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DETERMINANTS OF SEVERITY IN DILATED CARDIOMYOPATHY: THE GAP OF TRICUSPID AND MITRAL VALVE OPENING

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Abstract

Objectives: The purpose of this study is to analyze factors that influence the gap of opening timing between the mitral valve (MV) and the tricuspid valve (TV) in patients with dilated cardiomyopathy (DCM).

Background: The DCM patients with heart failure often show shorter left ventricular (LV) isovolumic relaxation time (IRT) and longer right ventricular (RV) IRT, which may influence the gap of opening timing between TV and MV.

Method: We evaluated consecutive 34 patients with DCM. The time between QRS initial and TV opening (Q-T time), and that between QRS initial and MV opening (Q-M time) were measured by pulsed Doppler recording of each ventricular inflow. The time interval between MV and TV opening (M-T time) was determined by subtracting Q-M time from Q-T time. In addition, the other Doppler time intervals including pre-ejectional period, ejection time, IRT were determined. We analyzed the relation between Doppler time intervals and factors including NYHA classification and right-sided cardiac pressure.

Result: There is significant relationship ($p<0.001$) between M-T time and PCWP ($r=0.65$), and NYHA ($rs=0.67$), respectively. The Δ IRT determined by subtraction of LV IRT from RV IRT, correlated significantly with M-T time ($r=0.83$, $p<0.001$), however, the difference between LV and RV in PEP and ET did not correlated significantly with M-T time.

Conclusion: The gap of opening timing between TV and MV, determined as M-T time, correlates strongly with ΔIRT and also the severity of congestive heart failure in DCM patients.

Key words: dilated cardiomyopathy, heart failure, mitral valve, tricuspid valve, isovolumic relaxation

Introduction

Tei *et al.*[1,2] demonstrated the deterioration of left ventricular (LV) global function in patients with dilated cardiomyopathy by a new Doppler index combining LV systolic and diastolic performance, TEI index, which was defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ejection time (ET). And now, it has known as the standard technique not only for dilated cardiomyopathy but also for the other cardiac disease[3]. Right ventricular (RV) Doppler index, similarly obtained from the RV Doppler time intervals, reflects the severity of heart failure in patients with dilated cardiomyopathy and behave differently toward left one, because RV ICT and RV IRT prolong with elevation of pulmonary artery systolic and diastolic pressure [4-6]. On the other hand, LV IRT decreases in severe heart failure. Prolongation of RV IRT may get the tricuspid valve opening later, while that of LV IRT may get the mitral valve opening earlier. Therefore, the gap of opening timing between tricuspid and mitral valve may be caused in patients with severe heart failure. In order to confirm this phenomenon and clarify the mechanism of this phenomenon, we analyzed the gap of opening timing between tricuspid and mitral valve in patients with dilated cardiomyopathy, and compared them with New York Heart Association (NYHA) functional class[7] and right-sided cardiac pressure data obtained by cardiac catheterization.

Patients and methods

Study population

The study group consisted of 26 normal subjects (14 males, 12 females, mean age 61±11 years) and 34 consecutive patients with idiopathic dilated cardiomyopathy (17 males, 17 females, mean age 61±17 years). Idiopathic dilated cardiomyopathy was considered in the presence of normal coronary arteries at coronary angiography or autopsy with LV global dysfunction. All of them were treated traditionally. LV ejection fraction was 32±9% (range 17 to 49) in study patients. NYHA functional class was I in 3, II in 12, III in 11 and IV in 8 patients. Study patients were divided into group A with NYHA II or I, and group B with NYHA III or IV, respectively. Patients with atrial fibrillation, atrial flutter, or frequent extrasystoles, and patients with organic valvular diseases or severe regurgitation of grade III-IV were excluded from this study.

We used the terms of IRT to simplify the terminology following previous reports[1,2-5] which do not exist in patients with mitral or tricuspid regurgitation in a strict sense. Severe valvular diseases may affect Doppler time intervals including IRT and M-T time and so on; therefore, we excluded patients with organic valvular diseases or severe regurgitation of grade III-IV from this study.

Echocardiographic examination

A two-dimensional, pulsed wave and color flow Doppler echocardiographic examination by commercially available ultrasound instrumentation (SSD-5500 Pro-Sound II, ALOKA TOKYO JAPAN) was performed. The LV diastolic and systolic dimensions were measured at the mid-ventricular level on the M-mode echocardiogram obtained by directing the cursor perpendicularly to the parasternal short-axis view. LV ejection fraction was calculated by Teichholz method[7] on the M- mode echocardiogram. Pulsed Doppler examination was performed as previously described[1,2-5]. The mitral and tricuspid flow signals were recorded from the apical four chamber or long-axis view, positioning the sample volume at the tip of the valve leaflets during diastole. Following this, LV and RV outflow signals were recorded from apical long-axis view and parasternal short-axis view, respectively. Doppler tracings were recorded with a strip chart recorder at a paper speed of 50 or 100 mm/s and measured in five consecutive beats and averaged for each parameter.

Fig. 1 shows the measurement of Doppler time intervals. The time between QRS initial and TV opening (Q-T time), and that between QRS initial and MV opening (Q-M time) were measured as the interval from the QRS initial to the onset of the ventricular inflow Doppler profile. Atrioventricular regurgitation signal was referred to determine the onset of the ventricular inflow. The time interval between MV and TV opening (M-T time) was determined by subtracting Q-M time from Q-T time. The ejection time (ET) of each ventricular outflow was measured as the interval from the onset to the end of the ventricular outflow

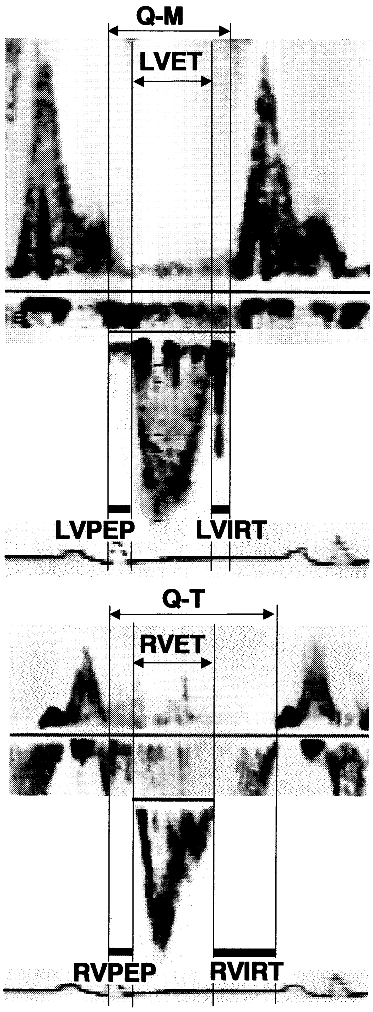

Fig. 1 Measurement of Doppler time intervals. The time between QRS initial and TV opening (Q-T time), and that between QRS initial and MV opening (Q-M time) were measured as the interval from the QRS initial to the onset of the ventricular inflow Doppler profile. The time interval between MV and TV opening (M-T time) was determined by subtracting Q-M time from Q-T time. The ejection time (ET) of each ventricular outflow was measured as the interval from the onset to the end of the ventricular outflow Doppler profile, and also the pre-ejection period (PEP) was measured as the interval from the QRS initial to the onset of the ventricular outflow Doppler profile. The LV IRT was determined by subtracting the sum of LV PEP and ET from Q-M time. RV IRT was also similarly determined by subtracting the sum of RV PEP and ET from Q-T time.

Doppler profile, and also the pre-ejection period (PEP) was measured as the interval from the QRS initial to the onset of the ventricular outflow Doppler profile. The LV IRT was determined by subtracting the sum of LV PEP and ET from Q-M time, because Q-M time is the sum of LV PEP, LV ET and LV IRT. RV IRT was also similarly determined by subtracting the sum of RV PEP and ET from Q-T time. In addition, the difference between RV and LV in PEP (⊿PEP), ET (⊿ET) or IRT (⊿IRT), was determined by subtraction of LV Doppler time interval from corresponding RV Doppler time interval, respectively. The M-T time is the sum of ⊿PEP, ⊿ET and ⊿IRT under this setting.

Cardiac catheterization

Right-sided cardiac catheterization was performed in 7 patients for monitoring hemodynamics, including pulmonary capillary wedge pressure, right atrial pressure and pulmonary artery systolic and diastolic pressure. A balloon-tipped pulmonary artery catheter was inserted into the right femoral or internal jugular vein and advanced to the pulmonary artery, where mean pulmonary capillary wedge pressure was recorded with the reference level at mid-chest. Echocardiographic and pressure data were obtained simultaneously in these patients. Then cardiac output was measured by the thermodilution technique. In addition, 14 patients underwent diagnostic right-and left-sided cardiac catheterization in the catheterization room. Echocardiographic data were obtained within 6 hours before diagnostic cardiac catheterization. Twenty-three measurements of echocardiographic and pressure data were obtained in a total of 18 patients with dilated cardiomyopathy, and the correlations between right-sided cardiac pressure and Doppler time intervals were analyzed. None of normal subjects underwent cardiac catheterization. Measurement of Doppler intervals was made by a single investigator who was unaware of the cardiac pressure data.

Statistical analysis

The echocardiographic data were compared between normal subjects, group A and group B by ANOVA followed by Scheffe test. The correlation between NYHA functional class and Doppler time intervals was analyzed by Spearman's rank correlation. The correlations between right-sided cardiac pressure and Doppler time intervals were analyzed by linear regression analysis. In addition, M-T time was compared with the ⊿PEP, ⊿ET or ⊿IRT, respectively by linear regression analysis. All data were expressed as mean±SD. A value of $p<0.05$ was considered statistically significant.

Reproducibility of Measurements

To estimate intra-observer variability, measurements of Q-M time, Q-T time and M-T time were done in 10 patients by two independent observers, and one observer repeated the measurement later.

Results

Clinical profile and echocardiographic measurements

Table 1 shows the clinical profile and echocardiographic measurements of normal subjects, group A and group B. Group B had the highest heart rate, the largest LV diastolic dimension and the lowest ejection fraction in 3 groups.

Table 1 Clinical profiles and echocardiographic findings in normal subjects, patients group with NYHA I-II (group A) and patients group with NYHA III-IV (group B)

	Normal (n=26)	Group A (n=16)	Group B (n=18)	p*
NYHA		I-II	III-IV	
Age (yr)	61±11	64±13	59±20	0.33
Male/female	14/12	8/8	9/9	
HR (bpm)	65±8	73±16	88±21†	0.022
LVDd (mm)	48±6	63±8†	70±11†	0.075
LVEF (%)	73±6	36±8†	29±8†	0.0091

*p value comparing Group A versus Group B. Data presented are mean value±SD. † $p<0.001$ versus normal subjects; NYHA=New York Heart Association functional class; HR=heart rate; LVDd=left ventricular diastolic dimension; LVEF=left ventricular ejection fraction.

Correlation between NYHA functional class and Doppler time intervals

Table 2 summarizes the Doppler time intervals of both ventricles. LV ET and RV ET decreased with the severity of NYHA functional class. LV PEP and RV PEP were significantly greater in DCM patients than in normal subjects; however, there was no significant difference in LV PEP and RV PEP between group A and group B. Group A showed the longest LV IRT in 3 groups, and LV IRT in group B was comparable to normal subjects. In contrast with LV IRT, RV IRT increased with the severity of NYHA functional class. The Q-M time in group B was significantly shorter than that in group A, while Q-T time in group B was comparable to that in group A. There was no significant difference in ⊿PEP and ⊿ET between group A and group B. However, ⊿IRT and M-T time were greater in group B than in group A (Fig. 2). The ⊿IRT also correlated significantly with M-T time, while ⊿PEP and ⊿ET did not (Table 3). There was no significant correlation between heart rate and M-T time (r=0.17, ns).

Table 4 shows Spearman's rank correlation coefficient between Doppler time intervals and NYHA functional class in study patients, excluding normal subjects. LV ET, RV ET, ⊿ET, LV IRT and Q-M time correlated negatively, while RV IRT, ⊿IRT and M-T time correlated positively with NYHA functional class.

LV PEP, RV PEP, ⊿PEP and Q-T time did not correlate significantly with NYHA functional class.

Correlation between right-sided cardiac pressure and Doppler time intervals

Table 5 shows the correlation coefficient by linear regression analysis between right-sided cardiac catheterization data and Doppler time intervals in 18 DCM patients. RV PEP, LV PEP, ⊿PEP and Q-

Table 2 Doppler time intervals in normal subjects, patients group with NYHA I-II (group A) and patients group with NYHA III-IV (group B)

	Normal (n=26)	Group A (n=16)	Group B (n=18)	p*
RV PEP (ms)	74±19	110±29§	103±22§	0.70
RV ET (ms)	322±32	292±40†	230±37§	<0.001
RV IRT (ms)	25±23	47±44	139±61§	<0.001
Q-T time (ms)	421±30	450±47	474±86†	0.23
LV PEP (ms)	73±17	138±45§	123±25§	0.16
LV ET (ms)	309±25	261±30§	215±26§	<0.001
LV IRT (ms)	70±19	93±30†	59±37	0.0034
Q-M time (ms)	452±33	492±50†	397±48§	<0.001
(ms)				
⊿PEP (ms)	1±18	−28±47	−20±29†	0.77
⊿ET (ms)	13±27	32±27	15±24	0.18
⊿IRT (ms)	−44±25	−46±38	81±67§	<0.001
M-T time (ms)	−31±24	−42±65	77±70§	<0.001

*p value comparing Group A versus Group B. Data presented are mean value±SD. †$p<0.05$ versus normal subjects; § $p<0.001$ versus normal subjects; ET=ejection time; IRT=isovolumic relaxation time; LV=left ventricular; M-T time=time interval between mitral and tricuspid valve opening; Q-M time=time interval between the initial of QRS and mitral valve opening; Q-T time=time interval between the initial of QRS and tricuspid valve opening; PEP=pre-ejection period; RV=right ventricular; ⊿PEP=RV PEP-LV PEP; ⊿ET=RV ET-LV ET; ⊿IRT=RV IRT-LV IRT.

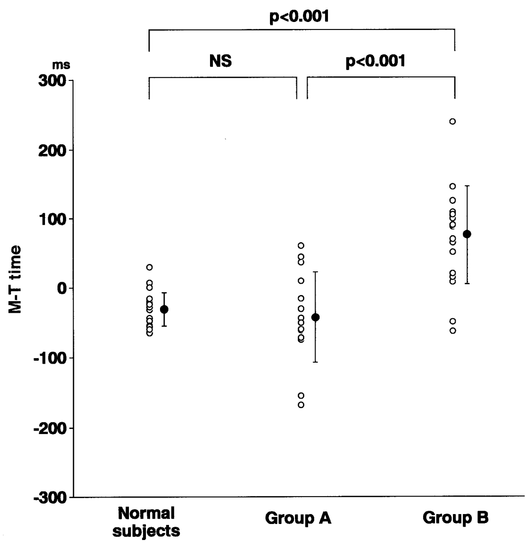

Fig. 2 Individual M-T time in each group.

T time did not correlate significantly with right-sided cardiac pressure. RV ET, LV ET, and Q-M time showed negative correlation with pulmonary capillary wedge pressure, pulmonary artery systolic and diastolic pressure, and right atrial pressure. LV IRT also correlated negatively with pulmonary capillary wedge pressure ($r=-0.50$, $p<0.05$). On the other hand, RV IRT correlated positively with pulmonary pressure, but not with right atrial pressure. The ⊿IRT correlated positively with pulmonary pressure and right atrial pressure. In addition, M-T time correlated positively with pulmonary capillary wedge pressure ($r=0.64$, $p<0.001$), pulmonary artery systolic pressure ($r=0.64$, $p<0.001$), pulmonary artery diastolic pressure ($r=0.57$, $p<0.01$), and right atrial pressure ($r=0.52$, $p<0.01$) (Fig. 3). None of the Doppler time intervals showed significant correlation with cardiac index.

Table 3 Correlation coefficients between ⊿PEP, ⊿ET, ⊿IRT and M-T time in normal subjects and patients with dilated cardiomyopathy

	r	p
⊿PEP	0.14	0.41
⊿ET	0.02	0.93
⊿IRT	0.83	<0.001

⊿ET = the difference between the right and left ventricle in the ejection time ; ⊿ET = RV ET - LV ET ; ⊿IRT = the difference between the right and left ventricle in the isovolumic relaxation time ; ⊿IRT = RV IRT - LV IRT ; ⊿PEP = the difference between the right and left ventricle in the pre-ejection period ; ⊿PEP = RV PEP - LV PEP ; M-T time = time interval between mitral and tricuspid valve opening ; M-T time = ⊿PEP + ⊿ET + ⊿IRT.

Table 4 Spearman's rank correlation coefficients between Doppler time intervals and NYHA functional class in patients with dilated cardiomyopathy

	rs	p
RV PEP	−0.019	0.91
RV ET	−0.70	<0.001
RV IRT	0.64	<0.001
Q-T time	0.12	0.50
LV PEP	−0.061	0.73
LV ET	−0.62	0.003
LV IRT	−0.51	0.003
Q-M time	−0.74	<0.001
⊿PEP	0.13	0.47
⊿ET	−0.35	0.043
⊿IRT	0.75	<0.001
M-T time	0.68	<0.001

ET = ejection time ; IRT = isovolumic relaxation time ; LV = left ventricular ; M-T time = time interval between mitral and tricuspid valve opening ; NYHA = New York Heart Association ; Q-M time = time interval between the initial of QRS and mitral valve opening ; Q-T time = time interval between the initial of QRS and tricuspid valve opening ; PEP = pre-ejection period ; RV = right ventricular ; ⊿PEP = RV PEP - LV PEP ; ⊿ET = RV ET - LV ET ; ⊿IRT = RV IRT - LV IRT.

We also analyzed the influence of complete left bundle branch block on the Doppler time intervals. Six of 34 patients had complete left bundle branch block, and these patients had significantly lower ⊿PEP than the other patients (−56±52 ms vs. −17±30 ms, p=0.017). However, ⊿ET, ⊿IRT and M-T time did not differ significantly between patients with CLBBB and the others.

Reproducibility of Measurements

The inter-observer mean difference was 1.77±3.13 ms, 1.81±3.86 ms and 0.04±2.69 ms, and the inter-observer percent variability was 0.39±0.72%, 0.41±0.88% and 3.09±16.9% for Q-M time, Q-T time and M-T time, respectively. Similarly, the intra-observer mean difference was 0.21±1.53 ms, 0.90± 1.86 ms and 0.68±2.16 ms, and the inter-observer percent variability was 0.06±0.34%, 0.22±0.44% and 1.60±5.36% for Q-M time, Q-T time and M-T time, respectively. The interobserver and intraobserver correlation coefficient were over 0.90 for Q-M time, Q-T time and M-T time.

Discussion

The patients with severe congestive heart failure frequently have short LV IRT[6], and long RV IRT[5,9]. Our study also showed that LV IRT correlated negatively and RV IRT did positively with NYHA functional class and pulmonary capillary wedge pressure in DCM patients. In addition, ⊿IRT, determined by subtraction of LV IRT from RV IRT, significantly correlated with NYHA functional class, right-sided cardiac pressure and M-T time. M-T time also correlated significantly with NYHA functional class and right-sided cardiac pressure. In other words, contrary change in LV IRT and RV IRT provoked the gap of opening timing between MV and TV in DCM patients with severe heart failure. Therefore, TV opening was later than MV opening in DCM patients with severe congestive heart failure.

RV IRT theoretically depends on the following : 1) pulmonary artery systolic pressure at closure of

Table 5 Correlation coefficients between Doppler time intervals and right-sided catheterization data in patients with dilated cardiomyopathy

	PASP	PADP	PCWP	RAP	CI
RV PEP	0.11	−0.09	−0.01	−0.13	−0.04
RV ET	−0.84‡	−0.84‡	−0.87‡	−0.65‡	0.27
RV IRT	0.69‡	0.55†	0.58†	0.37	−0.11
Q-T time	−0.087	−0.35	−0.32	−0.25	0.22
LV PEP	0.24	0.014	0.101	−0.06	−0.24
LV ET	−0.66‡	−0.70‡	−0.70‡	−0.52†	0.36
LV IRT	−0.41	−0.40	−0.50*	−0.37	−0.16
Q-M time	−0.65‡	−0.77‡	−0.81‡	−0.66‡	0.033
⊿PEP	−0.14	−0.080	−0.010	−0.039	0.18
⊿ET	−0.45*	−0.39	−0.42*	−0.33	−0.10
⊿IRT	0.73‡	0.63†	0.71‡	0.49*	0.017
M-T time	0.64‡	0.57†	0.64‡	0.52†	0.13

CI ; CI=cardiac index ; ET=ejection time ; HR=heart rate ; IRT=isovolumic relaxation time ; LV=left ventricular ; M-T time=time interval between mitral and tricuspid valve opening ; NYHA=New York Heart Association ; Q-M time=time interval between the initial of QRS and mitral valve opening ; Q-T time=time interval between the initial of QRS and tricuspid valve opening ; PADP=pulmonary artery diastolic pressure ; PASP=pulmonary artery systolic pressure ; PCWP=pulmonary capillary wedge pressure ; PEP=pre-ejection period ; RV=right ventricular ; RAP=right atrial pressure.
*$p<0.05$, †$p<0.01$, ‡$p<0.001$

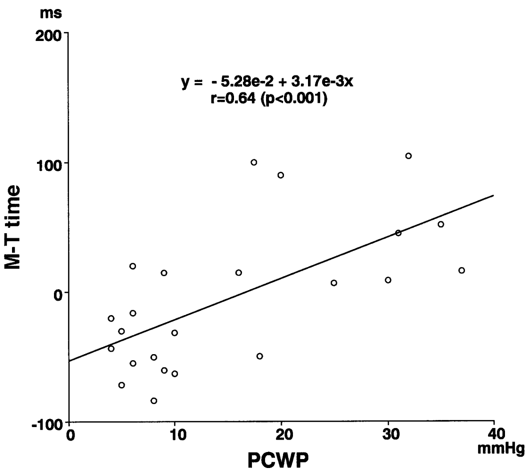

Fig. 3 The correlation between PCWP and M-T time in patients with DCM.

the pulmonary valve ; 2) the time constant of RV pressure during isovolumic relaxation ; and 3) the right atrial pressure at opening of the tricuspid valve[10]. Elevation of pulmonary artery end-systolic pressure probably cause early closure of the pulmonary valve, associating with short RV ET and long RV IRT in DCM patients with severe congestive heart failure[5]. On the other hand, the elevated right atrial pressure in congestive heart failure could shorten RV IRT theoretically, like LV IRT which becomes shorter with the elevation of left atrial pressure[6]. However, the elevation of the left atrial pressure and pulmonary artery pressure is prior to that of the right atrial pressure in left-sided heart failure, which may cause the elongation of RV IRT. In addition, RV IRT may be affected by abnormal RV relaxation property[8], because of RV lesion, the displacement of the interventricular septum or constraint of the pericardium in left-sided heart failure[11-13].

Not only IRT but also PEP and ET of each ventricle are determinants of Q-M time and Q-T time, because each of Q-M time and Q-T time is the

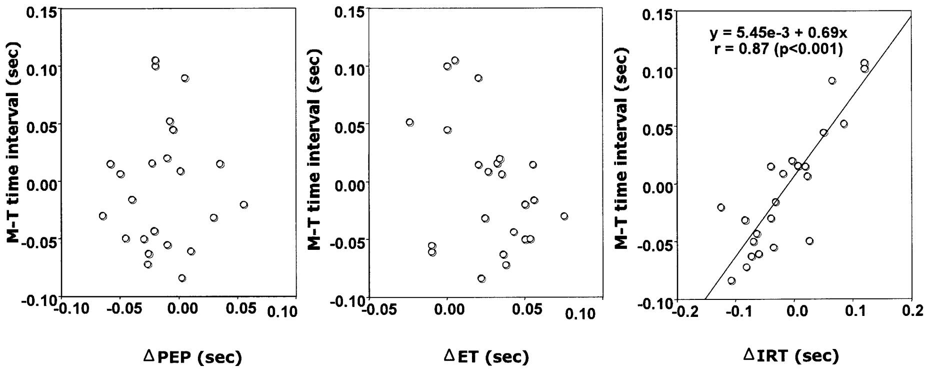

Fig. 4 The correlation between ⊿PEP, ⊿ET, ⊿IRT and M-T time.

sum of PEP, ET and IRT of each ventricle. Therefore, M-T time, determined by subtraction of Q-M time from Q-T time, is the sum of ⊿PEP, ⊿ET and ⊿IRT. However, ⊿PEP and ⊿ET did not correlated with M-T time significantly, while ⊿IRT was the largest division and M-T time was mainly dependent on ⊿IRT (Fig. 4).

M-T time showed considerable overlap among normal subjects, group A with NYHA I-II and group B with NYHA III-IV (Fig. 2), therefore, this measurement may have limitation to differentiate these 3 groups. M-T time is dependent on ⊿IRT, therefore, patients with both-sided heart failure who have compatible right and left atrial pressure, may show pseudo-normalization. However, none of study patients show such severe elevation of right atrial pressure. In addition, patients with severe diastolic dysfunction as cardiac amyloidosis, may have long LV IRT and small M-T time even with severe heart failure. Further analysis in patients with other cardiac diseases will be necessary.

Conclusion

The gap of opening timing between TV and MV, determined as M-T time, was strongly related to the severity of congestive heart failure in DCM patients.

Abbreviations and Acronyms

NYHA=New York Heart Association functional class
ET=ejection time
IRT=isovolumic relaxation time
PEP=pre-ejection period
LV=left ventricular
RV=right ventricular
M-T time=time interval between mitral and tricuspid valve opening
Q-M time=time interval between the initial of QRS and mitral valve opening
Q-T time=time interval between the initial of QRS and tricuspid valve opening
PADP=pulmonary artery diastolic pressure
PASP= pulmonary artery systolic pressure
PCWP=pulmonary capillary wedge pressure
RAP=right atrial pressure.

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