, function of the right ventricle (RV), and of both atria.

MATERIALS AND METHODS

Patients and Methods

Thirty-one patients (mean age 27, range 15–50 years, 17 males, and 14 females) with clinical diagnosis of MUL (Perheentupa et al., 1973) were examined. All patients were also genetically confirmed with DNA tests. We studied two groups of MUL patients. Ten of the 31 MUL patients had undergone pericardiectomy (0.5–25 years before our MR study) for constrictive pericarditis. Pericardiectomy was done when the patient had markedly limiting symptoms of congestive heart failure associated with elevated cardiac filling pressures at catheterization. In the surgical treatment, the parietal leaf of the pericardium had been removed from the anterolateral and diaphrag-

matic aspects of the LV. The removed pericardium was found to be thickened and consisting of scarlike fibrosis devoid of cellularity (Lipsanen-Nyman et al., 2003). Twenty-one MUL patients, however, did not have severe clinical symptoms of congestive heart failure and had not been operated on. Sixteen healthy volunteers (mean age 31, range 19–45 years, 8 males, and 8 females) were examined as controls. Although we tried to select control subjects to match the small body size of the patients, differences could not avoided. Body height averaged 1.47 ± 0.10 vs. 1.54 ± 0.06 m, weight 41.4 ± 8.1 vs. 55.4 ± 11.1 kg, and body surface area 1.28 ± 0.16 vs. 1.51 ± 0.15 m^2 in the MUL and control groups, respectively ($p < 0.05$). All patients and volunteers had sinus rhythm during imaging.

MRI

The MRI of the heart was performed with 1.5-T Siemens Vision body array coil. Nine turbo spin echo T1 weighted images were obtained for the assessment of pericardial thickness. Three images with a 7-mm slice thickness and a 5-mm gap were acquired in the sagittal, axial, and coronal planes. Acquisition parameters were repetition time of one or two RR intervals (mean = 1300 ms), echo time = 30 ms, flip angle = 180, matrix = 256×256, and field of view 280–350 mm.

Breath hold gradient echo turbo flash cine images in the LV short-axis planes with 10-mm-thick slices and a 5-mm gap were obtained for the volumetric study of ventricles (Alfakih et al., 2003). Cine images in the four-chamber planes with contiguous 10-mm-thick slices were obtained for atria (Järvinen et al., 1994a,b). Imaging parameters were repetition time = 30 or 40 ms, echo time = 4.8 ms, flip angle = 20, matrix 256×256, and field of view 250–300 mm.

Image Analysis

All images were manually traced with a National Institutes of Health image program (http://rsb.info.nih.gov/nih-image). Pericardial thickness was measured from turbo spin echo T1-weighted sagittal, axial, and coronal images (Fig. 1). Pericardial analysis was done, however, from cine images in the case of one patient,
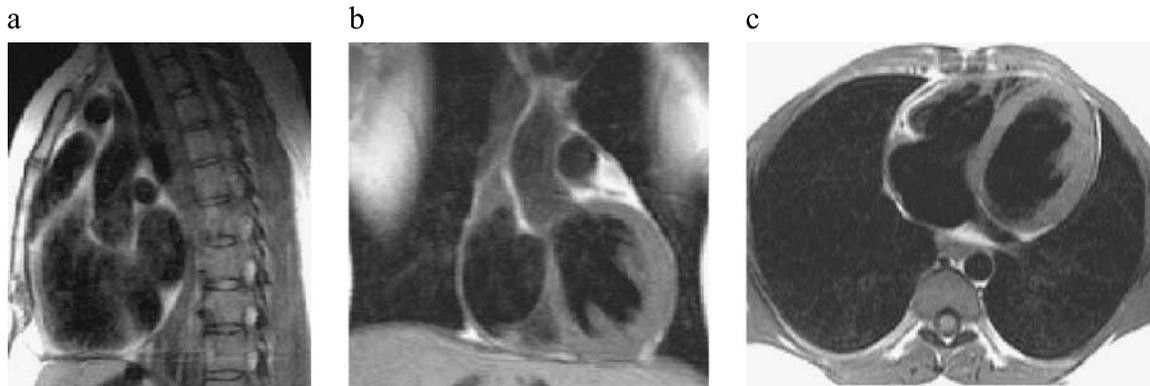
Figure 1. Turbo spin echo T1-weighted images were obtained for measurement of pericardial thickness. (a) Sagittal plane. (b) Coronal plane. (c) Axial plane.

because of the poor quality of turbo spin echo T1-weighted images. Assessment of the ventricles was done from LV short-axis images. End-diastolic volume, end-systolic volume, stroke volume, and ejection fraction of both ventricles were calculated according to modified Simpson's Rule (Alfakih et al., 2003; Soldo et al., 1994), which takes into account gap between slices. The LV end-diastolic length, width, and mass were also determined (Fig. 2). The LV mass was determined by subtracting the cavity volume from the total LV volume (= cavity + muscle), and using 1.05 g/mL as the density factor of the myocardium (Pluim et al., 1997). The LV time-volume curves were reconstructed by determining LV volume change per repetition time (30 or 40 ms) from LV short-axis cine images. The volume change during the first third of diastole, the maximal slope during diastole (peak filling rate), and the time from end-systole to peak rate of LV filling were determined (Fig. 3) (Rumberger and Lipton, 1989).

The largest and smallest volumes of both atria were assessed from four-chamber views (Fig. 4).

Modified Simpson's Rule was used to volume analysis as described (Järvinen et al., 1994a,b). Cyclic volume change (largest volume minus smallest volume) and fractional emptying (cyclic volume divided by largest volume) were also determined. One male patient and one female control were excluded from atrial analysis because of poor image quality.

Statistics

The MUL patients were divided into groups with ($n = 10$) and without ($n = 21$) a history of pericardiectomy. They were compared to each other and to normal controls ($n = 16$). Comparisons across the three group means were done by using an analysis of variance (ANOVA) incorporating sex as a second grouping factor. To adjust for differences in body size, body height, and weight were used as covariates when comparing the MRI data on cardiac anatomy between the MUL patients and the controls. A p value of < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with
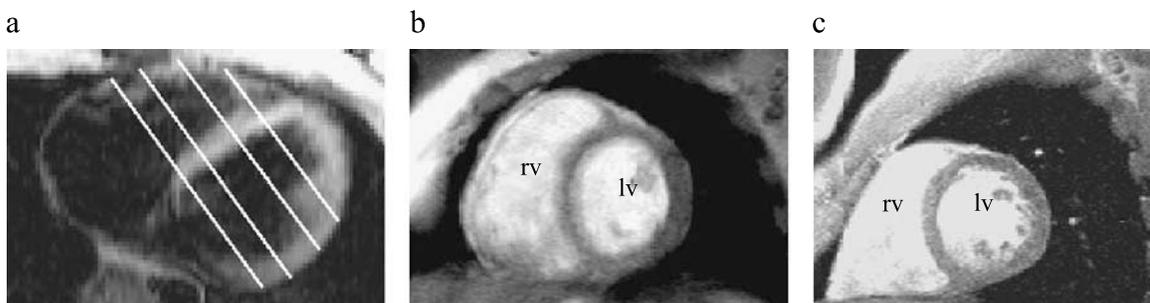
Figure 2. Breath hold left ventricular short-axis images were obtained for the volumetric measurements of both ventricles. (a) Four-chamber scout image. (b) Mulibrey nanism patient. (c) Control.
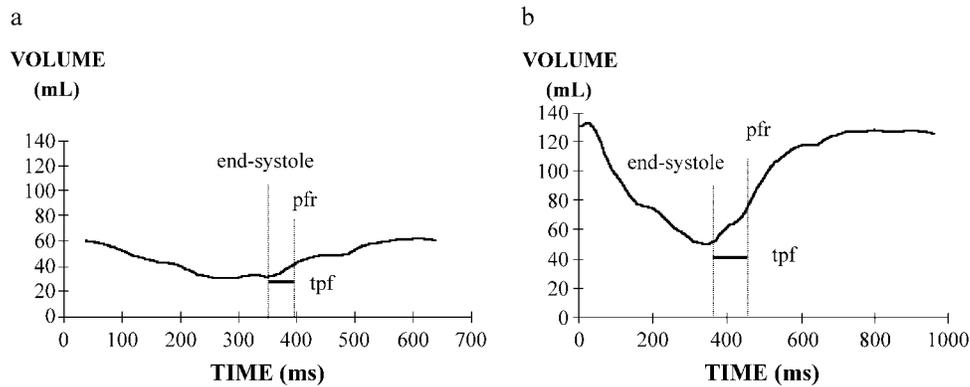
Figure 3. Left ventricular time-volume curves. (a) Mulibrey nanism patient (PFR = 254 mL/sec, TPF 0.04 sec). (b) Control (PFR = 482 mL/sec, TPF 0.12 sec). *Key*: PFR, absolute peak filling rate of the left ventricle; TPF, time from end systole to occurrence of peak rate of ventricular diastolic filling.

commercially available software (SYSTAT version 10.1, Systat Inc.).

The study was approved by the human research committee of the Helsinki University Central Hospital, and all subjects gave informed consent for the study.

RESULTS

Heart rate was similar in both groups (MUL $70 + 11$, controls $67 + 16$/min, $p = 0.29$). Significant valvular regurgitations were not observed (Lipton and Coulden, 1999).

The thickness of pericardium was normal (under 3.5 mm) in all 31 MUL patients (Hartnell et al., 1996; Stark et al., 1984). In the 10 pericardiectomized patients, the remnants of the pericardium were of normal thickness as well. Pericardial fluid was not present. Among MUL patients without a past pericardiectomy, one male had a 3.3-mm-thick parietal leaf near the posterior wall of the RV. In the rest, the maximal thickness of pericardium was less than 2.6 mm. In all of the MUL patients with past pericardiectomies ($n = 10$), the parietal leaf had been removed from the anterolateral and diaphracmatic aspects of the LV, but it was partly present in the atrioventricular sulci, and around the right atrium and ventricle in eight patients. The maximal thickness of parietal pericardium was 3.3 mm around the RV posterior wall in one patient and less than 2.9 mm in the rest.

The LV and RV volumes, mass, and wall thickness are presented in Table 1, which shows that LV and RV end-diastolic volumes were significantly smaller in MUL patients than in controls. In MUL patients, the
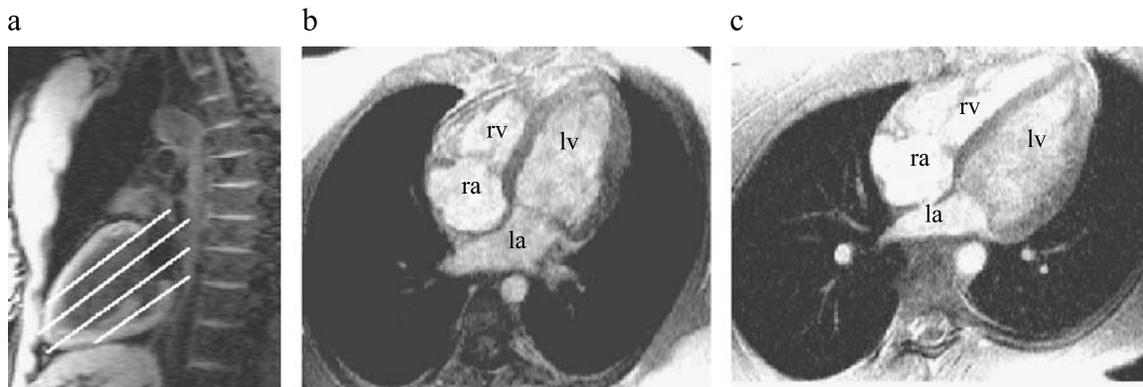
Figure 4. Four-chamber views were obtained for measurement of both atrial volumes and assessment of atrioventricular valve functions. (a) Sagittal scout image. (b) Mulibrey nanism patient. (c) Control.

Table 1. Ventricular volumes, LV mass, and wall thickness of 31 MUL patients and 16 healthy controls.

	MUL patients (*n* = 10) pericardiectomy +	MUL patients (*n* = 21) pericardiectomy −	Controls (*n* = 16)	*p*
LV end-diastolic volume (mL)	75 ± 5	76 ± 8	104 ± 6	0.008
LV mass (g)	107 ± 6	105 ± 9	85 ± 7	0.104
Interventricular septal thickness (mm)	9.0 ± 0.4	10.4 ± 0.6	6.6 ± 0.5	0.001
Posterior wall thickness (mm)	12.6 ± 0.4	11.2 ± 0.6	9.3 ± 0.5	< 0.001
LV ejection fraction (%)[a]	63 ± 2	61 ± 3	62 ± 2	0.755
RV end-diastolic volume (ml)	51 ± 5	57 ± 8	98 ± 6	0.000
RV ejection fraction (%)[a]	51 ± 2	47 ± 3	62 ± 2	< 0.001

Abbreviations: LV = left ventricle; RV = right ventricle.
Values are means ± SD. Adjusted for body height and weight.
The *p* values across the three groups from ANOVA with sex as a second grouping factor and height and weight as covariates.
[a]Group comparisons were made without adjusting for differences in body size.

Table 2. Diastolic filling variables assessed by LV diastolic time-volume curve in MUL patients and controls.

	MUL patients (*n* = 31)	Controls (*n* = 16)	*p*
The volume change during the first third of diastole (%)	72 ± 2	63 ± 3	0.030
PFR (mL/sec)	311 ± 23	393 ± 33	0.047
TPF (sec)	96 ± 9	131 ± 13	0.030

Abbreviations: PFR = absolute peak filling rate; TPF = time from end systole to occurrence of peak rate of ventricular diastolic filling.
Values are means ± SD.
The *p* values across the tree groups from ANOVA with sex as a second grouping factor. Sex had no statistically significant main effects or interactions on any variable.

Table 3. Atrial volumes of 30 MUL patients and 15 healthy controls.

	MUL patients (*n* = 10) pericardiectomy +	MUL patients (*n* = 20) pericardiectomy −	Controls (*n* = 15)	*p*
LA largest volume (mL)	49 ± 4	45 ± 6	48 ± 5	0.860
LA smallest volume (mL)	34 ± 2	33 ± 4	28 ± 3	0.321
RA largest volume (mL)	50 ± 4	48 ± 6	49 ± 5	0.972
RA smallest volume (mL)	35 ± 3	35 ± 5	30 ± 4	0.618
Left atrium-ventricle ratio	0.63 ± 0.04	0.64 ± 0.06	0.50 ± 0.04	0.062
Right atrium-ventricle ratio	0.64 ± 0.04	0.67 ± 0.06	0.53 ± 0.05	0.093
LA cyclic volume (mL)	14 ± 1	13 ± 2	20 ± 2	0.048
RA cyclic volume (mL)	13 ± 2	12 ± 2	20 ± 2	0.041
LA fractional emptying (%)	31 ± 2	26 ± 2	40 ± 2	0.009
RA fractional emptying (%)	29 ± 2	25 ± 3	38 ± 2	0.001

Abbreviations: LA = left atrium; RA = right atrium.
Values are means ± SD.
The *p* values across the three groups from ANOVA with sex as a second grouping factor and height and weight as covariates. Sex had no statistically significant main effects or interactions with disease status.

interventricular septum and LV posterior wall were thicker, but LV mass was not significantly higher than in controls. The end-diastolic length-width ratio of LV was significantly smaller in patients than in controls (MUL 1.55 ± 0.2; controls 1.73 ± 0.3; $p < 0.05$). The LV ejection fraction did not differ across the groups, but the RV ejection fraction was lower in MUL patients. Sex had an independent main effect on thickness of the LV posterior wall (male 10.0 ± 0.5; female 12.0 ± 0.5 mm; $p = 0.025$) and the LV ejection fraction (male 67 ± 2; female $57 \pm 2\%$; $p < 0.001$). There were no statistical differences between the patient groups with and without pericardiectomy.

Table 2 shows the variables derived from LV diastolic time-volume curves compared across patients and controls. MUL patients had a larger early one-third diastolic volume change, a reduced absolute peak filling rate, and a shorter time to the point of peak rate of LV filling.

Table 3 summarizes left and right atrial measurements. The atrium-ventricle ratio of both sides was found to be increased, indicating mild dilatation of both atria in MUL patients. The cyclic volume change and fractional emptying of both atria were lower in MUL patients, especially in those who had not had a pericardiectomy.

DISCUSSION

The major observations on hearts of MUL patients were as follows. Pericardial thickness was normal in all MUL patients. In the 10 pericardiectomized patients, the remnants of the pericardium were of normal thickness as well. Both left and right ventricular diastolic volumes were decreased whereas LV wall thickness was increased. The length–width ratio of the LV was significantly smaller in MUL patients. The LV diastolic filling was altered in a restrictive manner, although systolic function was preserved. The RV ejection fraction was reduced. Both atria were mildly enlarged, and the reservoir function of both atria was diminished.

In addition to earlier echocardiographic findings (Lipsanen-Nyman et al., 2003), we discovered the following features of MUL cardiopathy. 1) The thickness of the pericardium was normal in the patient group ($n = 21$) that had not needed pericardiectomy for congestive heart disease. 2) There was a difference in the shape of LV cavity in MUL patients, indicated by the smaller end-diastolic length–width ratio, than that of normal controls. With MRI we acquired more accurate results for LV mass and cyclic volumes than

echocardiography, which uses ellipsoidal model for measurements (Pluim et al., 1997). 3) By using the accurate measures afforded by MRI, the RV diastolic volumes have been decreased compared to controls. 4) Volumetric data of both atria showed relative dilatation compared with the ventricles as well as decreased reservoir function. Both of these findings are indicative of ventricular restriction in MUL cardiopathy.

The thickness of the pericardium was normal and free of calcification in all 31 MUL patients, including the remnants of pericardium in patients who had undergone pericardiectomy before MRI. We chose to determine pericardial thickness using turbo spin echo T1-weighted images, where the iso- or hypointense pericardium can be differentiated from the myocardium. This is because spin echo imaging does not overestimate the thickness as often as gradient echo sequences do in the presence of pericardial fluid and calcification (Masui et al., 1992; Soulen, 1991). Thus, normal pericardial thickness is usually less than 3.5–4 mm in turbo spin echo images (Hartnell et al., 1996; Stark et al., 1984). Importantly, a pericardium with normal thickness can also cause constriction if it is fibrotic or found to be adhered to the myocardium (Frank and Globits, 1999; Hartnell et al., 1996).

MR cine imaging is a method of choice in the volumetric assessment of both left and right side of the heart (Järvinen et al., 1994a,b; Pattynama et al., 1995; Soldo et al., 1994). We analyzed ventricular volumes from short-axis images (Pattynama et al., 1995; Soldo et al., 1994) and atrial volumes from four-chamber view images (Järvinen et al., 1994a,b). In MUL patients, the muscle of interventricular septum and posterior wall were thicker than in controls. Because of the shorter left ventricle, the LV mass was increased, but not significantly. Autopsies of 11 MUL patients have shown myocardial hypertrophy and mild myocardial fibrosis (Lipsanen-Nyman et al., 2003). In MUL cardiopathy, end-diastolic volumes of both ventricles were reduced. The volumes were also small in the patients with past pericardiectomy. It is known that LV end-diastolic volumes increase after a pericardiectomy if the myocardium is not atrophic (prolonged pericardial compression) or fibrotic (radiation-induced cardiac diseases or autoimmune diseases) (Senni et al., 1999). In MUL cardiopathy, myocardial fibrosis and hypertrophy, combined with an adhered visceral pericardium, explain the reduced diastolic ventricular volumes even in patients with previous pericardiectomy. The RV ejection fraction was reduced, suggesting elevated afterload due to LV diastolic impairment.

The volume change during the first third of diastole was larger, the absolute peak filling rate was

reduced, and the time to peak filling was significantly shorter in MUL patients relative to controls, and there was no difference in these measurements between patients with and without past pericardiectomy. Viewed together with the reduced LV end-diastolic volume, these changes suggest an increased speed of early LV filling due to impaired passive filling during later diastole. The LV filling is altered in a restrictive manner and is due to both myocardial and pericardial abnormality. The MR results on LV diastolic function of MUL cardiopathy are in concordance with the Doppler echo findings reported previously (Lipsanen-Nyman et al., 2003).

Considering the rarity of the disease, our patient group was homogeneous and large. The limitations of our study were that the MUL and control groups were not fully matched for body size and that we were not able to study the same patients before and after their pericardiectomy. Time-dependent LV volume analysis has a relatively low time resolution, which reduces its ability to show changes in ventricular diastolic filling. Flow velocity mapping through mitral and tricuspid valves would have given more detailed information about ventricular diastolic filling.

Magnetic resonance imaging is a reliable, noninvasive method for characterization of different types of cardiomyopathies. It has been established as a method of choice in the assessment of LV systolic function and pericardial disease. The same imaging sequences can be used to analyze all four cardiac chambers throughout the systole and the diastole. With this method we observed early changes of MUL cardiopathy. Modern cardiac MRI protocol should include the analysis of all cardiac chambers during systole and diastole to assess the early marks of cardiac diseases affecting first diastolic function and function of both atria and RV.

CONCLUSION

Using MRI we have been able to show that MUL cardiopathy is characterized by concentric LV hypertrophy and restrictive filling. Although LV systolic function was preserved, both atria were mildly enlarged and RV ejection fraction and contraction of both atria were reduced, suggesting elevated afterload due to LV diastolic impairment.

ACKNOWLEDGMENTS

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