MEDIUM-TERM VENTRICULAR FUNCTION IN POST-FONTAN OPERATION PATIENTS

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Abstract. The Fontan operation is a definitive palliative cardiovascular surgery for single ventricle physiology in congenital heart diseases. Ventricular failure is a serious long-term complication associated with this operation that results in decreased quality of life and increased mortality. This cross sectional study evaluated myocardial function by echocardiography at various medium-term time intervals in 48 patients who underwent Fontan operation during January 1989 to June 2012. Patients were divided into 3 groups according to duration since Fontan operation (Group I: <5 years; Group II: 5-10 years; and, Group III >10 years). While we found no differences in systolic ventricular function by Simpson method or in diastolic function by pulse wave Doppler among the three groups of post-Fontan operation patients, diastolic function by pulse wave Doppler and tissue Doppler imaging (TDI) revealed significantly changed E wave, A wave, E/A ratio, and E/E' in all patients compared to a normal population. We also observed progressively increasing myocardial function impairment over time. Importantly, tissue Doppler imaging by E'/A' in Group III was significantly lower than in Group I and Group II (p=0.016). Moreover, in Group III, the medial TDI Tei index of right ventricular morphology was significantly increased compared to normal population (p=0.041), which is suggestive of impaired myocardial function. From these findings, we conclude that post-Fontan patients gradually develop ventricular diastolic dysfunction over time, and that the parameters for early detection of worsening diastolic dysfunction are tissue Doppler imaging by medial E'/A' to detect significantly decreased diastolic function and Tei index to detect overall RV dysfunction.

Keywords: Fontan operation, ventricular function, single ventricle

INTRODUCTION

The Fontan procedure is a standard palliative operation for single ventricle physiology that connects systemic veins to pulmonary arteries that has been used since 1968 when it was first described by Fontan and Baudet (1971). Candidates for this operation are patients with single ventricular physiology, including those with tricuspid atresia, double inlet left ventricle, hypoplastic right ventricle, pulmonary atresia with intact ventricular septum, hypoplastic left heart syndrome (HLHS), and heterotaxy syndromes. Despite improvements in surgical technique to minimize long-term complications, complications continue to be observed in long-term follow-up (d'Udekem *et al*, 2007). Late compli-

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cations, including pathway obstruction, cardiac arrhythmias, ventricular failure, thromboembolic events, progressive cyanosis, and protein-losing enteropathy, can all adversely affect length and quality of life in this patient population (Gentles *et al*, 1997; van den Bosch *et al*, 2004; Ono *et al*, 2006; d'Udekem *et al*, 2007; Khairy *et al*, 2008). Follow-up evaluation in these patients should, therefore, aim for early detection of progressively worsening myocardial function.

A failing systemic ventricle can be the result of diastolic dysfunction, systolic dysfunction, or both. Ejection fraction of the systemic ventricle <60% was reported to be associated with increased early mortality (Yoshimura *et al*, 2001). Various modalities have been used to assess ventricular function, including echocardiography, cardiac catheterization, radionuclide study, and magnetic resonance imaging (MRI) (Brown *et al*, 2010; Basu *et al*, 2013). Echocardiography is a non-invasive modality that is relatively inexpensive, widely available, and relatively uncomplicated to perform.

According to our review of the literature, many studies have been conducted in evaluation of myocardial function after Fontan operation. However, early detection of myocardial dysfunction by echocardiography is still an issue of interested. Accordingly, the aim of this study was to assess myocardial function in post-Fontan operation patients using advanced Doppler imaging to determine myocardial dysfunction that develop over the medium term, as well as the sensible echocardiographic parameters for the early detection.

MATERIALS AND METHODS

This cross sectional study evaluated myocardial function by echocardiography at various medium-term time intervals in patients who underwent Fontan operation at the Department of Pediatrics, Siriraj Hospital during January 1989 to June 2012. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. Written informed consent was obtained from all study participants. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (approval no. *Si*062/2011). This study complied with all of the principles set forth in the Declaration of Helsinki (1964) and all of its subsequent provisions.

Patients were divided into 3 groups according to duration since Fontan operation (Group I: <5 years; Group II: 5-10 years; and, Group III >10 years) and a retrospective chart review was conducted. Demographic, cardiovascular examination, echocardiographic, cardiac catheterization, perioperative, and follow-up (oxygen saturation, functional class, and clinical status) data were collected. Data relating to the intervention or reoperation and complications were also recorded and analyzed. Data from normal population that were used for comparative purposes in this study were available from a previously published studies (O'Leary *et al*, 1998; Cui and Roberson, 2006; Roberson and Cui, 2007).

Every included patient was scheduled to return to Siriraj Hospital to undergo full structural study and study of ventricular function by echocardiography. Study was performed using a Philips iE 33 echocardiography machine (Philips Healthcare, Andover, MA). Cardiac structure was evaluated using 2-dimentional and color Doppler flow to evaluate the Fontan circuit, pulmonary venous drainage, size of pulmonary artery branches, degree of systemic atrioventricular valve regurgitation, ventricular outflow tract, and morphology of the systemic ventricle. Systolic ventricular function was assessed via ejection fraction using Simpson's method and diastolic function was evaluated by pulse wave Doppler (PWD) and tissue Doppler imaging (TDI) (*ie*, E wave and E' wave velocities, A wave and A' wave velocities, E/A and E'/A'

ratios, respectively, as well as deceleration time and isovolumic relaxation time). Lastly, global ventricular function was evaluated using ventricular myocardial performance index (MPI) by PWD Tei index and TDI Tei index, which are shown in Fig 1 and Fig 2, respectively. Fig 3 describes the position of the echocardiographic cursor when measuring medial TDI.

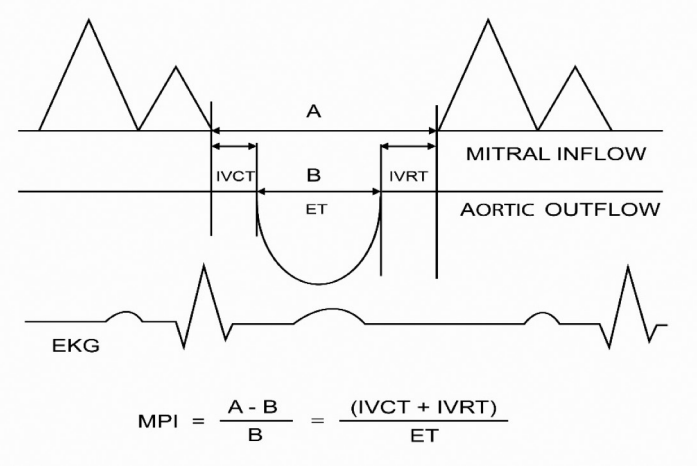

Fig 1– Measurement of pulse wave Doppler myocardial performance index (MPI) or Tei index. ET, ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; MPI, myocardial performance index.

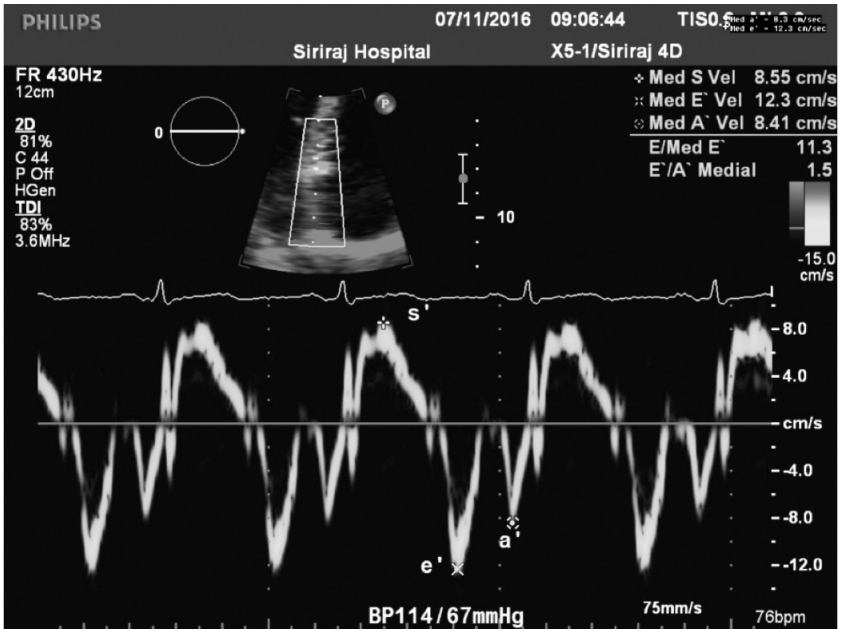

Fig 2– Measurement of tissue Doppler imaging Tei index. A', tissue Doppler imaging during late diastole; E', tissue Doppler imaging during early diastole; S', tissue Doppler imaging during systole.

All data analysis was performed using SPSS Statistics version 15 (SPSS, Chicago, IL). Continuous variables are expressed as mean ± standard deviation or median and range. Categorical variables are presented as frequency and percentage. Baseline data of patients in the three study groups were analyzed by one-way ANOVA, followed by Bonferroni correction for multiple comparisons of continuous variables. Chi-square test was used to analyze categorical variables. One-sample *t*-test was used to analyze data compared to normal values. A *p*-value<0.05 was regarded as being statistically significant.

RESULTS

Forty-eight patients were included in this study, including 25 males and 23 females. There were 15, 19, and 14 patients in Group I, Group II, and Group III, respectively. Demographic and clinical data of patients in each group are shown in Table 1. Patients in Group III had significantly lower mean oxygen saturation than patients in Groups I and II. Most of the patients in Groups I and II were diagnosed with univentricular heart, whereas most of the patients in Group III were diagnosed with tricuspid atresia. The majority of morphologic systemic ventricle in Group I was mixed morphology, but most of the patients in Group II and Group III had left ventricular morphology.

Pre-Fontan operation data from echocardiography and cardiac catheterization were not significantly different among groups, as shown in Table 2. Every patient in Group I and the majority of patients in Group II (89.5%) underwent extracardiac Fontan operation, whereas the majority of patients in Group III (50%) underwent lateral tunnel Fontan operation. Only one (7.1%) patient in Group III underwent extracardiac Fontan. There was no significant difference among groups regarding degree of either systemic atrioventricular valve regurgitation or branch pulmonary artery stenosis. Fontan circuit obstruction and abnormal pulmonary venous drainage were not observed in all patients.

Fig 3– The black arrow indicates the location where the cursor of the echocardiography machine should be positioned when measuring medial tissue Doppler imaging (TDI).

Table 1
Demographic data, oxygen saturation, functional class, and diagnosis in each patient group.

Parameters	Group I (*n*=15)	Group II (*n*=19)	Group III (*n*=14)	*p*-value
Age (yrs), mean±SD	10.9±4.3	15.7±6.5	24.1±8.8	<0.001*
Gender, *n* (%)				
Male	10 (66.7)	11 (57.9)	4 (28.6)	0.098
Female	5 (33.3)	8 (42.1)	10 (71.4)	-
Weight (kg), mean±SD	29.7±11.7	45.9±15.8	53.6±8.8	<0.001*
Height (cm), mean±SD	133.4±16.9	151.0±15.0	161.8±9.0	<0.001*
Duration after Fontan operation (yr), mean±SD	3.43±1.40	7.31±1.29	13.43±2.01	-
O_2 saturation (%), mean±SD	96.2±2.8	95.8±2.3	92.3±3.9	0.03*
Functional class (FC), *n* (%)				
FC I	13 (86.7)	17 (89.5)	11 (78.6)	0.452
FC II	1 (6.6)	2 (10.5)	3 (21.4)	0.165
FC III	1 (6.6)	0 (0)	0 (0)	-
Clinical heart failure, *n* (%)				
No	14 (93.3)	19 (100)	14 (100)	0.325
Yes	1 (6.7)	0 (0)	0 (0)	-
Diagnosis, *n* (%)				
Tricuspid atresia	2 (13.3)	7 (36.8)	8 (57.0)	0.037*
Single ventricle	8 (53.3)	10 (52.6)	6 (43.0)	0.342
Heterotaxy syndrome	5 (33.3)	1 (5.3)	0 (0)	-
Hypoplastic left heart syndrome	0 (0)	1 (5.3)	0 (0)	-
Systemic ventricular morphology				
LV morphology	3 (20.0)	10 (52.6)	9 (64.3)	0.067
RV morphology	2 (13.3)	4 (21.1)	2 (14.3)	0.233
Intermediate morphology	10 (16.7)	5 (26.3)	3 (21.4)	0.212

*p<0.05 indicates statistical significanc. LV, left ventricle; RV, right ventricle.

Table 2
Pre-Fontan operation echocardiographic, cardiac catheterization, and surgical data in each patient group.

Pre-surgical data	Group I (*n*=15)	Group II (*n*=19)	Group III (*n*=14)	*p*-value
Systemic AVVR, *n* (%)				
No regurgitation	5 (33.3)	8 (42.1)	5 (35.7)	0.456
Trivial regurgitation	5 (33.3)	6 (31.6)	8 (57.1)	0.321
Mild regurgitation	4 (26.7)	5 (26.3)	1 (7.2)	0.223
Moderate regurgitation	1 (6.7)	0 (0)	0 (0)	-
McGoon ratio, mean±SD (echocardiography)	1.96±0.41	2.13±0.26	1.92±0.41	0.354
McGoon ratio, mean±SD (catheterization)	2.24±0.61	2.12±0.41	1.93±0.41	0.490
O_2 saturation (%), mean±SD	82.7±5.4	82.7±5.4	78.5±4.6	0.770
PAP (mmHg), mean±SD	11.8±2.1	14.8±4.4	16.8±16.3	0.364
PVR (Wood.unit.m^2), mean±SD	1.24±0.62	1.60±1.67	2.75±0.64	0.322
Ventricular EDP, mean±SD	11.1±2.9	12.4±2.9	7.6±2.8	0.331
Glenn operation, *n* (%)				
No	6 (40)	13 (68.4)	11 (78.6)	0.079
Yes	9 (60)	6 (31.6)	3 (21.4)	0.121
Type of Fontan operation, *n* (%)				
Lateral tunnel	0 (0)	0 (0)	7 (50.0)	<0.001*
Extracardiac	15 (100)	17 (89.5)	1 (7.1)	<0.001*
APC	0 (0)	2 (10.5)	6 (42.9)	-
Age at Fontan operation, mean±SD	7.2±3.0	8.2±5.6	10.1±7.6	0.391

*p<0.05 indicates statistical significance. APC, atriopulmonary connection; AVVR, atrioventricular valve regurgitation; EDP, end diastolic pressure; PAP, pulmonary artery pressure.

Post-Fontan operation echocardiographic data of myocardial function in each patient group are shown in Table 3. There was no significant difference in systolic and diastolic ventricular function by 2D and PWD among groups for mean ejection fraction by Simpson's method, E/A ratio, PWD Tei index, medial TDI Tei index, and lateral TDI Tei index. E wave deceleration time (DT) and isovolumic relaxation time (IVRT) were slightly progressively longer in Group II and Group III than in Group I, but the difference did not reach statistical significance.

Regarding medial TDI, a significant decreased in E'/A' ratio was observed among groups (p=0.016). However, there were no significant differences in E' wave velocity, A' wave velocity, or E'/A' ratio by lateral TDI, or for medial and lateral E/E' among groups. When we compared ventricular function by PWD Tei index and TDI Tei index among groups and with normal population (Cui and Roberson, 2006; Roberson and Cui, 2007) (Table 4), there was no difference among groups and normal population, except between medial TDI Tei index in patients who underwent Fontan operation more than 10 years (Group III) and normal population – especially patients with

Table 3
Post-Fontan operation echocardiographic data of myocardial function in each patient group.

Echocardiographic data	Group I (*n*=15)		Group II (*n*=19)		Group III (*n*=14)		*p*-value
	Mean	SD	Mean	SD	Mean	SD	
Ventricular function							
%EF (by Simpson)	60.6	7.4	60.2	9.5	62.3	8.8	0.784
PWD Tei index	0.31	0.14	0.31	0.15	0.35	0.18	0.658
Medial S' wave (cm/sec)	7.74	2.94	9.04	3.90	7.71	3.28	0.467
Lateral S' wave (cm/sec)	9.96	2.95	10.95	3.77	8.57	2.10	0.124
Medial TDI Tei index	0.41	0.09	0.40	0.09	0.47	0.15	0.249
Lateral TDI Tei index	0.40	0.07	0.43	0.13	0.42	0.21	0.899
Diastolic function							
- By PWD							
E wave (cm/sec)	75.3	18.6	70.3	21.5	70.6	18.9	0.736
A wave (cm/sec)	70.2	23.9	58.2	17.5	56.9	11.7	0.103
E/A ratio	1.12	0.28	1.23	0.23	1.24	0.39	0.469
Deceleration time (msec)	150.5	51.2	167.5	45.9	177	46.5	0.325
IVRT (msec)	66.5	16.3	68.1	18.6	77	12.2	0.207
- By medial TDI							
E' wave (cm/sec)	9.63	3.41	8.49	2.66	6.40	1.77	0.110
A' wave (cm/sec)	7.56	2.54	7.43	1.76	8.33	2.61	0.536
E'/A' ratio	1.40*	0.66	1.20	0.36	0.85*	0.38	0.016*
Medial E/E'	8.17	3.37	8.52	2.23	8.82	3.87	0.86
- By lateral TDI							
E' wave (cm/sec)	13.12	3.00	11.00	2.68	11.30	3.35	0.118
A' wave (cm/sec)	8.84	2.30	8.32	2.32	9.84	5.60	0.491
E'/A' ratio	1.55	0.46	1.42	0.56	1.30	0.53	0.468
Lateral E/E'	5.93	2.48	6.45	2.13	7.26	4.53	0.529

*$p<0.05$ indicates statistical significance. EF, ejection fraction; IVRT, isovolumic relaxation time; msec, millisecond; PWD, pulse wave Doppler; TDI, tissue Doppler imaging.

Table 4
Mean PWD Tei index and TDI Tei index for normal population and for each patient group.

Parameters	Normal population**	Group I (*n*=15)	Group II (*n*=19)	Group III (*n*=14)	*p*-value		
					Gr I and normal population	Gr II and normal population	Gr III and normal population
PWD Tei index							
RV Tei index	0.34±0.06	0.31±0.14	0.31±0.15	0.35±0.18	0.415	0.373	0.769
LV Tei index	0.36±0.07	0.31±0.14	0.31±0.15	0.35±0.18	0.194	0.148	0.911
Medial TDI Tei index							
RV Tei index	0.37±0.05	0.41±0.09	0.40±0.09	0.47±0.15	0.192	0.235	0.041*
LV Tei index	0.38±0.06	0.41±0.09	0.40±0.09	0.47±0.15	0.337	0.416	0.061
Lateral TDI Tei index							
RV Tei index	0.37±0.05	0.40±0.07	0.43±0.13	0.42±0.21	0.141	0.071	0.390
LV Tei index	0.38±0.06	0.40±0.07	0.43±0.13	0.42±0.21	0.285	0.128	0.486

Data presented as mean ± standard deviation. *$p<0.05$ indicates statistical significance. **(Cui and Roberson, 2006; O'Leary *et al*, 1998; Roberson and Cui, 2007). DT, deceleration time; IVRT, isovolumic relaxation time; LV, left ventricle; PWD, pulse wave Doppler; RV, right ventricle; TDI, tissue Doppler imaging.

Table 5
Mean diastolic function by PWD for normal population and for each patient group.

Parameters	Normal population**	Group I (*n*=15)	Group II (*n*=19)	Group III (*n*=14)	*p*-value		
					Gr I and normal population	Gr II and normal population	Gr III and normal population
E wave (cm/sec)	88.0 ± 14.0	75.3 ± 18.6	70.3 ± 21.5	70.6 ± 18.9	0.019*	0.002*	0.004*
A wave (cm/sec)	39.0 ± 8.0	70.2 ± 23.9	58.2 ± 17.5	56.9 ± 11.7	<0.001*	<0.001*	<0.001*
E/A ratio	2.3 ± 0.6	1.12 ± 0.28	1.23 ± 0.23	1.24 ± 0.39	<0.001*	<0.001*	<0.001*
DT (msec)	172.0 ± 22.0	150.5 ± 51.2	167.5 ± 45.9	177.0 ± 46.5	0.127	0.684	0.692
IVRT (msec)	74.0 ± 22.0	66.5 ± 16.3	68.1 ± 18.6	77.0 ± 12.2	0.11	0.213	0.393

Data presented as mean ± standard deviation. *p<0.05 indicates statistical significance; **(O'Leary *et al*, 1998). DT, deceleration time; IVRT, isovolumic relaxation time; msec, millisecond; PWD, pulse wave Doppler.

Table 6
Mean diastolic function by TDI for normal population and for each patient group.

Parameters	Normal population**	Group I (*n*=15)	Group II (*n*=19)	Group III (*n*=14)	*p*-value		
					Gr I and normal population	Gr II and normal population	Gr III and normal population
By medial TDI							
E' wave (cm/sec)	20.6 ± 3.8	9.63 ± 3.41	8.49 ± 2.68	6.4 ± 1.77	<0.001*	<0.001*	<0.001*
A' wave (cm/sec)	6.7 ± 1.6	7.56 ± 2.54	7.43 ± 1.76	8.33 ± 2.61	0.211	0.107	0.044*
Medial E/E'	4.7 ± 1.3	8.17 ± 3.37	8.52 ± 2.23	8.82 ± 3.87	<0.001*	<0.001*	0.002*
By lateral TDI							
E' wave (cm/sec)	20.6 ± 3.8	13.12 ± 3.0	11.0 ± 2.68	11.3 ± 3.35	<0.001*	<0.001*	<0.001*
A' wave (cm/sec)	6.7 ± 1.6	8.84 ± 2.3	8.32 ± 2.32	9.84 ± 5.6	0.004*	0.007*	0.056
Lateral E/E'	4.7 ± 1.3	5.93 ± 2.48	6.45 ± 2.13	7.26 ± 4.53	0.088	0.002*	0.055

Data presented as mean ± standard deviation. *$p<0.05$ indicates statistical significance; **(O'Leary *et al*, 1998). TDI, tissue Doppler imaging.

RV morphology (p=0.041). For diastolic function by PWD, E wave velocity, A wave velocity, and E/A ratio in post-Fontan patients were statistically different from normal population, as shown in Table 5 (O'Leary *et al*, 1998).

DISCUSSION

In this study, normal systolic function (mean ejection fraction >60% and mean systolic velocities by TDI >7 cm/sec) was demonstrated in all post-Fontan patient groups by 2D echocardiogram and TDI. This was consistent with previous studies which reported that a majority of post-Fontan patients had normal systolic function (even those with abnormal diastolic filling) by 2D echocardiography and TDI (Vitarelli *et al*, 2005; Anderson *et al*, 2008; Nakamura *et al*, 2011). We found only medial E'/A' to be significantly lower in patients with a post-Fontan duration of longer than 10 years, as compared to those with a postoperative duration less than 10 years. Consistent with the findings by Bassareo *et al* (2010), we found E'/A' by tissue Doppler imaging to be the parameter for early detection of worsening diastolic dysfunction .

This study, thus, provides novel data regarding how these patients should be diagnosed and followed. These findings supplement and build upon data from previous studies that reported systolic and diastolic dysfunction in post-Fontan patients to be single ventricle physiology that was demonstrated by various modalities (Sano *et al*, 1989; Akagi *et al*, 1993; Cheung *et al*, 2000; Williams *et al*, 2000; Mahle *et al*, 2001; Hershenson *et al*, 2010). Reported causes of ventricular dysfunction included alteration in arrangement of muscle fibers and altered ventricular geometry, which resulted from underlying congenital heart disease, chronic hypoxia secondary to myocardial necrosis/fibrosis, myocardial remodeling, reduced compliance, poor ventricular filling, asynchronous contractility, and possible continual decline in cardiac output (Penny *et al*, 1991; Gewillig, 2005). This study also found tissue Doppler imaging to be more sensitive in revealing subtle ventricular function abnormalities (both systolic and diastolic function of single ventricle physiology), as compared to age matched normal children (Hershenson *et al*, 2010). This was also able to overcome the problems associated with geometric distortion and limitations of conventional echocardiographic methods that were reported in a previous study (Bassareo *et al*, 2010). The RV TDI Tei index was higher than normal population in Fontan patients with postoperative duration greater than 10 years. These findings indicate that longer duration after Fontan operation is associated with progressive decrease in overall ventricular dysfunction especially in patients with RV morphology, which is consistent with the reported findings from other studies (Anderson *et al*, 2008; Bassareo *et al*, 2010).

In this study, impaired diastolic function demonstrated by PWD as decreased E/A ratio, decreased E wave, increased A wave, and decreased E/A ratio in post-Fontan patients and as compared to normal population were observed gradually over time, which is suggestive of progressively impaired diastolic function. The same findings were reported in other studies, as well as prolonged deceleration time and isovolumic relaxation time in post-Fontan patients (Cheung *et al*, 2000; Milanesi *et al*, 2002; Olivier *et al*, 2003), which are signs of a relative shift in diastolic filling to the later period of diastole. This may be due to reduction in ventricular compliance that is caused by increased ventricular mass. Abnormality in diastolic filling by PWD was also detected preoperatively, which suggested that abnormal diastolic performance was an inherent characteristic of a single ventricle (Olivier *et al*, 2003). In this study, diastolic function by E'/A' and ventricular Tei index, especially medial TDI, were demonstrated to be the earliest worsening parameters of ventricular function in post-Fontan patients. This data can be used by cardiologists to monitor and guide treatment in post-Fontan

individuals. This might improve quality and longevity of life in this group of patients.

This study has some mentionable limitations. First; due to the retrospective nature of this study, some patient data may have been missing or incomplete. Second, the size of the study population was relatively small. As a result, our study may have lacked sufficient power to identify all significant associations. Finally, it is possible that a longer follow-up period would have facilitated more precise identification of cardiac function deterioration.

In conclusion, in post-Fontan patients, oxygen saturation, diastolic function, and overall ventricular function decreased over time, especially in patients with a postoperative duration of >10 years and in patients with RV morphology. Tissue Doppler imaging was found to be a sensitive method for detecting ventricular dysfunction in post-Fontan patients.

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CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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