Is Myocardial Performance Index an Independent Echocardiographic Marker of Death in Children with Idiopathic Dilated Cardiomyopathy?

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ABSTRACT

Background: Myocardial performance index (MPI) was reported as a parameter of ventricular systolic and diastolic function, as well as a useful tool to predict the outcome in patients with ventricular dysfunction.
Hypothesis: To compare MPI with classical echocardiographic parameters as an independent marker of death in children with idiopathic dilated cardiomyopathy (IDCM).
Methods: Fifty-five children (13 deaths) underwent 104 echocardiograms from January 1996 to May 2005. Right ventricle (RV) MPI and left ventricle (LV) MPI, and 9 classical echocardiographic parameters (left atrium [LA]/body surface area [BSA], distance between mitral E point and ventricular septum, LV mass/body surface area, RV shortening fraction, LV end-systolic and end-diastolic dimensions/body surface area, LV ejection fraction, fiber circumferential shortening velocity, and mitral deceleration time) were compared. Statistical analysis was performed by chi-square, Pearson's correlation and Student t-test, Kaplan-Meier method, Cox's method, and receiver operating curve (ROC). Statistical significance was considered with $\alpha < 0.05$ and $p = 0.80$.
Results: Univariate analysis showed that all studied parameters were markers of death. There was a high correlation between RVMPI and LVMPI ($r = 0.847$–$p = 0.0001$); therefore, to avoid bias, RVMPI was discharged from multivariate analysis. In the deceased group, moderate/severe mitral regurgitation was frequent (76.9%; confidence interval [CI] 95% = 46.2%–94.9%) and it was considered in multivariate analysis. In Cox's multivariate analysis, LVMPI was the only independent marker of death ($p = 0.0213$). The ideal cut-off was 0.63 with 92.3% sensitivity, 66.7% specificity, and fitted ROC area = 0.918.
Conclusions: In children with IDCM, LVMPI is an independent marker of death.

Key words: heart failure, cardiomyopathy, cardiac transplantation, pediatric clinical cardiology, echocardiography

Introduction

Heart failure may be defined as a clinical syndrome in which the heart's pumping function is impaired by not supplying the necessary oxygenated blood flow for normal tissue metabolism, growth, and development.[1] Ventricular dysfunction may be caused by an increase in after-load, or in pre-load, or by intrinsic lesion to the heart muscle as in myocarditis or dilated cardiomyopathy.[2]

According to the World Health Organization, idiopathic dilated cardiomyopathy (IDCM) is characterized by dilatation and impaired contraction of the left ventricle (LV), or both ventricles.[3] In children, it is responsible for a large number of emergency treatments and hospitalizations due to heart failure not associated with congenital heart diseases.[4] It has a high mortality rate, reported at 50%–80% in 5 y.[5,6] In patients who do not respond to clinical treatment, heart transplantation remains the only therapeutic possibility.[7,8] It would be useful to have a marker of death to anticipate heart transplantation.

Myocardial performance index (MPI), as described by Tei et al., was reported as a parameter of ventricular systolic and diastolic function. It has been reported as a useful tool to predict the outcome in patients with ventricular dysfunction.[9] The purpose of this study was to evaluate the potentiality of MPI as an independent echocardiographic marker of death in children with IDCM.

Methods

Fifty-five consecutive children with IDCM (13 deaths) were submitted to 104 echocardiographic studies from January 1996 to May 2005. The echocardiograms were performed using probes of 3.5 MHz and 5.0 MHz, according to the patient's age and video recorded. The tapes were retrospectively reviewed by 2 authors, and the interobserver and intraobserver reliability rates were 92.3% and $\kappa = 0.918$.

The criteria for inclusion were the presence of heart failure, association with hypokinesis of LV, and LV end-diastolic dimension (LVEDD)/body surface area (BSA) >2 *z*-scores observed in the echocardiogram. Patients with congenital heart disease, Kawasaki's disease, arrhythmogenic cardiomyopathy, ischemic injury due to neonatal asphyxia or cardio-respiratory arrest, cardio-toxic agents, inborn errors of metabolism, primary arrhythmias, rheumatic heart

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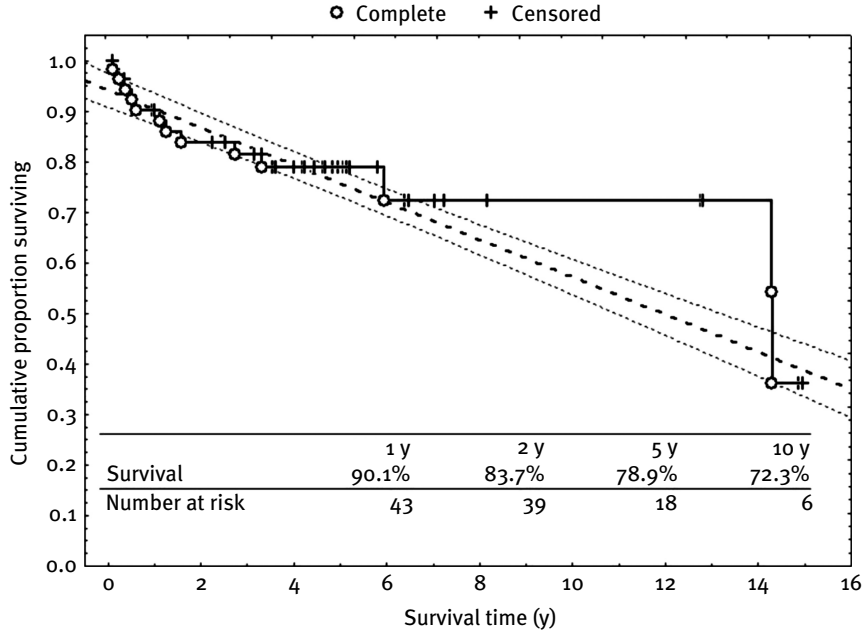

Figure 1: Cumulative proportional survival of 55 children and adolescents with IDCM.

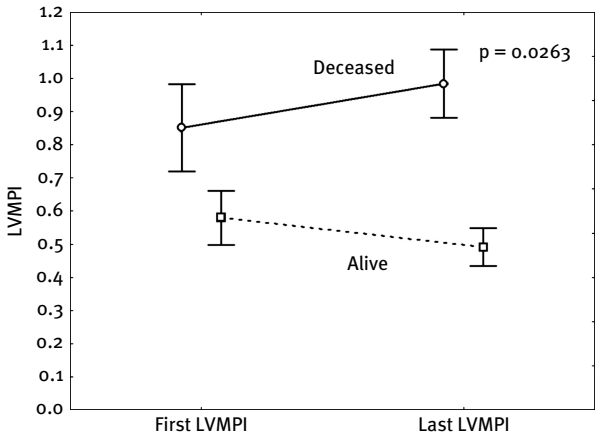

Figure 2: Analysis of variance for repeated measurements of LVMPI by groups (living versus deceased) between first and last LVMPI measurement. Vertical bars denote CI 95%.

disease, neuromuscular disease, systemic arterial hypertension, septicemia, human immunodeficiency virus (HIV), Chagas' disease, or diphtheria were excluded.

Right ventricle MPI (RVMPI) and LVMPI were measured. The MPI represented the sum of isovolumetric relaxation time (IRT) and isovolumetric contraction time (ICT) divided by ventricular ejection time (VET). The sum of IRT and ICT was obtained by subtracting VET from the interval between cessation and onset of the mitral inflow velocity to increase accuracy on measuring MPI due to the high heart rate in infants. Individual IRT and ICT were also measured to determine if they could predict death. To avoid significant impact on blood pressure and heart rate, sedation with chloral hydrate 20% was used in 9 small infants (16.4%) and was assisted by an anesthetist. The LVMPI was compared with classical echocardiographic markers of death in IDCM: mitral deceleration time (MDT), left atrium (LA)/BSA, LV ejection fraction (LVEF) by Simpson's biplane method, RV shortening fraction, distance between mitral E point and ventricular septum separation (EPSS), left ventricle mass (LVM)/BSA, fiber circumferential shortening velocity (Vcf), LV end-systolic dimensions (ESD)/BSA, and LVEDD/BSA. Mitral regurgitation (MR) was assessed by pulsed and color Doppler according to the American Society of Echocardiography guidelines.[10]

The medical treatment employed was optimized for patients' clinical status and included digitalis (69.1%), diuretics (80.0%) and spironolactone (65.4%), angiotensin converting enzyme inhibitors (69.1%), hydralazine (12.7%), and acetylsalicylic acid (30.9%) for prevention of thromboembolic events. The analysis of the treatment influence on outcome, however, was not the purpose of this study.

Statistical analysis was carried out using the Epi Info 6.04 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and the Statistica 6 software (Statsoft South America, Sao Caetano, Brazil). Values were expressed as mean and standard deviation (SD). Statistical analysis was performed using chi-square, Pearson's correlation, Student's t-test, Kaplan-Meier method, log-rank test, and analysis of variance (ANOVA) for repeated measurements. Multivariate analysis was performed by Cox's method.

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TABLE 1: Univariate analysis by Student t-test of echocardiographic parameters by group (survivor versus deceased) from all examinations performed

	All group (n = 104) Mean±SD	Survivor (n = 82) Mean±SD	Deceased (n = 22) Mean±SD	p-value
LVMPI	0.593±0.245	0.505±0.145	0.923±0.262	0.0001
RVMPI	0.559±0.219	0.486±0.136	0.842±0.252	0.0001
MDT (msec)	116±50	121±52	89±29	0.0365
LA/BSA	3.96±1.65	3.67±1.47	5.09±1.86	0.0003
LVEF	59.1±18.8	64.4±17.0	39.3±10.4	0.0001
RVSF	0.271±0.088	0.285±0.084	0.195±0.077	0.0003
EPSS (mm)	11.67±6.33	10.02±4.88	21.07±5.48	0.0001
LVM/BSA	140.06±32.16	119.91±72.66	215.17±91.42	0.0001
Vcf	1.072±0.464	1.145±0.462	0.661±0.183	0.0006
LVESD/BSA	4.83±2.70	4.37±2.46	6.52±2.91	0.0007
LVEDD/BSA	6.48±2.83	6.15±2.61	7.72±3.32	0.0201

Abbreviations: BSA = body surface area; EPSS = E point and ventricular septum separation; LA = left atrium; LVEDD = left ventricle end diastolic dimension; LVESD = left ventricle end systolic dimension; LVEF = left ventricle ejection fraction; LVM = left ventricle mass; LVMPI = left ventricle myocardial performance index; MDT = mitral deceleration time; RVSF = right ventricle shortening velocity; SD = standard deviation; Vcf = circumferential shortening velocity.

TABLE 2: Univariate analysis by Student t-test of echocardiographic parameters by group (survivor versus deceased) from first examination performed

	All group (n = 55) Mean±SD	Survivor (n = 42) Mean±SD	Deceased (n = 13) Mean±SD	p-value
LVMPI	0.630±0.250	0.545±0.154	0.904±0.309	0.0001
RVMPI	0.579±0.203	0.521±0.144	0.792±0.245	0.0001
MDT (msec)	102±45	107±48	83±19	0.1631
LA/BSA	3.34±1.89	3.03±1.77	5.42±2.01	0.0242
LVEF	55.7±20.2	61.0±19.3	38.5±11.8	0.0002
RVSF	0.265±0.081	0.279±0.075	0.207±0.088	0.0111
EPSS (mm)	12.43±6.40	10.41±4.77	20.70±5.64	0.0001
LVM/BSA	149.46±91.77	130.41±85.73	211.01±86.07	0.0046
Vcf	1.019±0.472	1.099±0.479	0.655±0.184	0.0090
LVESD/BSA	5.50±3.12	5.10±3.14	6.78±2.78	0.0912
LVEDD/BSA	7.15±3.28	6.88±3.26	8.06±3.31	0.2612

Abbreviations: BSA = body surface area; EPSS = E point and ventricular septum separation; LA = left atrium; LVEDD = left ventricle end diastolic dimension; LVESD = left ventricle end systolic dimension; LVEF = left ventricle ejection fraction; LVM = left ventricle mass; LVMPI = left ventricle myocardial performance index; MDT = mitral deceleration time; RVSF = right ventricle shortening velocity; SD = standard deviation; Vcf = circumferential shortening velocity.

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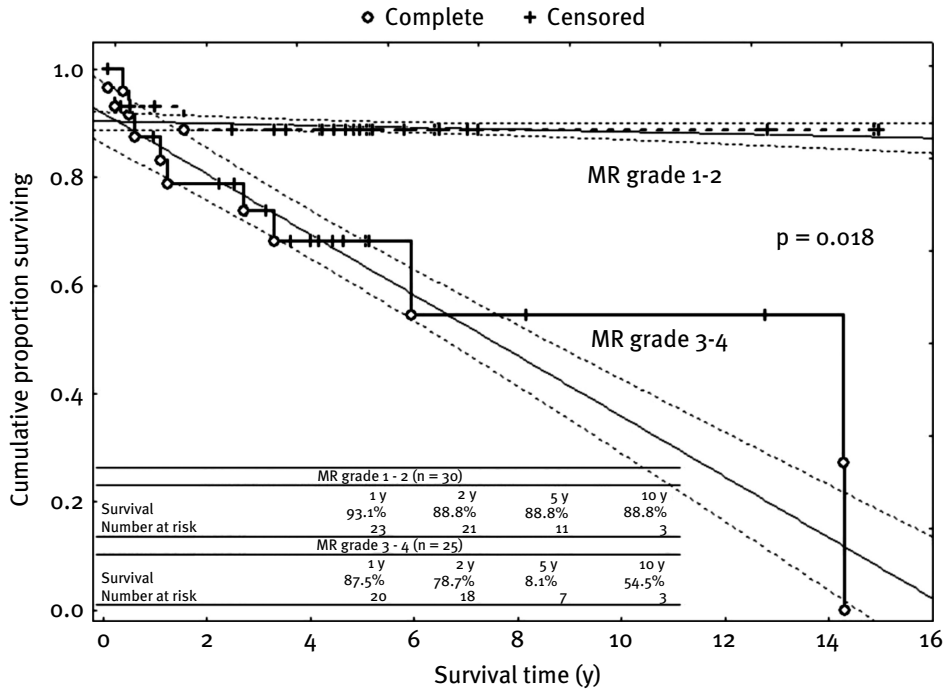

Figure 3: Survival analysis by Kaplan-Meier method and log-rank test by groups of MR severity.

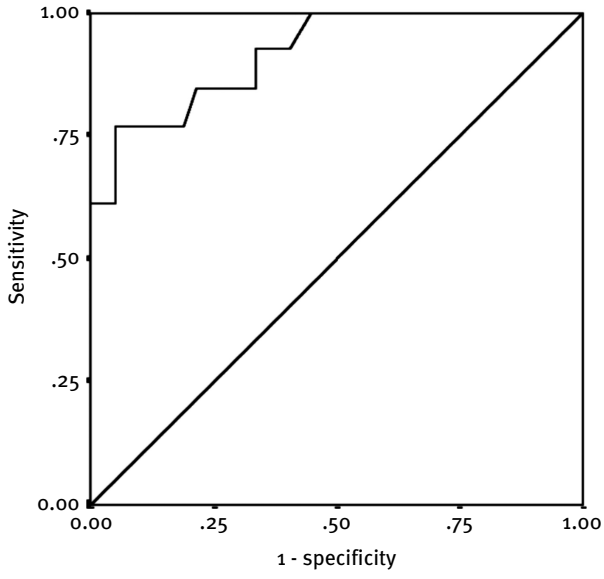

Figure 4: The ROC of LVMPI.

Receiver operating curve (ROC) was built to find the ideal cut-off. Statistical significance was considered with $\alpha < 0.05$ and $p = 80\%$. The authors state that the investigation conforms to the principles outlined in the Declaration of Helsinki. The institutional review committee approved this study and the subjects, or their guardians, gave informed consent. The authors have no conflicts of interest.

Results

Mean age at presentation was 3.36 y (median age was 1.06 y, 0.42–15.41), there were 24 male patients (43.6%–confidence interval [CI] 95% = 30.5% –57.6%) ($p = 0.18$), and 34 African-American patients (61.8%–CI 95% = 47.7%–74.3%) ($p = 0.013$). They were younger than 3 y of age, 66.7% in deceased patients, and 46.1% in survivors ($p = 0.178$). In deceased patients, death occurred at 9.5 y±6.5 y of age. Forty children (72.7%–CI 95% = 58.8% –83.4%) were in functional class III and IV, and all 13 deaths occurred in these functional classes (RR = 1.56–CI 95% = 1.24–1.95) ($p = 0.008$). Cumulative survival was 90.1% at 1 y of age, 83.7% at 2 y of age, 78.9% at 5 y of age, and 72.3% at 10 y of age (Figure 1). The median follow-up was 48.1 mo (lower and upper quartile = 12 mo–62 mo). The median interval from presentation to first MPI was 6.58 mo, and no difference between survivors and deceased was observed ($p = 0.235$). The gap between presentation and the first MPI allowed therapeutic optimization and decreased its influence on echocardiographic parameters. In the deceased group, the median time between the last MPI and death was 1.45 mo (0.56–2.96), and for first and last MPI it was 1.82 mo (0.56–5.48). In survivors, the median time between first and last MPI was 35.6 mo (11.7–57.1). Univariate analyses from all examinations performed are summarized in Table 1 and show that all echocardiographic parameters studied

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TABLE 3: Analysis of variance for repeated measurements of echocardiographic parameters by group (survivor versus deceased) from first to last examination performed

	First echocardiogram		Last echocardiogram		
	Survivor Mean±SD	Deceased Mean±SD	Survivor Mean±SD	Deceased Mean±SD	p-value
LVMPI	0.579±0.081	0.851±0.131	0.492±0.057	0.984±0.103	0.0263
RVMPI	0.552±0.077	0.783±0.137	0.461±0.057	0.889±0.102	0.0504
MDT (ms)	112±22	95±48	116±16	87±32	0.6923
LA/BSA	4.04±0.72	5.32±1.19	3.52±0.52	5.04±0.91	0.7747
LVEF	58.0±6.9	36.6±11.2	67.7±4.9	39.8±8.7	0.4406
RVSF	0.285±0.036	0.222±0.072	0.287±0.038	0.180±0.054	0.3764
EPSS (mm)	11.4±2.0	22.2±4.0	8.6±1.4	20.4±3.0	0.6968
LVM/BSA	132.4±34.9	202.0±56.5	112.7±24.6	230.8±44.3	0.2521
Vcf	1.057±0.197	0.600±0.441	1.226±0.158	0.691±0.311	0.7946
LVESD/BSA	5.31±1.21	6.63±1.95	4.06±0.86	6.64±1.53	0.3877
LVEDD/BSA	7.07±1.30	7.79±2.09	5.84±0.92	7.87±1.64	0.4035

Abbreviations: BSA = body surface area; EPSS = E point and ventricular septum separation; LA = left atrium; LVEDD = left ventricle end diastolic dimension; LVESD = left ventricle end systolic dimension; LVEF = left ventricle ejection fraction; LVM = left ventricle mass; LVMPI = left ventricle myocardial performance index; MDT = mitral deceleration time; RVSF = right ventricle shortening velocity; SD = standard deviation; Vcf = circumferential shortening velocity.

were markers of death. Nevertheless, IRT (0.064±0.014 versus 0.071±0.034, p = 0.18) and ICT (0.050±0.022 versus 0.066±0.052, p = 0.09) were not predictors of death. Table 2 summarizes univariate analysis by Student t-test from the first echocardiogram. All parameters, with the exception of MDT, LVESD/BSA, or LVEDD/BSA, were markers of death. There was a high correlation between RVMPI and LVMPI (r = 0.847, p = 0.0001); thus, to avoid bias in multivariate analysis, RVMPI was not used. Analysis of variance between the first and last echocardiogram showed differences among groups only for LVMPI, which increased in the deceased group (p = 0.0263) (Table 3, Figure 2). Right ventricle MPI was very close to significance (p = 0.0504), but as described above, it was not included in multivariate analysis. Mirtral regurgitation grades 3–4 were detected in 76.9% (CI 95% = 46.2%–94.9%) of children in the deceased group and 35.7% (CI 95% = 21.5%–52.0%) in the survivors group (RR = 2.15, CI 95% = 1.3–3.56, p = 0.0091), and it was deleterious to survival (p = 0.018) (Figure 3). Considering MR grades 3–4, LVMPI was different between groups: it was 0.867±0.256 in deceased patients and 0.539±0.168 (p<0.001) in survivors. Mirtral regurgitation is dependent on LVEF, LVESD/BSA, and LVEDD/BSA, and acts on LA/BSA. Therefore, to avoid bias, we performed multivariate analysis grouping by MR severity. In Cox's multivariate analysis, LVMPI was the only independent marker of death (p = 0.0213) (Table 4). The ideal LVMPI cut-off was 0.63 with 92.3% sensitivity, 66.7% specificity, and a ROC area of 0.918±0.043 (Figure 4).

Discussion

For a long time, despite the most obvious indicators of severity, it was not possible to predict the outcome of IDCM. At the beginning of M-mode echocardiography, heart function assessment was limited to the measurement of cavities, estimation of LV shortening fraction, and EPSS. After introduction of bi-dimensional and Doppler techniques, new approaches were implemented: LVEF, LV mass estimation, Vcf, MDT, IRT, and ICT.

In the present study, mean LA/BSA was higher in the deceased group, indicating an LV diastolic dysfunction and more severe MR, despite optimal therapy.[11] The LVESD/BSA and LVEDD/BSA were larger in the deceased group. Lewis, using the z score of LVEDD during follow-up, reported a reduction in the recovery group and unchanged values in the deceased group.[12] Mean LVEF was higher in the surviving group.[11] Some studies reported average

TABLE 4: Cox's multivariate analysis of echocardiogram parameters

	β	Standard error	t-value	Exponent β	Wald statistics	p-value
LVMPI	3.4877	1.5148	2.3023	32.711	5.301	0.0213
RVSF	7.5164	5.0539	1.4873	1837.976	2.212	0.1370
LVM/BSA	−0.0080	0.0054	1.4793	0.992	2.188	0.1391
Vcf	1.9819	1.4315	1.3844	7.256	1.916	0.1662
EPSS	1.1834	1.0323	1.1461	3.265	1.313	0.2518
LVEF	−4.8041	6.3548	−0.7560	0.008	0.572	0.4496
LA/BSA	0.1361	0.2953	0.4608	1.146	0.212	0.6449
MDT	3.3187	10.0237	0.3311	27.624	0.110	0.7406
LVEDD/BSA	0.3770	1.1393	0.3309	1.458	0.109	0.7407
LVESD/BSA	−0.1609	1.3486	−0.1193	0.851	0.014	0.9050

Dependent variable: evolution time to echocardiogram; Censoring: death; n = 104; chi-Square = 35.5688; degree of freedom = 10, p = 0.00010.
Abbreviations: BSA = body surface area; EPSS = E point and ventricular septum separation; LA = left atrium; LVEDD = left ventricle end diastolic dimension; LVESD = left ventricle end systolic dimension; LVEF = left ventricle ejection fraction; LVM = left ventricle mass; LVMPI = left ventricle myocardial performance index; MDT = mitral deceleration time; RVSF = right ventricle shortening velocity; SD = standard deviation; Vcf = circumferential shortening velocity.

LVEF, but only Akagi and Matitiau et al. reported differences among the deceased and the survivors.[4,6,13]

Mean LVM/BSA was increased in the deceased group. Left ventricle mass above the expected values for age was already observed at presentation and during follow-up, with significant decrease in the recovery group and increasing values, although nonsignificant, in the deceased group.[14,15] This observation was not, however, shared by others.[13]

Engle et al. were the first to describe EPSS as a marker of LV dysfunction in children. It was larger in the deceased group than in survivors, suggesting a more spherical shape of LV.[16] Karagiannis et al. related a reduction in EPSS with dobutamine infusion and correlated it with increased LVEF in adulthood.[17]

The MDT was lower in the deceased group than in survivors, suggesting a higher left atrial pressure. Nishimura et al. made simultaneous Doppler echocardiographic and cardiac catheterization studies of LV filling pressures in adult patients with dilated and hypertrophic cardiomyopathies. In the dilated group, they found an inverse correlation between left atrial pressure and MDT, and proposed that MDT <180 msec indicate a mean left atrial pressure >20 mm Hg.[18]

The Vcf was lower in the deceased group than in the survivors, in whom it was in the normal range.[19] Estimation of wall stress-fiber shortening relationship shows that this index is lower in patients with depressed contractility rather than in those with high after-loads.[20]

Tei et al. compared normal adults and patients with IDCM and found normal MPI as 0.39 ± 0.05, 0.59 ± 0.10 in functional class II, and 1.06 ± 0.24 in functional class III/IV patients.[9] Eto et al. described expected values in normal children under 3 y of age more than children over 3 y of age, and increased values in IDCM group, independent of age.[21]

Eidem et al. described RVMPI and LVMPI in preoperative children with Ebstein anomaly. They found abnormally increased values compared with age-matched normal children in both ventricles, and observed that increased RV dysfunction was directly proportional to increased RVMPI. Even patients with Ebstein anomaly, who had visually normal LV function, had an increased value on LVMPI.[22]

In children who received anthracycline treatment, Ocal et al. reported a prolonged ICT, a shortened VET, and no change in IRT, producing a prolonged MPI. They concluded that MPI was useful in monitoring incipient LV dysfunction in anthracycline treatment.[23] Elbl et al. found elevation of LVMPI in 7% of patients with subclinical cardio toxicity, and in 1 patient with heart failure. They suggested monitoring LVMPI in these patients for a longer period of time.[24]

Our group recently reported that LVMPI was an independent marker of death in children with IDCM.[25,26] In a similar cohort of 54 children with dilated cardiomyopathy, McMahon et al. described that combined lower LVEF and lower tricuspid early diastolic velocities in tissue Doppler predicted the combined end points of hospitalization, transplantation, or death.[27] They did not find MPI to be an

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independent predictor of death in children with IDCM. This apparent discrepancy is perhaps due to the difference in severity between the cohorts. In our cohort, the majority of children were in functional class III/IV, in contrast to their cohort in which the majority was in functional class I/II (75.9%). Another difference between these studies is that the end point in our study is death, and the McMahon report is a composite end point.

One remaining question is that, in the deceased group, the first MPI was almost 7 mo after presentation; the last MPI <2 mo later and 6 wk before death. Repeated measurements at these points of follow-up seem to be of limited value. Although, when the study was performed the date of death was not predicable, it is sure now that the gap for therapeutic optimization and first MPI needs to be shorter; perhaps in the first 2 wk of management.

In conclusion, in children with IDCM, LVMPI is easy to use, nongeometric dependent, and an independent marker of death. We have clearly shown that it adds value to classical echocardiographic parameters in the evaluation of death risk in children with IDCM. The children with LVMPI over 0.63, after initial therapeutics, need to be followed-up closely and be prepared for heart transplantation by inclusion in the waiting list.

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