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New Index of Combined Systolic and Diastolic Myocardial Performance: A Simple and Reproducible Measure of Cardiac Function — A Study in Normals and Dilated Cardiomyopathy

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Abstract

Background Because systolic and diastolic dysfunction frequently coexist, it is hypothesized that a combined measure of left ventricular chamber performance may be more reflective of overall cardiac dysfunction than systolic or diastolic measures alone.

Methods Study patients consisted of 170 subjects: 70 normals, 47 patients with severe dilated cardiomyopathy in NYHA class III–IV awaiting cardiac transplantation and 53 patients with idiopathic dilated cardiomyopathy of intermediate severity [NYHA class II, ejection fractions (EF) 30–50%]. EF, stroke volume and cardiac indexes were measured using conventional echo-Doppler methods. Pre-ejection period/ejection time (PEP/ET), isovolumetric relaxation time (IRT), isovolumetric contraction time/ET (ICT/ET) were also measured. A new derived index of myocardial performance: (ICT+IRT)/ET, was obtained by subtracting ET from the interval between cessation and onset of the mitral inflow velocity to give the sum of ICT and IRT.

Results The index was easily measured, reproducible, and had a narrow range in normals. The mean value of the index was significantly different between normal, intermediate and pre-transplant subjects (0.39 ± 0.05, 0.59 ± 0.10 and 1.06 ± 0.24, respectively, $p<0.001$ for all comparisons). The degree of inter-group overlap was smaller for the index compared to PEP/ET, ICT/ET and other parameters. Within functional groups, the value of the index did not appear to be related to heart rate, mean arterial pressure and the degree of mitral regurgitation.

Conclusion (ICT+IRT)/ET is a conceptually new, simple and reproducible Doppler index of combined systolic and diastolic myocardial performance in patients with primary myocardial systolic dysfunction.

Key Words

cardiac function, myocardial performance, Doppler time intervals, systolic time intervals, Doppler echocardiography

INTRODUCTION

Studies in recent years have documented the frequent coexistence of systolic and diastolic dysfunction in the presence of dilated cardiomyopathy[1,2]. The systolic dysfunction is reflected in a decrease in

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left ventricular ejection fraction and a prolongation of the pre-ejection and shortening of the ejection phases of the cardiac cycle[3–6]. The diastolic dysfunction is reflected in alterations in the pattern of the inflow velocity of the left ventricle in early and late diastole[7,8] as well as prolongation of the relaxation phase of the cardiac cycle[9]. The present study of a newly devised index of left ventricular dysfunction was designed to test whether a combined measure of systolic and diastolic function may improve the accuracy in detecting left ventricular global dysfunction over that determined by measures of systolic and diastolic function alone. This index of left ventricular dysfunction takes advantage of the ease of measurement of the isovolumetric and ejection phases of the cardiac cycle that become available in the echocardiographic Doppler recording of the mitral and aortic flow velocity profile[10]. The study emphasizes the changes in patients with dilated cardiomyopathy as a diagnostic group in whom the primary alterations in cardiac function are related to disordered myocardial systolic and diastolic performance.

METHODS

Study population

Three groups were selected in order to study and compare the new index of combined systolic and diastolic myocardial performance with several more conventional, purely systolic and diastolic parameters. Group I comprised 70 normal volunteers (37 males, 33 females, mean age 50 ± 17 years), in whom complete Doppler examinations were available. All of these subjects were asymptomatic, had a normal physical examination, chest roentgenogram, electrocardiogram, and two-dimensional transthoracic echocardiogram. Group II consisted of 53 consecutive patients from the Echocardiographic Laboratory database, selected on the basis of a diagnosis of idiopathic dilated cardiomyopathy, New York Heart Association (NYHA) functional class II and ejection fraction (EF) between 30 and 50% (32 males, 21 females, mean age 58 ± 16). Group III consisted of 47 patients with severe dilated cardiomyopathy, and NYHA III–IV symptoms who were awaiting cardiac transplantation (38 males, 9 females, mean age 52 ± 10 years, EF 17 ± 7%). Of these 47 patients, 31 had idiopathic dilated cardiomyopathy and 16 had dilated cardiomyopathy on an ischemic basis. None of the patients selected had atrial fibrillation, atrioventricular block or organic valvular disease.

Echocardiographic examination

A complete two-dimensional, pulsed wave, continuous wave and color flow Doppler echocardiographic examination using commercially available ultrasound instrumentation was performed as previously described[11,12]. Left ventricular dimensions were measured at mid-ventricular level from the two-dimensional guided M-mode echocardiogram obtained by directing the cursor perpendicularly to the parasternal short-axis view. Left ventricular ejection fraction (LVEF) in groups I and II were measured by a modified Quinones' method[13].which eliminated subjective assessment of left ventricular apical function. LVEF in group III was measured using the apical biplane Simpson's method because of pronounced segmental asynergy in some patients.

Doppler examination

The mitral inflow velocity pattern was recorded from the apical four chamber view with the pulsed wave Doppler sample volume positioned at the tips of the mitral leaflets during diastole. Following this, the left ventricular outflow velocity was recorded from the apical long-axis view with the pulsed wave Doppler sample volume positioned just below the aortic annulus. Doppler tracings were recorded using a strip-chart recorder at a paper speed of 50 or 100 mm/sec or on 3/4 inch video tape. Doppler color flow imaging was used to semi-quantitate mitral regurgitation.

Echo/Doppler measurements

All echo/Doppler parameters were measured from strip charts or video tape recordings. Analysis of videotape recordings was performed on a Freeland Systems analyzer. Three consecutive beats were measured and averaged for each parameter. **Fig. 1** shows a schema for analysis of Doppler time intervals. Mitral closure-to-opening interval (a) is the time from the cessation to the onset of mitral inflow. Ejection time (ET) was measured as the duration of left ventricular outflow (b). Isovolumetric contraction time (ICT)+isovolumetric relaxation time (IRT) was obtained by subtracting 'b' from 'a', and a new index : (ICT+IRT)/ET was derived as (a–b)/b. To compare this new index with traditional

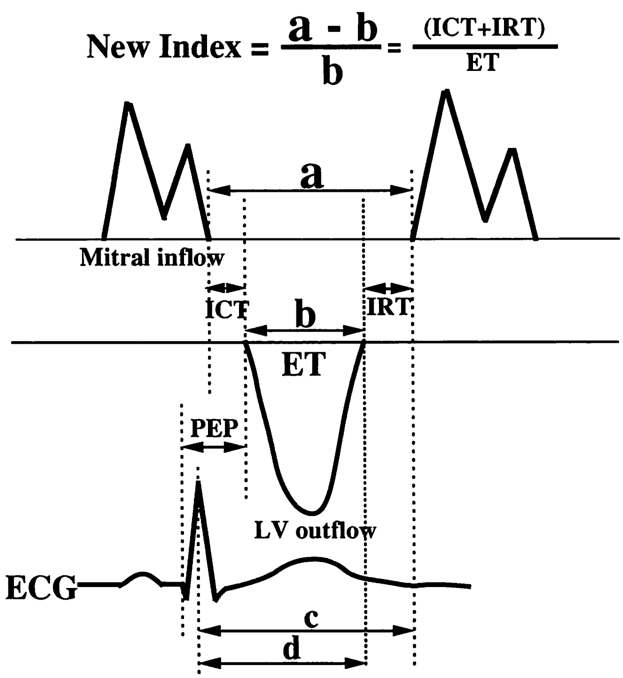

Fig. 1 Schema of Doppler time intervals

The new index (ICT+IRT)/ET is derived as (a–b)/b, where 'a' is the interval between cessation and onset of the mitral inflow and 'b' is ejection time (duration of left ventricular outflow). IRT (isovolumetric relaxation time) is measured as (c–d), where 'c' is the interval between the ECG R wave and the onset of mitral flow, and 'd' is the interval between the R wave and the cessation of left ventricular outflow. ICT (isovolumetric contraction time) is obtained by subtracting IRT from (a–b). PEP (pre-ejection period) is the interval from the onset of the QRS waveform to the onset of left ventricular outflow.

parameters, IRT, ICT and pre-ejection period (PEP) were also measured. IRT was measured as (c–d) by subtracting the interval (d) between the electrocardiography (ECG) R wave and the cessation of left ventricular outflow from the interval (c) between the R wave and the onset of mitral flow. ICT was obtained by subtracting IRT from (a–b). PEP was measured from the onset of the QRS waveform to the onset of left ventricular outflow.

Stroke volume was determined by recording a pulsed wave Doppler signal at the level of the aortic annulus, and performing volumetric analysis using the time velocity integral and left ventricular outflow tract diameter. Cardiac output was calculated as the product of heart rate and stroke volume. Peak velocities of mitral inflow in early diastole (E) and late diastole from atrial filling (A) were measured. The deceleration time (DT) was measured as the time from the peak E velocity to the intercept of the deceleration of flow with the baseline. DT was not measured in patients with summated E and A waves. Mitral regurgitation was diagnosed by color Doppler echocardiography and the severity of mitral regurgitation semi-quantitated from the area of the maximum regurgitant jet[13].

Statistical analysis

Continuous data are expressed as mean ±1 standard deviation (SD) and categorical data as frequency percentages. Analysis of the comparative discriminatory power of each variable was approached by using a paired comparison between each pair of variables. Each variable was first standardized to have mean zero and unit variance, when considered in any two groups combined. The differences between each pair of standardized variables was then subjected to a two-sample *t*-test between the two groups. Significance of this test would imply a significantly larger standardized group difference for one variable than the other, and hence more discriminating power. For example, if the standardized version of the new index (ICT+IRT)/ET is significantly higher than the standardized version of PEP/ET in group II, relative to their respective values in group I, this would imply that the former has greater ability than the latter to discriminate patients in group II from group I.

The relative strengths of the variables were also summarized by standardizing the data in terms of normals (group I), *i.e.* by expressing the data for the intermediate and pre-transplant groups relative to the normal mean and standard deviation. This represents a method for looking at each variable on the same scale (standard deviations from the normal mean).

Discrimination between groups was also illustrated and compared by means of a group overlap parameter. This parameter was defined in terms of the area under the receiver operator characteristic (ROC) curve, as overlap $=2\times(1-\text{area})$. The test for equality of this parameter between different variables is equivalent to the test for equality of areas under the ROC curve, and represents a nonparametric test of equality of discriminatory power.

RESULTS

Table 1 shows the clinical profile and echo-Doppler findings of the 3 study groups. Heart rate was significantly greater, and blood pressure lower in group III as compared to groups I and II. Mitral E/A ratio was smaller in group II and greater in group III

Table 1 Clinical profile and general echo-Doppler findings

	Group I (Normals)	Group II (Intermediate)	Group III (Severe)
Number of patients	70	53	47
Age (yrs)	50±17	58±16	51±10
Male	37	32	38
Body surface (m^2)	1.78±0.19	1.87±0.28	1.96±0.18
NYHA class	I	II	III or IV
Heart rate (bpm)	63±8	69±11	80±19
Systolic BP (mmHg)	126±13	127±16	108±12
Diastolic BP (mmHg)	75±7	77±8	70±10
Mean BP (mmHg)	92±8	94±10	82±9
LVDd (mm)	49±5	63±7	74±9
EF (%)	62±4	36±6	17±7
Mitral regurgitation			
Absence or trivial	70 (100%)	23 (43%)	6 (13%)
Mild	0	20 (38%)	17 (36%)
Moderate	0	6 (11%)	11 (23%)
Severe	0	4 (8%)	13 (28%)
Mitral flow : E/A	1.5±0.5	1.0±0.6	1.9±1.4
Mitral DT	192±34	209±63	173±58
SI (ml/m^2)	51±10	35±10	26±10
CI (l/m^2)	3.22±0.70	2.44±0.57	1.92±0.53

NYHA=New York Heart Association; BP=blood pressure; LVDd=left ventricular end diastolic dimension; E/A=peak velocity of early diastole/peak velocity of atrial systole; DT=deceleration time; SI=stroke index; CI=cardiac index.

as compared to that of group I. However, it was not measurable in 45% of group III patients due to summation of E and A waves. For the same reason, DT was not measurable in 49% of group III patients. Mild mitral regurgitation was detected in 38% of group II and 36% of group III patients. Moderate or severe regurgitation was observed in 19% of group II and 51% of group III patients. Stroke index and cardiac index were significantly lower in group II and further depressed in group III patients.

Fig. 2 shows an example of a measurement of the index in a normal subject (*upper*) and a patient with dilated cardiomyopathy (*lower*). **Table 2** summarizes the measured Doppler time intervals. The new index, PEP, PEP/ET, ICT, ICT/ET, ICT+IRT were all significantly greater in group II as compared to group I ($p<0.001$), and in group III as compared to group II ($p<0.001$). ET was significantly shorter in group II as compared to group I ($p<0.001$), and was most abbreviated in group III. IRT was greater in group II ($p<0.001$) and III ($p<0.05$) as compared to group I, but mean values were smaller in group III than in group II. The new index had a narrow range

Table 2 Summary of Doppler time intervals

	Group I ($n=70$)	Group II ($n=53$)	Group III ($n=47$)
New index	0.39±0.05	0.59±0.10	1.06±0.24
PEP (msec)	115±25	136±29	154±46
ET (msec)	310±43	289±36	236±42
PEP/ET	0.36±0.04	0.46±0.10	0.66±0.19
IRT (msec)	81±14	107±26	95±47
ICT (msec)	40±11	64±22	151±40
ICT+IRT (msec)	121±15	172±28	251±63
ICT/ET	0.13±0.03	0.22±0.08	0.65±0.21

PEP=pre-ejection period; ET=ejection time; IRT=isovolumetric relaxation time; ICT=isovolumetric contraction time.

in normals and significantly differed between the three groups.

Table 3 summarizes the results of comparison of the new index and other parameters between pairs of groups. The new index and PEP/ET variables in group II were 4.6 SD and 2.2 SD above the group I mean, respectively, suggesting that the index was more powerful than PEP/ET at differentiating mild left ventricular dysfunction from normals ($p<0.001$). Similar comparisons to other Doppler time interval parameters indicated the new index to be the measure which best discriminated the three study groups.

Table 4 shows the degree of overlap of variables between the various functional groups. This was least for the new index followed by ICT/ET. **Fig. 3** shows box plots of PEP/ET, ICT/ET and new index : (ICT+IRT)/ET by group.

Table 5 shows the correlation between heart rate and each parameter in normal subjects. Although ET, ICT, ICT+IRT showed significant correlation with heart rate, ratios such as PEP/ET, ICT/ET, (ICT+IRT)/ET were not significantly correlated with heart rate. **Fig. 3** shows the scatter of values of (ICT+IRT), ET and (ICT+IRT)/ET in relation to heart rate in normal subjects. Similar findings were noted for group II and III patients. Systolic, diastolic and mean blood pressures during Doppler echo recordings were also not significantly correlated with the new index in each group. **Fig. 4** shows the scatter of values of ICT+IRT, ET and (ICT+IRT)/ET in relation to heart rate in normal subjects. Similar findings were noted for group II and III patients. Systolic, diastolic and mean blood pressures during Doppler echo recordings were also not significantly correlated with the new index in each group. **Fig. 5**

Table 3 Comparison of the new index and other parameters

Variable	Group I vs group II		Group II vs group III		Group I vs group III	
Comparison variable	Mean in group II Standardized to group I	*p* value	Mean in group III Standardized to group II	*p* value	Mean in group III Standardized to group I	*p* value
New index DT	4.5±2.1 0.5±1.9	<0.001	4.3±2.1 0.6±0.9	0.004	13.8±4.5 0.6±0.6	<0.001
New index E/A	4.4±2.1 0.8±1.1	<0.001	4.2±2.1 1.6±2.5	0.04	13.5±4.4 1.0±2.9	<0.001
New index PEP/ET	4.6±2.1 2.2±2.2	<0.001	4.9±2.5 2.1±2.0	<0.001	14.9±5.2 6.8±4.3	0.004
New index ICT/ET	4.6±2.1 2.9±2.3	0.007	4.9±2.5 5.5±2.7	0.81	14.9±5.2 15.6±6.2	0.55
New index SI	4.6±2.1 1.6±1.0	0.02	5.0±2.5 0.9±0.9	<0.001	15.1±5.2 2.5±0.9	0.04
New index CI	4.6±2.1 1.1±0.8	<0.001	5.0±2.5 0.8±0.9	<0.001	15.1±5.2 1.8±0.8	0.003
New index EF	— —	—	— —	—	14.9±5.2 10.2±1.5	0.002

Abbreviations as in Tables 1, 2.

Table 4 Summary of inter-group overlap using various echo-Doppler parameters

Variable	Group I vs II Overlap %	Group II vs III Overlap %	Group I vs III Overlap %
New index	4%	1%	0%
DT	88%	63%	66%
E/A	51%	55%	89%
PEP/ET	33%	31%	3%
ICT/ET	24%	3%	0%
SI	26%	48%	8%
CI	37%	58%	13%

Abbreviations as in Tables 1, 2.

Table 5 Correlation of echo-Doppler parameters with heart rate in normal subjects

	r (n=70)	p value
New index	0.169	NS
PEP	0.179	NS
ET	0.411	$p<0.001$
PEP/ET	0.077	NS
ICT	0.301	$p<0.05$
ICT/ET	0.196	NS
IRT	0.197	NS
ICT+IRT	0.394	$p<0.001$
E/A	0.168	NS
DT	0.216	NS
FT	0.944	$p<0.0001$
SI	0.256	$p<0.05$
CI	0.394	$p<0.01$
EF	0.132	NS

FT=diastolic filling time. Other abbreviations as in Tables 1, 2.

shows the scatter of values of the index in relation to mean blood pressure in each group. In addition, the value of the new index did not appear to be related to the severity of mitral regurgitation in group III patients (1.07±0.28 in 23 patients with absence or mild regurgitation vs 1.08±0.24 in 24 patients with moderate or severe regurgitation, p=NS).

Reproducibility of measurements

When the Doppler recordings were analyzed in 30 randomly selected patients by the same observer on separate occasions, measurements of the new index were well correlated (r=0.98) with a mean percentage error of 2.1%. When two observers independently analyzed the data in 20 randomly selected patients, the mean interobserver difference (mean of three measurements per observer) was 4±3 msec for both 'a' and 'b', and the coefficient of variation was 0.9±0.6% for 'a', 1.5±1.0% for 'b' and 4.2 ±4.1% for the new index : (a–b)/b.

DISCUSSION

Global left ventricular performance is a function of both ventricular filling and ejection. Numerous

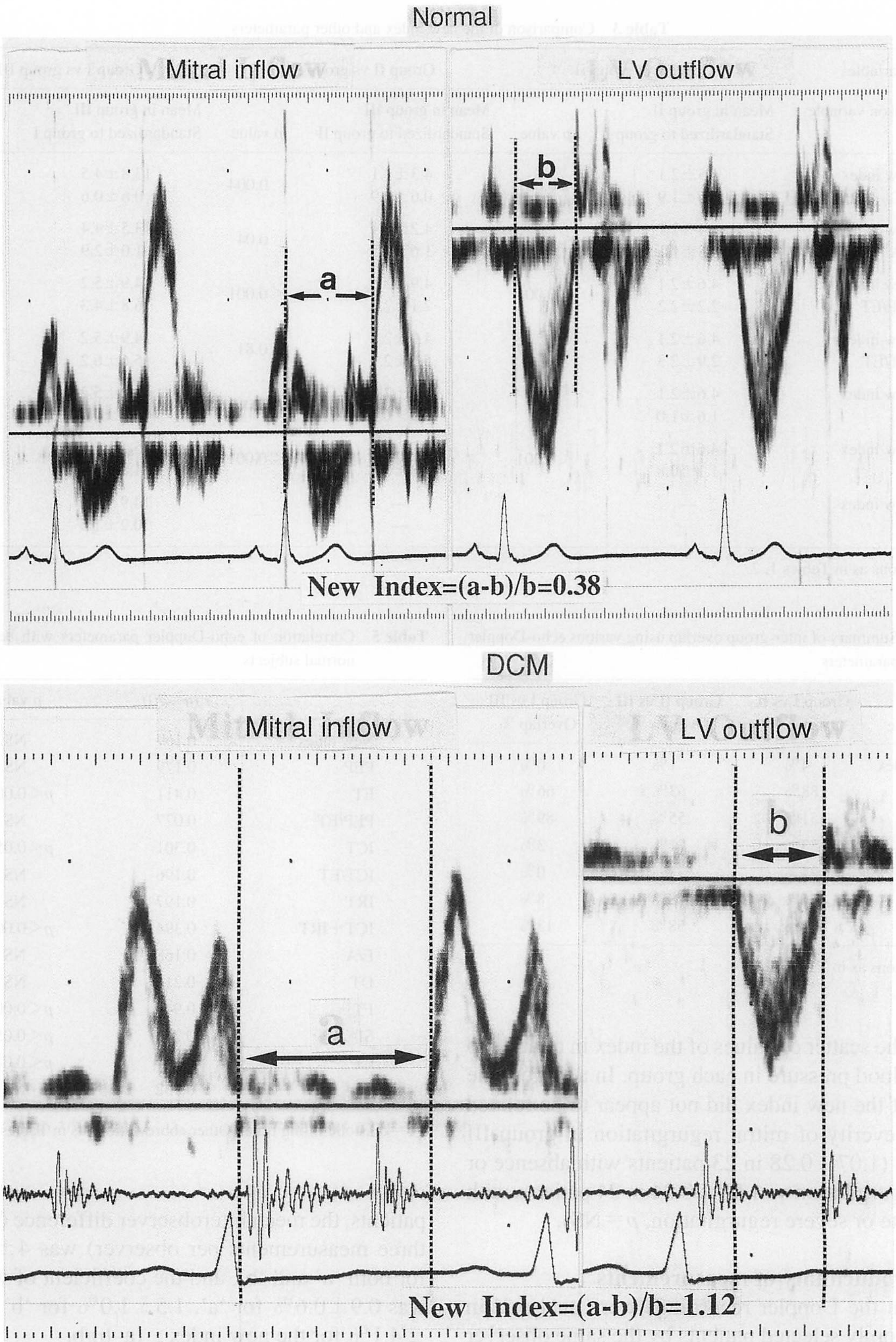

Fig. 2 An example of the measurement of Doppler time intervals from the pulsed wave Doppler echocardiograms of mitral and left ventricular outflow velocities in a normal subject (*upper*) and a patient with severe dilated cardiomyopathy (DCM; *lower*)
The value of the index '(a–b)/b' is 0.38 in the normal subject and 1.12 in the patient with DCM.

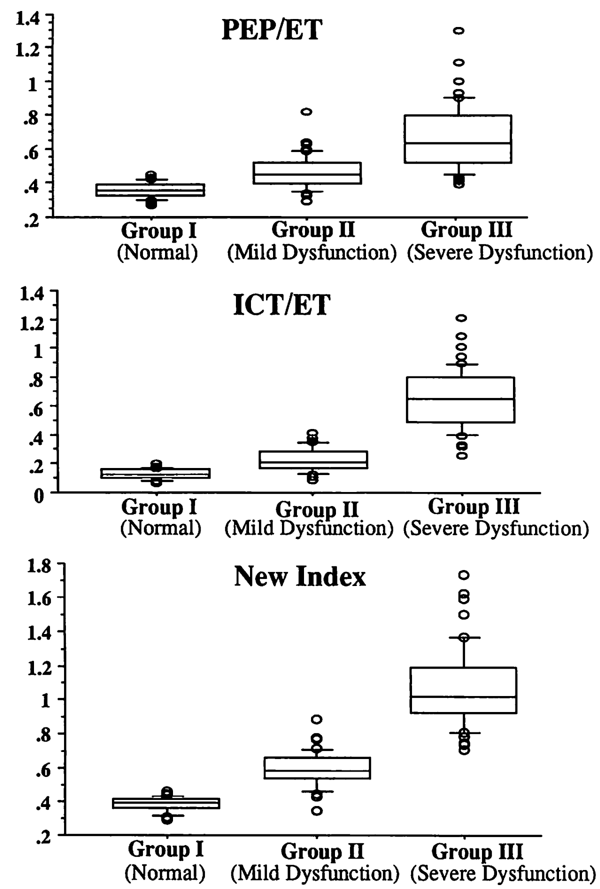

Fig. 3 Comparison of PEP/ET, ICT/ET and (ICT+IRT)/ET values between the three patient groups

The boxes indicate the lower and upper quartiles; the center lines represent the median value. The bars below and above the boxes indicate the 10% and 90% values, respectively.
Group I : Normal subjects.
Group II : Intermediate (mild dysfunction).
Group III : Pre-transplantation (severe dysfunction).
PEP=pre-ejection period; ET=left ventricular ejection time; ICT=isovolumetric contraction time; IRT=isovolumetric relaxation time.

indices have been used to assess either systolic or diastolic cardiac function and to date, the assessment of cardiac function in dilated cardiomyopathy has focused primarily on systolic dysfunction, or been dichotomized into systolic and diastolic phases. Since diastolic dysfunction is commonly associated with primary systolic dysfunction[1,2], a measure which combines assessment of systolic and diastolic function may better reflect 'global' function than the isolated evaluation of either ejection or relaxation. In this study, we report a new index for assessment of 'global' cardiac function which incorporates elements of both systole and diastole.

Previous studies have established that isovolumetric contraction time (ICT) is important in the assessment of systolic function[15] and isovolumetric relaxation time (IRT) in the assessment of diastolic function[16,17]. These intervals correspond to periods of active left ventricular chamber contraction and early relaxation[18]. Although individual measurements of ICT or IRT are more involved, the new index is derived from two easily measured Doppler time intervals (mitral closure-to-opening interval

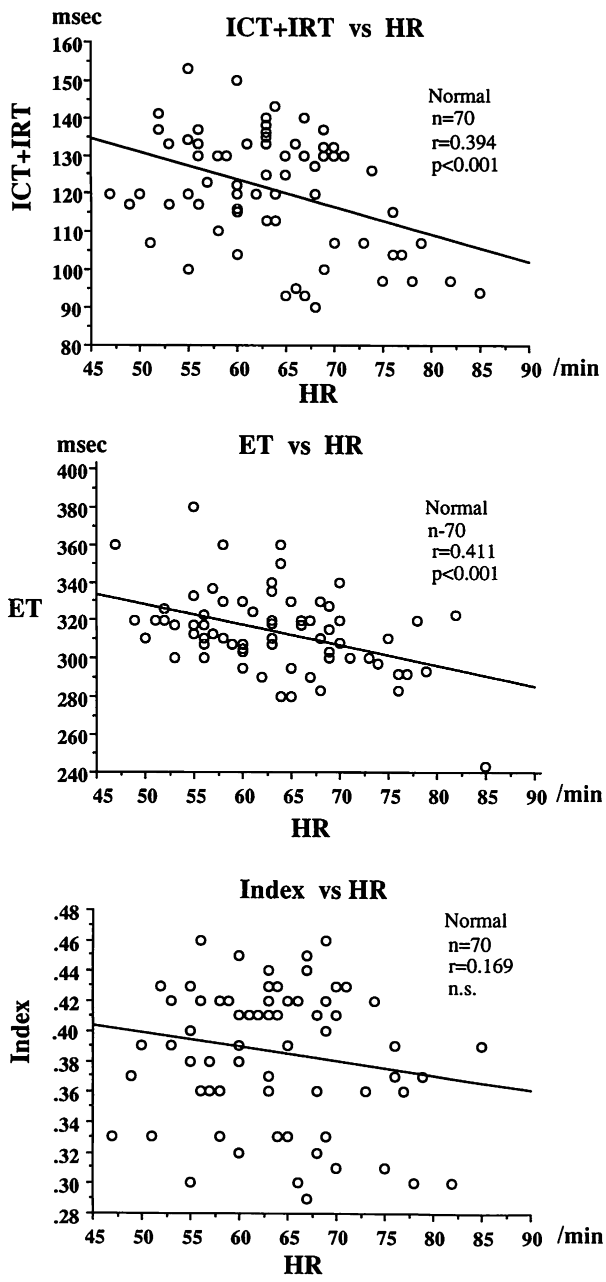

Fig. 4 Correlation between (ICT+IRT), ET, (ICT+IRT)/ET and heart rate in normal subjects

(ICT+IRT) and ET are significantly correlated to heart rate, but the ratio (ICT+IRT)/ET shows no significant correlation with heart rate.

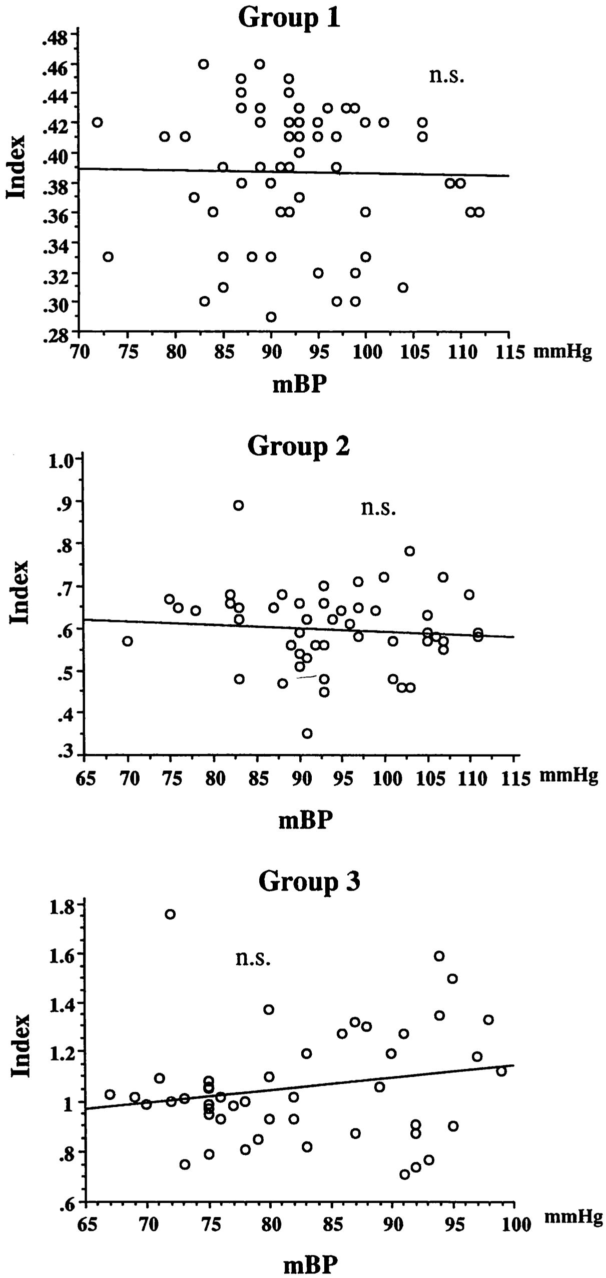

Fig. 5 Scatter-plot of the new index (ICT+IRT)/ET vs mean blood pressure for each patient group

No significant correlation is noted between mean blood pressure and the index in each group.

and ejection time). In addition, there was minimal variability of these measurements, consistent with a highly reproducible technique.

It is important to recognize that in a strict sense, ICT and IRT do not exist in patients with mitral regurgitation. In these patients, the 'duration of mitral closure-to-aortic opening' and 'duration of aortic closure-to-mitral opening' are more appropriate terms than ICT and IRT, respectively. However, in this communication, we have used the more intuitive terms ICT and IRT to simplify terminology.

The rationale for the utility of the new index in left ventricular dysfunction lies in the fact that (ICT +IRT)/ET encompass important periods of contractility and relaxation. Calcium influx and efflux at the myocellular level consequent to active ATP utilization occur during ICT and IRT[19]. Active myocardial processes are suppressed in patients with congestive heart failure and result in prolongation of active contraction and relaxation. The former is reflected by an increase in ICT resultant from : (a) severely reduced contractility (decreased *dp/dt*) and (b) earlier crossover of the left ventricular and left atrial pressure curves due to elevated left ventricular end-diastolic pressure[20]. While prolonged relaxation (decreased negative *dp/dt*) is initially associated with an increase in IRT, progressively worsening degrees of ventricular dysfunction will abbreviate this interval because of the dependence of IRT on factors other than active relaxation, such as left atrial pressure and the degree of mitral regurgitation[21]. Despite the variable change in IRT, the present study demonstrates that the sum of ICT and IRT progressively lengthens as left ventricular dysfunction evolves. As anticipated[4,22,23], ET was shorter in patients with severe left ventricular dysfunction compared to those with mild dysfunction and normals. Thus, with worsening left ventricular dysfunction (ICT+IRT)/ET increases disproportionately to any change in the individual components of the index. Consequently, the ratio was markedly different between each group, and the new index proved to be the best discriminator of each 'functional' group compared to other variables.

In the absence of an easily obtained measure of contractile function, EF is the parameter most commonly used for the assessment of systolic function. It has consistently proved to be a good indicator of cardiovascular outcome and thus has immense clinical relevance[24]. However, EF as determined by all technologies relies on assumptions of ventricular geometry and may not hold true in the case of abnormally shaped ventricles[25]. The adjunctive use of the proposed index may potentially provide useful information in these circumstances.

Use of EF alone may also result in erroneous assessment of contractility in patients with mitral regurgitation[26]. On the other hand, the severity of mitral regurgitation did not appear to influence the value of the new index in group III patients. With significant mitral regurgitation associated with severe left ventricular dysfunction, ICT is expected to be prolonged. On the other hand, mitral regurgitation shortens both ET and IRT, the latter due to a more elevated left atrial pressure. These alterations in the ejection and relaxation phase indices do not appear, however, to be reflected in the value of the derived index which remained constant in patients with both mild and severe mitral regurgitation.

Limitations of the present study

As with EF or any other clinically used parameter, heart rate and loading conditions may potentially alter the value of the new index. In the present study, however, there was no correlation between heart rate and blood pressure and the index in normals as well as patients with mild or severe left ventricular dysfunction. Likewise, there did not appear to be an appreciable difference in the index in patients with severe cardiac dysfunction and varying degrees of mitral regurgitation. However, further study is necessary to clarify the effect of loading conditions on the new index, particularly in an experimental setting where preload and afterload are more easily manipulated.

The new Doppler index was measured only in normal subjects and in patients with primary systolic dysfunction due to dilated cardiomyopathy. In the presence of significant valvular disease and secondary myocardial dysfunction, Doppler time intervals may be influenced by abnormal hemodynamics related to valvular dysfunction. The results of this study should also not be extrapolated to patients with congestive heart failure from primary diastolic dysfunction such as hypertrophic cardiomyopathy and restrictive cardiomyopathy. Finally mitral inflow may be significantly affected by atrioventricular block and atrial flutter and further study will be required to clarify the effect of arrhythmias on this index.

CONCLUSIONS

(ICT+IRT)/ET is a conceptually new Doppler index combining systolic and diastolic function parameters. It is technically easy to obtain and highly reproducible. Our data suggests this index to be a promising indicator of 'global' systolic and diastolic myocardial performance in patients with primary myocardial systolic dysfunction. Further study is necessary to clarify the utility of this index in other patient populations and in the determination of cardiovascular outcome and prognosis.

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