Age-related variations of left ventricular endocardial and midwall function in healthy infants, children, and adolescents

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Key words:
Echocardiography; Left ventricular function.

Background. **In pediatric age echocardiographic evaluation of left ventricular systolic function is usually based on indexes obtained by measurements at the endocardial level. In the presence of ventricular hypertrophy this may lead to an overestimation of systolic function. The aim of this study was to assess the developmental changes of left ventricular systolic mechanics measured at the endocardial and midwall levels.**

Methods. **In 239 normal subjects divided into six age groups we measured left ventricular end-diastolic volume, mass and mass/volume ratio, fractional shortening, and rate-corrected mean velocity of circumferential shortening at the endocardial and midwall levels. Endocardial meridional end-systolic stress and midwall circumferential end-systolic stress were considered as indexes of afterload. Relations of extent and velocity of fiber shortening to afterload at the endocardial and midwall levels were used to assess left ventricular contractility.**

Results. **Blood pressure, left ventricular afterload, volume and mass increased, whereas the mass/volume ratio remained stable during growth. Fractional shortening and mean velocity of circumferential shortening at the endocardial level decreased and showed an inverse relation to afterload. Midwall fractional shortening and rate-corrected mean velocity of circumferential shortening were lower during the first months and did not change during the first year of life.**

Conclusions. **Left ventricular volume and mass increase with age, mass/volume ratio remains almost constant while afterload increases. Endocardial systolic function indexes are higher in the first period of life, due to low afterload and increased mass/volume ratio. In the first months of life the left ventricular myocardium shows a greater sensitivity to changes in afterload and a reduced contractility measured at the midwall level.**

(Ital Heart J 2005; 6 (8): 634-639)

Received November 9, 2004; revision received February 7, 2005; accepted February 10, 2005.

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Introduction

The fractional shortening (FS%) and the rate-corrected mean velocity of circumferential fiber shortening (VCFc) are the most widely used echocardiographic indexes of left ventricular systolic pump function in pediatric age. By correlating these parameters to end-systolic wall stress it is possible to estimate the left ventricular myocardial contractility[1-4]. The end-systolic stress/velocity relation has been shown to be an afterload-adjusted, preload and heart rate-independent index of contractility[2,5]. The assessment of left ventricular systolic function plays an important role in the management of many heart disorders in childhood, may influence the timing of surgery and the long-term survival[6-10]. An age-related alteration of the end-systolic stress/velocity relation has been reported[4,11-13], but there are few published reports evaluating the contractile state in newborns and infants by using this load-independent index[11,13]. Moreover all the systolic pump function indexes are obtained by measuring the extent and velocity of fiber shortening at the endocardium, whereas many experimental data show that the systolic thickening in subendocardial layers exceeds that of the subepicardial layers, with a consequent nonuniform left ventricular wall thickening during systole[14,15]. Left ventricular systolic function parameters derived from endocardial shortening may therefore overestimate the systolic performance[16-18]. Left ventricular hypertrophy is a frequent compensatory mechanism in many cardiac defects in childhood and an assessment of left ventricular systolic function that takes into account the migration of the midwall circumferential fibers during systole is warranted. There are only few published reports evaluating the left ventricular mechanics by midwall indexes in the pediatric age[19-21]. Our study was carried out to assess the left ventricular systolic pump function and contractile state obtained by endocardial and midwall indexes in a large group of normal infants, children and adolescents and to investigate the developmental changes of these parameters in the early years of life.

Methods

Study population. We examined 239 normal children and adolescents (129 males, 110 females, mean age 51.4 ± 60.1 months, range 0.5-216 months) with a body surface area (BSA) of 0.66 ± 0.46 m^2 (range 0.18-2 m^2), and with no clinical evidence of cardiac disease. The investigation conforms with the principles outlined in the Declaration of Helsinki[22]. All newborns were born at term, were healthy and had normal Apgar scores. Neonates in the first 2 weeks of life were excluded because, at this age, there is the possibility of a distortion of the left ventricular systolic shape induced by right ventricular hypertension[23]. A cardiac disorder was excluded in all the subjects. Criteria for inclusion in the study were: 1) no history of systemic disorder, 2) normal blood pressure for age[24], 3) normal two-dimensional echocardiography. Because developmental alterations in contractile state occur in early age[4,11,13], we divided the subjects into six age groups: 2 weeks-1 month (group 1, n = 33), 1-6 months (group 2, n = 31), 6-12 months (group 3, n = 31), 1-3 years (group 4, n = 37), 3-12 years (group 5, n = 75), and 12-18 years (group 6, n = 32). The characteristics of the six study groups are reported in table I. Knowing that blood pressure starts diverging in the two genders after 12 years of age, we performed a comparison between values of males and females in the adolescent group, but did not find any significant differences.

Echocardiographic and Doppler examination. The echocardiographic and Doppler investigations were performed with a phased array sector scan (Acuson 128 XP or Sonos 5500, Hewlett-Packard), with a 3.5, 5 or 7 MHz transducer without use of any form of sedation in the younger groups. The examination included two-dimensional echocardiographic imaging of the left ventricle from the subcostal, apical and parasternal views and complete Doppler scanning. A circular short-axis configuration of the left ventricle throughout the cardiac cycle was confirmed in all patients. Peak systolic and diastolic blood pressure was measured with a Dynamap vital sign monitor at the time of echocardiographic examination. All echocardiographic measurements were performed by the same observer. The reported parameters were obtained by averaging at least three consecutive cardiac cycles (from three to five). Moreover, the intraobserver variability of any single measurement was approximately 2 or 3%.

Analysis of the left ventricular volume, mass, wall stress, systolic function and contractile state at the endocardial and midwall levels. From a parasternal short-axis view of the left ventricle with the M-mode beam passing through the tips of the mitral valve leaflets, the following measurements were obtained, according to the criteria of the American Society of Echocardiography[25]: end-diastolic (Dd) and end-systolic (Ds) left ventricular diameters, posterior wall thickness at end-diastole (PWd) and end-systole (PWs), and septal thickness at end-diastole. Pulsed wave Doppler of the left ventricular outflow tract from the apical view was used for measuring the ejection time (ET).

These parameters were used to calculate the left ventricular end-diastolic volume (EDVi)[26] and mass (Mi)[27], which were normalized for BSA, and the mass/volume ratio (M/V). Left ventricular meridional end-systolic stress (ESSm) was determined by the method of Grossman et al.[28]:

$$ESSm = 1.35 \times Pes \times Ds/4 \times PWs \times (1+PWs/Ds)$$

where 1.35 is the conversion factor from mmHg to g/cm^2 and Pes is the end-systolic pressure estimated from the peak systolic and diastolic pressure using a regression equation validated by invasive measurements[29].

Table I. Features of the six study groups.

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	p (ANOVA)
No. patients	33	31	31	37	75	32	–
Age (months)	0.8 ± 0.17	3.7 ± 1.4	8.7 ± 1.4	26.7 ± 6.6	91.4 ± 31.8	169.6 ± 24.4	–
Sex (M/F)	16/17	13/18	15/16	19/18	40/35	24/8	–
BSA (m^2)	0.21 ± 0.02	0.29 ± 0.45*	0.37 ± 0.03*°	0.55 ± 0.07*°§	0.97 ± 0.24*°§^	1.54 ± 0.25*°§^#	< 0.0001
SBP (mmHg)	88.6 ± 4.2	92.4 ± 7.8	94.4 ± 7.6*	96.3 ± 6.9*	102.6 ± 9.3*°§^	113.2 ± 8.9*°§^#	< 0.0001
DBP (mmHg)	49.9 ± 5.7	53.9 ± 6.7*	53.0 ± 7.4	57.6 ± 7.6*§	67.5 ± 8.2*°§^	72.7 ± 7.8*°§^#	< 0.0001
ESBP (mmHg)	69.6 ± 5.2	73.6 ± 6.0*	73.9 ± 7.4*	77.6 ± 6.5*°§	86.3 ± 8.1*°§^	94.0 ± 7.9*°§^#	< 0.0001
HR (b/min)	132.6 ± 6.5	133.9 ± 4.6	123.2 ± 12.7*°	100.8 ± 13.5*°§	85.3 ± 14.1*°§^	80.4 ± 11.4*°§^	< 0.0001

Group 1 (2 weeks-1 month), Group 2 (1-6 months), Group 3 (6-12 months), Group 4 (1-3 years), Group 5 (3-12 years), Group 6 (12-18 years). Data are expressed as means ± SD. BSA = body surface area; DBP = diastolic blood pressure; ESBP = end-systolic blood pressure; HR = heart rate; SBP = systolic blood pressure. Post-hoc analysis: * significant vs Group 1; ° vs Group 2; § vs Group 3; ^ vs Group 4; # vs Group 5.

Because it is theoretically more correct to relate the extent or velocity of fiber shortening with the stress calculated in circumferential direction, we estimated the left ventricular circumferential end-systolic stress at the midwall level (mwESSc) according to a cylindrical model as previously reported[30,31]:

$$mwESSc = Pes \times (Ds/2)^2 \times [1+(Ds/2+PWs)^2/(Ds/2+PWs/2)]/(Ds/2+PWs)^2 - (Ds/2)^2.$$

FS% and VCFc were considered as indexes of left ventricular systolic pump function at the endocardial level. Midwall left ventricular systolic function was evaluated by using the modified two-shell cylindrical model with uniform wall thickness proposed by Shimizu et al.[16], which reflects the relative transmural position of a theoretical midwall fiber during the cardiac cycle as previously reported[19,21,31,32]. The left ventricular end-diastolic midwall dimension (mwDd) was calculated as

$$mwDd = Dd+0.5\ (PWd)+0.5\ (PWd)$$

and the end-systolic midwall dimension (mwDs) as

$$mwDs = [(Ds)^2 + PWs\ (2Dd+PWd)(Ds+PWs)/Dd+PWd)]^{0.5}.$$

These formulas are based on the assumption that septal and posterior wall thicknesses are equal. The left ventricular midwall fractional shortening (mwFS%) was calculated from these midwall dimensions and the midwall VCFc (mwVCFc) as mwVCFc = mwFS/ETc, where ETc = ET corrected for heart rate. Relations of FS% and VCFc to ESSm as well as mwFS% and mwVCFc to mwESSc were used to assess the left ventricular contractility at the endocardial and midwall levels in the entire group and in the six age groups.

Statistical analysis. All parameters were expressed as mean ± SD. Comparison of clinical and echocardiographic parameters under the six age groups has been performed by analysis of variance (ANOVA) and the *post-hoc* analysis obtained by the Bonferroni test. Best-fit regression analysis was used to examine the relation between the echocardiographic parameters and age. Best fit regressions of FS% and VCFc to ESSm, as well as mwFS% and mwVCFc to mwESSc in the total population and in the six age groups were then calculated. Statistical significance for all analyses was defined as $p < 0.01$.

Results

The echocardiographic parameters in the six age groups are reported in table II. Significant differences were found between the six groups for left ventricular EDVi and Mi, whereas the M/V ratio was slightly increased in the infants. The ESSm and mwESSc were lower in the early ages. The left ventricular endocardial shortening and velocity indexes (FS% and VCFc) were higher in the younger age groups. The midwall indexes (mwFS% and mwVCFc) were lower during the first months and did not change significantly during the first year of life.

The systolic, diastolic and estimated end-systolic pressure increase with age. Left ventricular EDVi and Mi also increase with age, whereas the M/V ratio remains relatively stable. The gradual increase in pressure despite a relatively stable M/V ratio resulted in a substantial increase in afterload (ESSm and mwESSc). The endocardial FS% and VCFc of the left ventricle decrease with age, whereas the mwFS% and mwVCFc showed a weak relation to age (Table III).

In the entire study population the FS% and VCFc were inversely correlated with ESSm [$FS\% = 1/(0.0193+0.0002*ESSm)$, $r = 0.74$, $p < 0.0001$; $VCFc = 2.687*ESSm^{-0.219}$, $r = -0.69$, $p < 0.0001$], whereas the mwFS% and mwVCFc showed a weak correlation with mwESSc [$mwFS\% = mwESSc/(0.593+0.044\ mwESSC)$, $r = 0.28$, $p < 0.0001$; $mwVCFc = mwESSc/(20.73+1.324\ mwESSc)$, $r = 0.29$, $p < 0.0001$]. The regression equations between FS%, VCFc and ESSm of the six age

Table II. Echocardiographic parameters in the six age groups.

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
No. patients	33	31	31	37	75	32
EDVi (ml/m²)	46.2 ± 5.0	53.2 ± 12.1	61.0 ± 8.1	68.8 ± 8.8	70.7 ± 10.9	64.4 ± 8.5
Mi (g/m²)	53.5 ± 2.6	52.9 ± 5.8	57.9 ± 8.9	59.6 ± 6.5	63.6 ± 11.3	68.8 ± 11.4
M/V (g/ml)	1.16 ± 0.09	1.01 ± 0.13	0.95 ± 0.09	0.87 ± 0.10	0.90 ± 0.14	1.07 ± 0.13
ESSm (g/cm²)	18.9 ± 4.2	24.5 ± 10.4	26.6 ± 6.3	33.9 ± 9.0	42.9 ± 10.2	46.0 ± 13.1
mwESSc (g/cm²)	34.6 ± 5.5	41.0 ± 10.0	43.9 ± 7.4	51.5 ± 9.1	61.4 ± 9.6	65.6 ± 11.6
FS%	44.7 ± 3.4	42.8 ± 4.5	41.3 ± 5.6	42.6 ± 4.1	39.2 ± 4.0	38.3 ± 5.1
VCFc (circ/s)	1.46 ± 0.11	1.32 ± 0.14	1.25 ± 0.17	1.27 ± 0.13	1.21 ± 0.15	1.21 ± 0.14
mwFS%	17.8 ± 3.2	17.1 ± 2.7	17.3 ± 4.9	21.3 ± 3.0	19.3 ± 3.2	18.4 ± 3.3
mwVCFc (circ/s)	0.54 ± 0.10	0.55 ± 0.09	0.57 ± 0.17	0.71 ± 0.11	0.62 ± 0.12	0.58 ± 0.12

Data are expressed as means ± SD. EDVi = end-diastolic volume index; ESSm = end-systolic meridional stress; FS% = fractional shortening; Mi = mass index; M/V = mass volume ratio; mwESSc = midwall end-systolic circumferential stress; mwFS% = midwall fractional shortening; mwVCFc = midwall rate-corrected mean velocity of circumferential shortening; VCFc = rate-corrected mean velocity of circumferential shortening.

Table III. Regression equations between different variables and age.

	SEE	r	p
SBP = 91.2 + 0.13·age	7.3	0.74	< 0.0001
DBP = 53.2 + 0.13·age	7.6	0.72	< 0.0001
ESBP = 72.7 + 0.14·age	6.8	0.77	< 0.0001
EDVi = 3.42 e^{-9}·$age^{5.46}$	1.43	0.62	< 0.0001
Mi = 55.0 + 0.09·age	8.75	0.53	< 0.0001
M/V = 0.94 + 0.15/age	0.14	0.45	< 0.0001
ESSm = 18.9·$age^{0.17}$	0.25	0.77	< 0.0001
mwESSc = 34.69·$age^{0.12}$	0.17	0.79	< 0.0001
FS% = 1/(0.023 + 2.09 $e^{-0.5}$·age)	0.003	0.43	< 0.0001
VCFc = 1.39·$age^{-0.03}$	0.11	-0.46	< 0.0001
mwFS% = 17.4·$age^{0.02}$	0.20	0.17	< 0.0001
mwVCFc = age/(0.2 + 1.68·age)	0.37	0.24	< 0.005

DBP = diastolic blood pressure; EDVi = end-diastolic volume index; ESBP = end-systolic blood pressure; ESSm = end-systolic meridional stress; FS% = fractional shortening; Mi = mass index; M/V = mass volume ratio; mwESSc = midwall end-systolic circumferential stress; mwFS% = midwall fractional shortening; mwVCFc = midwall rate-corrected mean velocity of circumferential shortening; SBP = systolic blood pressure; VCFc = rate-corrected mean velocity of circumferential shortening.

Table IV. Features of the six study groups. Regression equations between fractional shortening (FS%), rate-corrected mean velocity of circumferential shortening (VCFc) and end-systolic meridional stress (ESSm). Regression equation between midwall fractional shortening (mwFS%), midwall rate-corrected mean velocity circumferential shortening (mwVCFc) and midwall end-systolic circumferential stress (mwESSc).

	SEE	r	p
Group 1 (n=33)			
FS% = 37.5 + 129.7/ESSm	3.1	0.42	< 0.01
VCFc = 1.22 + 4.29/ESSm	0.09	0.43	< 0.01
mwFS% = 7.0 + 0.3·mwESSc	2.78	0.53	< 0.005
mwVCFc = 0.20 + 0.01·mwESSc	0.08	0.54	< 0.005
Group 2 (n=31)			
FS% = 29.8 + 286.0/ESSm	2.46	0.84	< 0.0001
VCFc = 0.96 + 7.83/ESSm	0.09	0.74	< 0.0001
mwFS% = 12.6 + 0.1·mwESSc	2.46	0.42	< 0.05
mwVCFc = 0.43 + 0.01·mwESSc	0.09	0.34	NS
Group 3 (n=31)			
FS% = 20.8 + 518.6/ESSm	3.48	0.78	< 0.0001
VCFc = 0.72 + 13.45/ESSm	0.12	0.69	< 0.0001
mwFS%= 25.1 - 0.2·ESSc	4.85	-0.26	NS
mwVCFc = 0.88 - 0.01·mwESSc	0.16	-0.30	NS
Group 4 (n=37)			
FS% = 30.6 + 378.3/ESSm	2.17	0.85	< 0.0001
VCFc = 0.99 + 8.86/ESSm	0.10	0.62	< 0.0001
mwFS% = 24.2 - 0.1·mwESSc	2.99	-0.17	NS
mwVCFc = 0.88 - 0.01·mwESSc	0.11	-0.27	NS
Group 5 (n=75)			
FS% = 27.6 + 472.0/ESSm	2.88	0.70	< 0.0001
VCFc = 0.82 + 16.10/ESSm	0.11	0.64	< 0.0001
mwFS% = 18.4 + 0.1·mwESSc	3.29	0.04	NS
mwVCFc = 0.59 + 0.01·mwESSc	0.12	0.05	NS
Group 6 (n=32)			
FS% = 21.4 + 730.0/ESSm	2.90	0.82	< 0.0001
VCFc = 0.82 + 16.5/ESSm	0.10	0.68	< 0.0001
mwFS% = 20.7 - 0.0·mwESSc	3.39	-0.12	NS
mwVCFc = 0.76 - 0.01·mwESSc	0.12	-0.25	NS

groups showed steeper slopes in the early age groups. We did not find any significant regression between mwFS%, mwVCFc and mwESSc, except for a weak correlation in the two groups < 6 months of age (Table IV).

Discussion

In normal individuals left ventricular end-diastolic volume and mass increase during childhood and adolescence, whereas the M/V ratio remains relatively constant; the progressive increase in arterial blood pressure explains the increase of afterload. Left ventricular systolic pump function parameters are higher in the first year of life, show an inverse relation to afterload and do not significantly change during childhood after the third year[2,4,13,33]. A decrease of slope and Y intercept of the stress/velocity relation has been reported during the first year of life[4,11]. Studies concerning left ventricular mechanics in pediatric age have been performed by measuring left ventricular dimensions at the endocardial level. When there is an abnormal left ventricular geometry as in ventricular hypertrophy, the systolic function parameters obtained by endocardial measurements can overestimate the myocardial function[16,21,31-34]. For this reason Shimizu et al.[16] developed a modified midwall model in order to assess more accurately the left ventricular myocardial function.

The typical fiber structure of the ventricular wall enables the circumferential and meridional shortening with contemporary thickening[35]. It is theoretically not correct to relate the circumferential shortening at the endocardial level, which is a shortening that works at a right angle to the longitudinally directed myocardial fibers, to the end-systolic stress, which is applied at the midwall level[16,32]. If we used the stress/shortening or stress/velocity relation to estimate the contractile state, it would be more correct if the vectors of stress and shortening had the same direction. Although this theoretical bias has a slight influence when we compare the myocardial function in the same patient in different conditions or among patients with a similar degree of wall thickness, it could lead to an overestimation of the inotropic state when patients with different left ventricular mass are compared[36,37]. Therefore, because circumferential myocardial fibers predominate at the midwall level of the left ventricle[38], the stress/shortening and stress/velocity relations should incorporate the data obtained at the midwall of the left ventricle. Our findings suggest that the stress/velocity relation of the left ventricle obtained from endocardial measurements is significantly different in infants in comparison with that found in older children and adolescents. The significantly higher VCFc values found in the first few months cannot be accounted for completely by a decreased afterload and would suggest a higher basal contractile state. These findings are in agreement with previous reports[4,11,13]. Some studies evaluating the left ventricular mechanics by midwall indexes in normal pediatric subjects, reported a weak correlation between systolic function and afterload[19,20]. In our study we also found a weak correlation between midwall stress and velocity indexes but only in the younger age groups; however these parameters are relatively independent in older children. If compared to the endocardial ones, which reflect the chamber systolic properties, the midwall indexes predict more accurately the left ventricular myocardial contractility. Healthy infants have a higher left ventricular systolic chamber function and a relatively higher M/V ratio; the midwall function (mwVCFc) is slightly reduced in the first few months of life. Our data suggest that the immature myocardium of the newborn and infant has a greater sensitivity to changes in afterload, as indicated by the steeper slopes of the stress/velocity regressions obtained at the endocardial level. The immature myocardium has a reduced contractile state with an increased diastolic stiffness, due to the higher amount of non-contractile proteins in its myocytes. The developmental changes of the myocardium are characterized by an increase in the number of sarcomeres and myofilament content, changes of the myocardial homeostasis of calcium related to the structure and function of the sarcoplasmic reticulum and maturational development of the sympathetic innervations[39]. The increase of left ventricular mass during growth suggests that this may play a role in the ability of the mature myocardium to tolerate variations in afterload[40].

In summary in the first few months of life there is an increased systolic chamber function with a reduced afterload and a slightly increased M/V ratio. The steeper stress/velocity relation obtained by endocardial measurements as well as the reduced midwall function are expression of the afterload dependence and reduced contractility of the immature left ventricular myocardium. Our data on systolic pump function obtained from endocardial indexes are in agreement with those reported by Colan et al.[4], however slightly discordant with data reported by others[19,21] on midwall function. We found lower values of midwall systolic function parameters in the first few months of life, while the values reported at later ages are comparable. This could partly be due to the fact that we had more infants < 6 months of age. In order to analyze in clinical practice the left ventricular systolic function by endocardial parameters, taking age into account, these should be corrected for the level of afterload by obtaining a z-score index from the stress/shortening and stress/velocity regression in a normal population. If we use the midwall parameters in order to assess the left ventricular systolic function, the same approach can be used in infants < 6 months of age, but later we just need to compare the measured values with the means of the normal population, taking age into account. Moreover, in order to assess the myocardial contractility, it seems more correct to relate stress with shortening if these vectors have the same direction, as in midwall function assessment.

The use of single-plane measures such as VCFc to represent global systolic function implies the absence of regional wall motion abnormalities and the presence of a circular short-axis configuration of the left ventricle[28]. The left ventricular ET used to calculate the VCFc was measured from the aortic flow obtained by pulsed wave Doppler[12,31] instead of a more complicated method using calibrated pulse pressure[2,5]. The formula developed by Shimizu et al.[16] to calculate midwall diameters is based on the assumption that the left ventricle is a two-shell cylinder with a uniform wall thickness. Although this approach avoids the overestimation of shortening due to the use of endocardial or simplified midwall indexes, it is not applicable to a left ventricle with asymmetric hypertrophy. This one-dimensional model does not account for variations in myocardial thickness between the posterior wall and septum or between base and apex, nor for regional variations in shortening. Moreover instead of measuring the septal thickness, this is just assumed to be equal to the left posterior wall. This seems to be rather advantageous since a reliable septal thickness is not always available because the right ventricular septal endocardium is very trabeculated and sometimes difficult to identify with M-mode echocardiography.

In conclusion, left ventricular end-diastolic volume and mass increase with growth, whereas M/V ratio remains relatively constant; the progressive increase of systemic blood pressure explains the increase in afterload. The VCFc at the endocardial level is higher in the first period of life compared to a later pediatric age, due to a reduced afterload and a slightly increased M/V ratio. In the first few months of life the left ventricular systolic chamber function shows a greater sensitivity to changes in afterload and a decreased contractility measured at the midwall level, expression of the immature development of the myocardium. Whenever the left ventricular systolic function in children is evaluated by using the stress/velocity relation from endocardial parameters, the age-related variability should be taken into consideration. In order to assess left ventricular systolic function and contractile state in children with pressure and volume overload hypertrophy, the systolic function parameters, measured at the midwall level, should be considered.

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