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Disparity in right vs left ventricular recovery during follow-up after ventricular septal defect correction in children

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ABSTRACT

Objectives Long-term prognosis after ventricular septal defect (VSD) correction in childhood is excellent. Nevertheless decreased biventricular systolic performance has been described immediately following VSD surgery in children. In an effort to better understand this decrease and its time-course, we characterized biventricular systolic performance following VSD closure in paediatric patients up to 20 months postoperatively.

Methods Thirty-nine children undergoing VSD surgery and 22 age-matched controls were included for echocardiographic follow-up of left (LV) and right ventricular (RV) systolic performance. LV fractional shortening and tricuspid annular plane systolic excursion (TAPSE) were assessed. Additionally, tissue Doppler imaging measurements were obtained at the basal LV lateral wall and RV free wall to assess both LV and RV systolic (S') performance. Studies were performed preoperatively, 1 day postoperatively, at discharge and 3-20 months postoperatively at medium-term follow-up.

Results After an initial decrease in biventricular systolic performance, a significant recovery was observed within the first year after VSD surgery. After a medium-term follow-up of 8.4 ± 5.3 months LV systolic performance parameters were normalized, while RV systolic performance parameters remained impaired in patients vs controls (TAPSE: 12.5 ± 1.2 vs 18.5 ± 3.2 mm, RV S': 8.9 ± 1.3 vs 12.5 ± 2.2 cm/s).

Conclusions Within the first year after VSD correction, LV systolic performance had normalized, while RV systolic performance remained significantly impaired up to 20 months after VSD closure. Both detrimental effects of open heart surgery with cardiopulmonary bypass and preoperative alterations may add to the observed postoperative impairment of specifically RV performance.

INTRODUCTION

Long-term prognosis after ventricular septal defect (VSD) correction in childhood is excellent¹. Nevertheless decreased biventricular systolic performance has been reported within the first 24 h following VSD surgery^{2,3}. In adult congenital heart defect (CHD) patients, including VSD patients, a recent study showed impairment of right ventricular (RV) systolic performance after surgery, which persisted up to 18 months postoperatively⁴. However, in paediatric VSD patients, follow-up of biventricular performance following the first postoperative month has not been described.

With the advent of echocardiographic techniques, including tissue Doppler imaging (TDI), the quantification of subtle impairment of biventricular systolic performance has been greatly enhanced. TDI has proven to be a reliable technique to comprehensively quantify both left ventricular (LV)⁵ and RV systolic performance⁶.

Hence, in the current study, we aimed to characterize, using TDI, biventricular systolic performance following VSD closure in paediatric patients up to 20 months postoperatively.

MATERIALS AND METHODS

Study subjects

In this prospective follow-up study we enrolled all consecutive paediatric patients with a VSD, who underwent surgical correction of their VSD in our institution between March 2009 and March 2011. Patients with all types of VSD were eligible for inclusion if no previous cardiac surgery was performed. Additionally, healthy children age-matched to patients were included as controls. The institutional review board approved this study, and written informed consent was obtained from the patients, controls and/or parents.

Surgical correction was carried out via a median sternotomy using moderately hypothermic cardiopulmonary bypass. The aorta was cross-clamped and cold crystalloid cardioplegia was infused. Furthermore, intermittent external myocardial cooling was used every 30 min. VSDs were approached through the right atrium, and subsequent closure of the VSD was carried out via a direct suture or with the use of a patch.

Demographic parameters including body weight, length, sex, body surface area (BSA) and age were documented at study inclusion. A 12-lead electrocardiogram (ECG) was performed postoperatively in every patient. Furthermore, all patients and control subjects underwent transthoracic echocardiography, including TDI, to comprehensively assess both LV and RV systolic performance. In VSD patients, the examinations were performed at several time points, namely: preoperatively, 1 day postoperatively, after short-term follow-up at hospital discharge and at medium-term follow-up (3-20 months postoperatively).

Echocardiographic measurements 1 day postoperatively were compared with preoperative measurements. Furthermore, the measurements in the three postoperative echocardiographs were used to model changes in biventricular performance up to 20 months after VSD correction. Finally all echocardiographic parameters were compared between patients at medium-term follow-up vs preoperatively and between patients at medium-term follow-up and controls.

Echocardiography

Echocardiography was performed using a commercially available system (Vivid-7.0.0, General Electric Vingmed Ultrasound, Horten, Norway). Images were stored in digital format to allow off-line analyses using EchoPac version 11.1.8 (General Electric Vingmed). Patients without sinus rhythm at the time of echocardiographic investigation were excluded.

Conventional echocardiography

LV systolic performance was assessed using M-mode recordings of the LV long axis by calculating fractional shortening (FS) (%). To calculate FS, LV internal diameter at end-diastole (LVIDd) and at end-systole (LVIDs) were assessed in millimetres and combined as follows $[(LVIDd - LVIDs)/LVIDd] \times 100\%$.

Furthermore, RV systolic performance was assessed using tricuspid annular plane systolic excursion (TAPSE) (mm) measurements in two-dimensional M-mode recordings of the apical four-chamber view. The cursor was placed at the tricuspid annulus free wall, as previously described⁷. TAPSE is defined as the maximal excursion of the tricuspid valve plane as assessed from end-diastole to end-systole.

Tissue Doppler imaging

In addition to TAPSE and FS, biventricular systolic performance was further characterized using pulsed-wave TDI. TDI images were obtained in two-dimensional images of the four-chamber view throughout three consecutive cardiac cycles. The angle of insonation was adjusted to align the ultrasound beam along the direction of myocardial motion. Subsequently, myocardial velocity curves were acquired by placing the cursor at the basal part of the LV lateral wall and at the basal part of the RV free wall. In both the LV and RV, peak systolic velocity (S') was assessed and recorded in cm/s as a parameter of systolic performance.

Statistics

Normally distributed data are expressed as mean \pm standard deviation (SD). Non-normally distributed data are expressed as median (interquartile range). The paired two-sample Student's

t-test was used to assess differences in biventricular performance in patients 1 day postoperatively and at medium-term follow-up compared with preoperatively. The unpaired two-sample Student's t-test was used to assess differences in echocardiographic parameters between controls and patients after medium-term follow-up. Furthermore, one-way analysis of variance was used to assess differences between patients with different subtypes of VSDs. The relation between echocardiographic parameters at medium-term follow-up and size of the VSD was evaluated using scatter plots and Pearson's correlation coefficient.

To assess changes in systolic performance in patients during short- and medium-term follow-up after VSD closure, linear mixed models were constructed for each echocardiographic parameter including FS, TAPSE, LV S' and RV S'. Measurements 1 day postoperatively, at hospital discharge and at medium-term follow-up were included in the models as repeated outcome measurements with an unstructured covariance matrix. All models contained the measurement occasion as a categorical independent variable represented by dummy variables. Furthermore, at first, the duration between the medium-term follow-up echo and the operation date was included in every model as an independent variable, as considerable variation in timing was observed. However, this parameter was not a significant contribution to any model. Therefore we have excluded this variable from further analyses and considered the medium-term follow-up measurement to be time-independent. Data analysis was performed using SPSS 20.0. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 40 VSD patients was enrolled in our study. One patient was excluded because of a reoperation during our follow-up period. Thus, 39 VSD patients were included in this prospective follow-up study. Additionally, 22 healthy children age-matched to patients at medium-term follow-up were included as controls. No significant differences were observed in patients vs controls with regard to age [1.0 (0.6, 1.7) vs 1.2 (0.4, 2.2) years, $p=0.959$], weight [8.6-(7.8, 11.1) vs 9.4 (7.8, 12.0) kg, $p=0.823$] or sex [N total (N male): 22 (12) vs 39 (22), $p=0.888$].

Demographic characteristics and operation parameters of VSD patients are summarized in Table 1. Postoperatively, the ECG showed a mean QRS duration (time between the beginning of Q and the end of the S in the ECG) of 78 ± 16 ms, and none of the patients had a complete right bundle branch block.

Table 1. Demographic characteristics of patients

Demographics	Total
N	39
Male	22 (56 %)
Age at inclusion (years)	0.3 (0.2, 0.5)
Length (cm)	64 (60, 69)
Weight (kg)	5.0 (4.5, 6.0)
BSA (m ²)	0.3 (0.3, 0.3)
Cardiopulmonary bypass time (min)	91 ± 28
Aortic cross-clamp time (min)	57 ± 18
Intensive care stay (days)	4.7 ± 3.3
Mechanical ventilation (h)	42 ± 50
Subtype VSD	
Perimembranous	25 (64 %)
Inlet	10 (25 %)
Muscular	1 (3 %)
Doubly committed	3 (8 %)
Size VSD (mm)	9 ± 2

Values are expressed as the number of patients (percentage) or as mean ± SD. Age, weight, length and BSA are expressed as median (interquartile range) and are measured at study inclusion.

In 38 patients, the VSD was closed with a patch, and in 1, direct surgical closure was carried out. In 24 patients, an open foramen ovale or atrial septal defect was closed with direct suture in addition to VSD correction, and in 4, an additional atrial septal defect was closed with a patch. None of the patients had signs of RV volume overloading on the echocardiogram. Furthermore, in 3 patients multiple VSDs were corrected. Since no differences were observed between different subtypes of VSDs for any of the echocardiographic parameters preoperatively or at medium-term follow-up, results are given for the complete group of 39 patients in the remainder of this article.

In the VSD patients, transthoracic echocardiography was performed preoperatively (N=39), 1 day postoperatively (N=38), after short-term follow-up at hospital discharge (8.7 ± 4.6 days postoperatively; N=39) and after medium-term follow-up (8.4 ± 5.3 months postoperatively; N=22). Table 2 presents LV and RV systolic performance parameters in patients during follow-up and in controls.

Preoperative vs 1 day postoperative biventricular performance

In VSD patients, parameters assessing LV systolic performance, including LV S' and FS, were significantly decreased 1 day postoperatively when compared with preoperatively (Figure 1). Similarly, RV systolic performance decreased following VSD closure; TAPSE and RV S' were significantly decreased in patients 1 day postoperatively when compared with preoperatively (Figure 1).

Biventricular performance within the first postoperative year

Following the first postoperative day, a significant recovery of LV systolic performance parameters was observed at both short and medium-term follow-up (Figure 1). This led to an increase in FS and LV S' in patients at medium-term follow-up compared with 1 day postoperatively (FS 39.6 ± 4.5 vs 28.0 ± 8.9 %, $p < 0.001$; LV S' 7.0 ± 1.9 vs 5.1 ± 1.9 cm/s, $p < 0.001$).

Likewise, RV systolic performance improved substantially during both short- and medium-term follow-up (Figure 1). As a result, TAPSE and RV S' were increased in patients at medium-term follow-up compared with 1 day postoperatively (TAPSE 12.5 ± 1.2 vs 4.5 ± 1.5 mm, $p < 0.001$; RV S' 8.9 ± 1.3 vs 3.7 ± 1.1 cm/s, $p < 0.001$).

Table 2. Summary of echocardiographic parameters in patients pre and post-VSD correction and in healthy controls

		Patients				Controls	<i>p-value</i> ^a
		Preoperatively	One day postoperatively	At discharge	Medium-term follow-up		
LV	FS (%)	38.6 ± 7.4	28.0 ± 8.9	33.0 ± 6.5	39.6 ± 4.5	39.3 ± 4.4	0.832
	S' (cm/s)	6.2 ± 2.5	5.1 ± 1.9	5.4 ± 1.6	7.0 ± 1.9	7.3 ± 2.7	0.673
RV	TAPSE (mm)	14.2 ± 4.7	4.5 ± 1.5	7.5 ± 1.9	12.5 ± 1.2	18.5 ± 3.2	<0.001
	S' (cm/s)	10.1 ± 2.2	3.7 ± 1.1	5.0 ± 1.5	8.9 ± 1.3	12.5 ± 2.2	<0.001

Figure 1 provides further insight in the significance of changes during follow-up.

The values are expressed as mean \pm SD.

^a patients vs controls at medium-term follow-up (8.4 \pm 5.3 months postoperatively).

FS, fractional shortening; LV, left ventricle; RV, right ventricle; S', peak systolic myocardial velocity; TAPSE, tricuspid annular plane systolic excursion.

Extent of recovery of biventricular performance up to 20 months postoperatively

A comparison of FS and LV S' in patients at medium-term follow-up vs preoperatively revealed no significant differences. In contrast, RV systolic performance parameters were still lower in patients at medium-term follow-up vs preoperatively (TAPSE: 12.5 ± 1.2 vs 14.2 ± 4.7 mm, $p=0.015$; RV S' 8.9 ± 1.3 vs 10.1 ± 2.2 cm/s, $p=0.031$). No significant correlation was observed between the size of the VSD and RV systolic performance parameters at medium-term follow-up.

Moreover, the comparison between patients and controls after medium-term follow-up revealed no significant differences in LV systolic performance parameters, as assessed using FS and LV S' (Table 2 and Figure 1). In contrast, RV systolic performance did not improve to normal values within the first 20 months after VSD surgery. At medium-term follow-up, both TAPSE and RV S' were lower in patients when compared with controls (TAPSE: 12.5 ± 1.2 vs 18.5 ± 3.2 mm, $p<0.001$; RV S' 8.9 ± 1.3 vs 12.5 ± 2.2 cm/s, $p<0.001$; Table 2 and Figure 1).

DISCUSSION

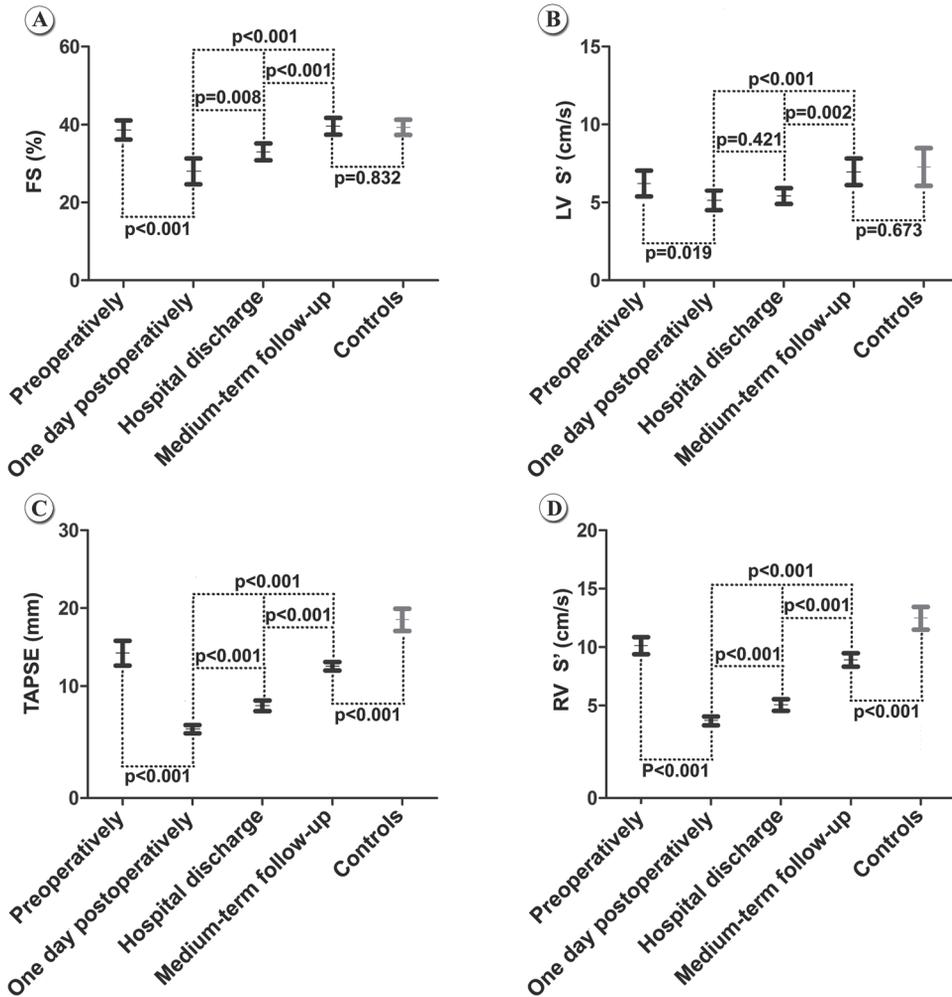
The present study describes a decrease of biventricular systolic performance in children directly following surgical VSD correction. Subsequently, both LV and RV systolic performance recover during short- and medium-term follow-up. Despite this recovery, RV systolic performance, in contrast to LV performance, remained significantly impaired in corrected VSD patients up to 20 months postoperatively.

Preoperative vs 1 day postoperative biventricular performance

Biventricular systolic performance was significantly decreased in patients 1 day after VSD closure compared with preoperatively. These results confirm, in a larger population of VSD patients, the results of the few previous studies evaluating systolic performance directly following VSD correction^{2,3,8,9}.

The exact pathophysiological processes behind the observed changes in both LV and RV systolic performance are as yet unidentified. Several peri- and postoperative factors may induce the observed decrease in ventricular performance, including direct surgical trauma, cardiopulmonary bypass associated ischaemia or inflammatory cascades, inadequate myocardial protection, mechanical properties of the patch and haemodynamic changes^{8,10-12}. The haemodynamic changes after VSD closure include a reduction in LV inflow and thus LV preload as a result of the removal of the left-right shunt. This preload reduction may have partly contributed to the changes in the outcome of TDI measurements preoperatively compared with 1 day postoperatively, since TDI parameters are possibly not load-independent¹³. Since most of these processes occur simultaneously, it is difficult to discriminate individual contributions of parameters in the pathophysiological process.

Figure 1 LV and RV systolic performance parameters in patients during follow-up and in controls



Box plots depicting mean and 95% confidence interval of the mean of LV systolic (A and B) and RV systolic (C and D) performance parameters in patients during follow-up and in controls. Each graph depicts P-values below the boxes indicating the significance of change in echocardiographic parameters preoperatively compared with 1 day postoperatively (left) and in patients after medium-term follow-up compared with controls (right). Furthermore p-values above the boxes describe the significance of change in echocardiographic parameters during postoperative follow-up as assessed with linear mixed models. FS, fractional shortening; LV, left ventricle; RV, right ventricle; S', peak systolic myocardial velocity; TAPSE, tricuspid annular plane systolic excursion.

Biventricular performance during the first postoperative year

After the initial decline in ventricular performance, a significant improvement was observed in both LV and RV systolic performance within the first year after VSD correction.

Previously, LV and RV performance were evaluated in the early postoperative period in paediatric VSD patients using the myocardial performance index; an index integrating systolic and diastolic performance. In agreement with our results, these studies showed impaired LV and RV performance 1 day after VSD surgery with subsequently a gradual improvement in ventricular performance in the following month^{14,15}. Our study extends these findings by prolonging the follow-up period from 1 month to a follow-up period of up to 20 months postoperatively. Additionally, specifically systolic ventricular performance was analysed in our study. Furthermore, our observation that biventricular systolic performance is incompletely recovered at discharge from the hospital stresses the importance of a close follow-up of both LV and RV systolic performance in corrected VSD patients.

Extent of recovery of biventricular performance up to 20 months postoperatively

The comparison of biventricular systolic performance between controls and patients at medium-term follow-up and between patients at medium-term follow-up vs preoperatively yielded contrasting results for the LV and RV. LV systolic performance recovered to normal values, while RV systolic performance remained impaired up to 20 months postoperatively.

LV systolic performance

Preoperatively, the heart of VSD patients with a haemodynamic significant left-to-right shunt is characterized by LV volume-overload. This can ultimately lead to LV dilatation and hypertrophy¹⁶. Volume unloading by surgical VSD closure disrupts this pathophysiological process and may therefore lead to reverse remodelling and restoration of these structural alterations¹⁷. The current comprehensive follow-up study of VSD patients emphasizes the rapid and significant recovery of LV systolic performance after VSD correction and LV unloading.

RV systolic performance

Recently, RV performance has gained interest as subtle changes in RV performance have shown to be correlated to an increased risk of cardiovascular events^{18,19}. The current report suggests that, despite postoperative recovery, RV systolic performance does not completely recover to preoperative levels. Furthermore, RV systolic performance was decreased in patients when compared with normal values up to 20 months after VSD correction.

It has been reported that following a variety of cardiac surgeries a persistent impairment of RV performance was observed^{4,12,20}. However, to our knowledge, this is the first study in

paediatric VSD patients to report a persistent impairment of RV systolic performance even beyond the first postoperative year. This is particularly interesting, as VSD patients constitute a large subgroup of paediatric CHD patients, who are generally perceived to be 'easily cured' by cardiac surgery. Low surgical mortality¹⁶, a fairly short cardiopulmonary bypass time and relatively low morbidity and mortality long-term after surgery²¹ are all factors contributing to this idea. However, our results show that, even in these patients, RV function is abnormal up to 20 months postoperatively. Although this subclinical impairment may not be of direct clinical relevance, it does stress the importance of evaluating RV systolic performance after VSD correction. Furthermore, these observations encourage research on cardiac performance after surgery in other types of CHD patients.

Much has been speculated on the reason why specifically RV, and not LV, performance parameters remain impaired in patients after cardiac surgery. It has been hypothesized that the thin-walled RV is more susceptible to inflammation due to local tissue damage than the LV, ultimately leading to RV dysfunction²². Additionally, cardiopulmonary bypass associated inflammatory cascades may have an influence on RV performance, which is absent or less on the LV⁴. Furthermore, the RV may be less protected by cold cardioplegia and external cooling than the LV^{11,23}. The anterior position of the RV renders it much more at risk of external heating than the LV during cardiac surgery. To quantify this difference, previous studies have used temperature probes in the myocardium and have shown differences of up to 19 °C between the LV and RV^{11,23}. Finally pericardiotomy and pericardial adhesions have been suggested to play a role in RV dysfunction after surgery, but these suggestions remain speculative thus far²⁰. In addition to surgical factors, preoperative volume and pressure overload may also add to postoperative dysfunction.

Study limitations

It is known that decreased RV performance can be of prognostic significance in patients with systolic heart failure¹⁸. However to further specify the clinical significance of our findings, it is important to establish whether the selective impairment of RV systolic performance persists during long-term follow-up and how it relates to clinical characteristics.

It was recently argued that the observed decrease in TAPSE and TDI measurements following cardiac surgery was merely a reflection of geometrical, rather than functional, changes²⁴. However, previous studies have shown RV TDI measurements and TAPSE to give a valid reflection of RV performance²⁵. Additionally, the only impairment that remained significant up to 20 months postoperatively was observed in RV performance parameters; while in VSD patients geometrical changes after cardiac surgery are expected to be more pronounced in the LV than in the RV.

In the current study patients were included with several subtypes of VSDs. The subtype analyses did not yield significant differences in echocardiographic parameters during follow-up. However, considering the small subgroups in our study, this does not exclude a possible heterogeneity in the follow-up of cardiac performance in different subtypes of VSD patients. Yet in our opinion the validity of our main message, that RV systolic performance remains impaired up to 20 months postoperatively in VSD patients, is not affected by this.

Conclusions

After an initial decrease in biventricular systolic performance following corrective VSD surgery, LV and RV systolic performance recovered during both short- and medium-term follow-up. This recovery led to normal values of LV systolic performance within the first year after VSD correction. In contrast, RV systolic performance remained significantly impaired in patients compared with controls up to 20 months postoperatively. This impairment may be the result of detrimental effects of open-heart surgery with cardiopulmonary bypass. Yet, preoperative alterations may also add to postoperative dysfunction. Considering the potential clinical and prognostic value of decreased RV performance parameters, our results encourage follow-up of specifically RV performance in VSD-corrected children. Furthermore, this observation warrants a comprehensive evaluation of biventricular performance in patients with other types of CHD after the immediate postoperative period.

REFERENCES

1. Scully BB, Morales DL, Zafar F, McKenzie ED, Fraser CD, Jr., Heinle JS. Current expectations for surgical repair of isolated ventricular septal defects. *Ann Thorac Surg* 2010;89:544-549.
2. Vassalos A, Lilley S, Young D et al. Tissue Doppler imaging following paediatric cardiac surgery: early patterns of change and relationship to outcome. *Interact Cardiovasc Thorac Surg* 2009;9:173-177.
3. Hart JP, Cabreriza SE, Walsh RF et al. Echocardiographic analysis of ventricular geometry and function during repair of congenital septal defects. *Ann Thorac Surg* 2004;77:53-60.
4. Schuurin MJ, Bolmers PP, Mulder BJ et al. Right ventricular function declines after cardiac surgery in adult patients with congenital heart disease. *Int J Cardiovasc Imaging* 2011;28:755-762.
5. Seo JS, Kim DH, Kim WJ, Song JM, Kang DH, Song JK. Peak systolic velocity of mitral annular longitudinal movement measured by pulsed tissue Doppler imaging as an index of global left ventricular contractility. *Am J Physiol Heart Circ Physiol* 2010;298:H1608-H1615.
6. Meluzin J, Spinarova L, Bakala J et al. Pulsed Doppler tissue imaging of the velocity of tricuspid annular systolic motion; a new, rapid, and non-invasive method of evaluating right ventricular systolic function. *Eur Heart J* 2001;22:340-348.
7. Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. *Am Heart J* 1984;107:526-531.
8. Quinn TA, Cabreriza SE, Blumenthal BF et al. Regional functional depression immediately after ventricular septal defect closure. *J Am Soc Echocardiogr* 2004;17:1066-1072.
9. Cheung MM, Smallhorn JF, Vogel M, Van Arsdell G, Redington AN. Disruption of the ventricular myocardial force-frequency relationship after cardiac surgery in children: noninvasive assessment by means of tissue Doppler imaging. *J Thorac Cardiovasc Surg* 2006;131:625-631.
10. Kozik DJ, Tweddell JS. Characterizing the inflammatory response to cardiopulmonary bypass in children. *Ann Thorac Surg* 2006;81:S2347-S2354.
11. Chen YF, Chen JS, Wang JR, Chiu CC, Lin YT. Uneven myocardial hypothermia among cardiac chambers during hypothermic myocardial preservation. *Eur J Cardiothorac Surg* 1990;4:618-623.
12. Hanseus KC, Bjorkhem GE, Brodin LA, Pesonen E. Analysis of atrioventricular plane movements by Doppler tissue imaging and M-mode in children with atrial septal defects before and after surgical and device closure. *Pediatr Cardiol* 2002;23:152-159.
13. Drighil A, Madias JE, Mathewson JW et al. Haemodialysis: effects of acute decrease in preload on tissue Doppler imaging indices of systolic and diastolic function of the left and right ventricles. *Eur J Echocardiogr* 2008;9:530-535.
14. Zacharska-Kokot E. The myocardial performance index in children after surgical correction of congenital malformations with intracardiac shunt. *Kardiol Pol* 2007;65:143-150.
15. Baghdady Y, Kamel Y, Amar W. Myocardial performance index after surgical correction of ventricular septal defects. *Arch Med Sci* 2010;6:328-335.
16. Penny DJ, Vick GW, III. Ventricular septal defect. *Lancet* 2011;377:1103-1112.
17. Drakos SG, Kfoury AG, Hammond EH et al. Impact of mechanical unloading on microvasculature and associated central remodeling features of the failing human heart. *J Am Coll Cardiol* 2010;56:382-391.
18. Meluzin J, Spinarova L, Hude P et al. Prognostic importance of various echocardiographic right ventricular functional parameters in patients with symptomatic heart failure. *J Am Soc Echocardiogr* 2005;18:435-444.
19. Shin HW, Kim H, Son J et al. Tissue Doppler imaging as a prognostic marker for cardiovascular events in heart failure with preserved ejection fraction and atrial fibrillation. *J Am Soc Echocardiogr* 2010;23:755-761.
20. Diller GP, Wasan BS, Kyriacou A et al. Effect of coronary artery bypass surgery on myocardial function as assessed by tissue Doppler echocardiography. *Eur J Cardiothorac Surg* 2008;34:995-999.
21. Meijboom F, Szatmari A, Utens E et al. Long-term follow-up after surgical closure of ventricular septal defect in infancy and childhood. *J Am Coll Cardiol* 1994;24:1358-1364.
22. Yadav H, Unsworth B, Fontana M et al. Selective right ventricular impairment following coronary artery bypass graft surgery. *Eur J Cardiothorac Surg* 2010;37:393-398.

23. Fisk RL, Ghaswalla D, Guilbeau EJ. Asymmetrical myocardial hypothermia during hypothermic cardioplegia. *Ann Thorac Surg* 1982;34:318-323.
24. Tamborini G, Muratori M, Brusoni D et al. Is right ventricular systolic function reduced after cardiac surgery? A two- and three-dimensional echocardiographic study. *Eur J Echocardiogr* 2009;10:630-634.
25. Pavlicek M, Wahl A, Rutz T et al. Right ventricular systolic function assessment: rank of echocardiographic methods vs cardiac magnetic resonance imaging. *Eur J Echocardiogr* 2011;12:871-880.

