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Clinical Investigations

Different Prognostic Significance of Right and Left Ventricular Diastolic Dysfunction in Heart Failure

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Summary

Background: Left (LV) and right (RV) ventricular diastolic dysfunction is common in heart failure but the prognostic value of RV diastolic dysfunction is not known.

Hypothesis: As a follow-up to a previously undertaken study, this study was carried out to investigate whether LV and RV diastolic dysfunction affect prognosis differently and, in addition, whether changes in diastolic filling patterns over time correlate with clinical outcome.

Methods: We studied a cohort of 105 patients (mean age 62.7 ± 1.3 years, 66% male) with heart failure (ejection fraction < 50%) by Doppler echocardiography in both RV and LV.

Results: An LV restrictive filling pattern (RFP) was present in 48% of the patients and, when compared with non-RFP subgroups, it was associated with poorer systolic function, higher New York Heart Association functional class, and higher cardiac mortality at 1 year (all $p < 0.001$). The coexistence of an LV-RFP and poor LV systolic function (ejection fraction < 25%) markedly decreased the 1-year survival that was significant when compared with other subgroups ($p = 0.001$). In contrast, RV diastolic dysfunction that occurred in 21% of patients was not a prognostic factor for mortality either alone or in combination with LV diastolic dysfunction, but predicted nonfatal hospital admissions for heart failure or unstable angina ($p = 0.016$).

Conclusion: An LV restrictive filling pattern is a powerful predictor of a poor prognosis, especially when combined with low ejection fraction, but in this study RV diastolic dysfunction did not appear to be an independent predictor of subsequent mortality.

Key words: heart failure, diastole, prognosis, echocardiography

Introduction

Left ventricular (LV) diastolic dysfunction is common in patients with congestive heart failure due to impaired systolic function.[1] Various methods can be used to assess diastolic function of the heart, including cardiac catheterization,[2] radionuclide cardiac imaging,[3, 4] and Doppler echocardiography.[5–10] It has been suggested that diastolic dysfunction, especially the restrictive filling pattern, is an important prognostic indicator in patients with systolic heart failure.[1, 11–14] Recently, we have also shown that right ventricular (RV) diastolic dysfunction is also not uncommonly present in patients with heart failure;[15] however, the separate prognostic effects of RV diastolic dysfunction is not known. Therefore, we have carried out a prospective follow-up study to investigate whether LV and RV diastolic dysfunction affect prognosis differently and, in addition, whether changes in diastolic filling patterns over time correlate with clinical outcome.

Methods

Study Design

The study, conducted in a University teaching hospital in Hong Kong, was a follow-up analysis of a prospective cohort.

Subjects

From November 1994 to April 1995, 105 consecutive patients (mean age 62.67 ± 1.31, 66% male) with heart failure presenting to the hospital, were recruited into the study.

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Inclusion criteria included standard clinical features of heart failure with LV ejection fraction < 50% by echocardiography. The cause of heart failure was idiopathic dilated cardiomyopathy (IDC) in 37 (35.2%), ischemic heart disease in 56 (53.4%), hypertensive heart disease in 8 (7.6%), and aortic valve disease (mixed aortic stenosis and regurgitation in 3 and regurgitation in 1) with severe LV dysfunction in 4 (3.8%) patients. Patients with significant systemic disease, major organ failure, or malignancy were excluded. Idiopathic dilated cardiomyopathy was diagnosed if there was no clear etiology and an ejection fraction < 50%. Coronary angiography and endomyocardial biopsy were not considered mandatory and were performed in 60 and 43% of patients, respectively. Patients with ischemic heart disease had either a history of myocardial infarction or severe coronary artery disease on arteriogram, ejection fraction < 50%, and LV enlargement on the echocardiogram (end-diastolic dimension > 5.6 cm on long-axis view by M-mode echocardiography). Patients were followed up in a heart failure clinic and received standard treatment with diuretics (100%), angiotensin-converting enzyme (ACE) inhibitor (85%), nitrates (80%), or beta blockers (42%). Any hospitalization in between the follow-up period was registered. At the end of 1 year, a follow-up echocardiogram was performed in the survivors. For those who had died, the cause was ascertained by reviewing the hospital record and coroner certification, or by personal contact with a family member. Morbidity was defined as deteriorating heart failure requiring hospital admission or unstable angina.

Doppler Echocardiographic Examination

Two-dimensional echocardiography with continuous and pulse-wave Doppler studies was performed as previously described.[15] Right ventricular diastolic function was assessed using the parasternal short-axis view at the level of the tricuspid valve (TV).[15] The presence of RV diastolic dysfunction was defined as shortening of the tricuspid valve (TV), deceleration time (DT) of the early filling E wave (TV-DT < 143 ms), and reverse in TV-peak E/peak atrial filling velocity (E/A ratio < 1). In patients with atrial fibrillation, it was defined as short TV-DT (< 143 ms) combined with a prolonged RV-isovolumic relaxation time (IVRT) (> 76 ms).

Statistical Analysis

Survival curves were estimated by the Kaplan-Meier method. The difference in mortality between subgroups was compared using the log-rank test. Cox regression multivariate survival analysis was used to evaluate the predictive value of various factors to mortality. Multiple regression was used to assess the association of various covariates with morbidity. The echocardiographic data between different subgroups were compared using unpaired *t*-test or paired *t*-test where appropriate. The differences between categorical data were assessed by chi-square test. All data were expressed as mean ± standard error of the mean. $P < 0.05$ was considered statistically significant.

Results

The baseline clinical and echocardiographic characteristics of the 105 subjects are summarized in Table I. All had impaired systolic function with a low fractional shortening (FS = mean 16.93 ± 0.45%) and ejection fraction (EF = mean 34.73 ± 0.82%). More than half (55.3%) were in New York Heart Association (NYHA) functional class III or IV.

Left and Right Ventricular Diastolic Dysfunction

Baseline echocardiography showed a high incidence of LV diastolic dysfunction in patients with heart failure with impaired systolic function, with restrictive filling pattern (RFP) in 50 (47.6%), abnormal relaxation in 43 (41.0%) and "normal" in 12 (11.4%) patients. Of all patients, 21% (n = 22) fulfilled the criteria of RV diastolic dysfunction, 14 of whom had a coexisting LV-RFP. There was no relationship between the presence or absence of RV diastolic dysfunction and the etiology of heart failure.

When the LV diastolic pattern was divided into restrictive and nonrestrictive (non-RFP) subgroups, it was found that patients with LV-RFP had significantly worse systolic function (FS: 15.38 ± 0.68% vs. 18.34 ± 0.53%, $p = 0.001$; EF: 32.02 ± 1.23% vs. 37.18 ± 0.99%, $p = 0.001$). Heart rate was faster (85.78 ± 2.49 beats/min vs. 76.39 ± 1.92 beats/min, $p = 0.004$) and pulmonary arterial systolic pressure (PASP) was also higher (40.73 ± 2.31 mmHg vs. 29.00 ± 1.97 mmHg, $p < 0.001$) (Table II). Most of the RV diastolic parameters were also different between the two groups. Patients with LV-RFP had a significantly smaller TV-A velocity (39.33 ± 1.71 cm/s vs. 45.56 ± 1.50 cm/s, $p = 0.008$), larger TV-E/A ratio (1.11 ± 0.06 vs. 0.95 ± 0.04, $p = 0.042$) as well as shorter TV-DT (153.80 ± 7.05 cm/s vs. 201.98 ± 8.72 cm/s, $p < 0.001$). In addition, 35 (70%) of 50 patients with LV-RFP were in NYHA class III/IV, compared with 23 (42%) of 55 patients in the LV non-RFP subgroup ($X^2 = 8.4$, $p = 0.0004$).

Relationship between Diastolic Dysfunction and Cardiac Mortality

At the end of 1 year, seven patients were lost to follow-up. Among the remaining 98 patients, 29 died (at 1 year, all-cause mortality was 29.6%). The causes of death in these patients were congestive heart failure in 15, acute myocardial infarction in 4, sudden cardiac death in 3, cerebrovascular accident in 2, peripheral vascular disease in 1, and noncardiovascular cause in 1 (drug overdose). Three patients died outside hospital without apparent cause and postmortem was not performed. Of those with cardiovascular deaths (n = 25), 17 patients (68%) had LV-RFP and 8 (32%) had a nonrestrictive pattern. By chi-square table analysis, LV-RFP was significantly associated with mortality ($X^2 = 6.14$, $p = 0.01$) (Table III). By Kaplan-Meier survival analysis, the life table-estimated probabilities of survival were 61.4% in patients with LV-RFP and 84.0% in the LV non-RFP subgroup, with significant log rank statistics ($X^2 = 4.58$, $p = 0.03$) (Fig. 1).

TABLE I Baseline clinical and echocardiographic characteristics of 105 patients with heart failure

Variable	Mean ± SEM
Age (years)	72.67 ± 1.31
Sex (male: female)	69: 36 (66%: 34%)
Diagnosis	
Idiopathic dilated cardiomyopathy (IDC)	37 (35.2%)
Ischemic heart disease (IHD)	56 (53.2%)
Hypertensive heart disease (HTHD)	8 (7.6%)
Aortic valve disease (AVD)	4 (3.8%)
NYHA functional class	
I	13 (12.3%)
II	34 (32.4%)
III	53 (50.5%)
IV	5 (4.8%)
Heart rate (HR) (beats/min)	81.14 ± 1.65
Pulmonary arterial systolic pressure (PASP) (mmHg)	34.69 ± 1.61
LV-end diastolic diameter (EDD) (cm)	6.46 ± 0.11
Fractional shortening (FS) (%)	16.93 ± 0.45
Ejection fraction (EF) (%)	34.74 ± 0.82
Left atrial dimension (LA) (cm)	4.15 ± 0.07
MV-peak early filling velocity (E wave) (cm/s)	58.36 ± 2.03
Peak atrial filling velocity (A wave), cm/s	53.57 ± 2.10
Ratio of peak early and atrial filling velocity (E/A)	1.32 ± 0.09
Deceleration time of early filling (DT) (ms)	155.82 ± 7.30
LV-isovolumic relaxation time (IVRT) (ms)	129.57 ± 5.06
TV-peak early filling velocity (E wave) (cm/s)	44.02 ± 1.04
Peak atrial filling velocity (A wave) (cm/s)	43.04 ± 1.17
Ratio of peak early and atrial filling velocity (E/A)	1.02 ± 0.04
Deceleration time of early filling (DT) (ms)	179.04 ± 6.11
RV-isovolumic relaxation time (IVRT) (ms)	98.54 ± 4.54

Abbreviations: SEM = standard error of the mean, NYHA = Hew York Heart Association, LV = left ventricular, RV = right ventricular, MV = mitral valve, TV = tricuspid valve.

To assess the effect of combined diastolic and systolic dysfunction on cardiac mortality, the patients were stratified according to LV EF (at 25%) and the presence of LV-RFP. As there were only three patients with LV non-RFP with an EF $\leq 25\%$, they were excluded from analysis. By chi-square table, patients with LV-RFP and EF $\leq 25\%$ had the highest mortality, while it was lowest in patients with LV non-RFP and EF $> 25\%$ ($X^2 = 11.72$, $p = 0.003$) (Table III). The life table-estimated survival was: Group 1: LV non-RFP and EF > 25% (n = 47), 83.0%; Group 2: LV-RFP and EF > 25% (n = 34), 70.6%; and Group 3: LV-RFP with EF $\leq 25\%$ (n = 10), 30.0% (log rank $X^2 = 13.8$, $p = 0.001$). The log rank chi-square test comparing Group 1 with Group 3 was 11.0 ($p = 0.001$), and comparing Group 2 with Group 3 was 3.8 ($p = 0.05$) (Fig. 2).

By contrast, only 5 (23%) of 22 patients with RV diastolic dysfunction died of a cardiac cause, a fact which was not significant ($X^2 = 0.001$, $p = 0.98$). The probabilities of survival in patients with and without RV diastolic dysfunction (DD) were 73 and 74%, respectively, (log rank $X^2 = 0.20$, $p = 0.65$). Combined LV-RFP and RV-DD was not associated with an increase in mortality compared with LV-RFP alone (1 year survival LV-RFP alone = 61.4% and RV-DD with LV-RFP = 61.4%).

By Cox regression survival analysis, the presence of LV-RFP with EF $\leq 25\%$ remained as an independent predictor of cardiac mortality ($X^2 = 8.03$, $p = 0.018$). Age was another significant factor ($X^2 = 16.34$, $p = 0.0001$). Other factors, including gender, NYHA functional class, cause of heart failure, LV fractional shorting, LV end-diastolic diameter (EDD), left atrial size, PASP, heart rate, individual LV and RV diastolic parameter, or treatment modality, were all insignificant.

Relationship between Diastolic Dysfunction and Cardiac Morbidity

During the 1-year period of follow-up, 14 patients (total of 31 admissions) were admitted to the hospital for nonfatal congestive heart failure (n = 10), or unstable angina in those with ischemic cardiomyopathy (n = 6). Two patients were admitted for two separate causes. In addition, four patients had multiple admissions for heart failure and three for unstable angina. There was no association between LV-RFP and morbidity ($X^2 = 0.06$, $p = 0.80$) (Table IV). However, the presence of RV diastolic dysfunction significantly predicted cardiac morbidity, with 6 of 14 patients (42.9%) admitted having RV diastolic dysfunction on baseline echocardiography ($X^2 = 5.76$, p =

TABLE II Comparison of baseline clinical and echocardiographic characteristics of patients with restrictive (RFP) and nonrestrictive (non-RFP) filling pattern of left ventricle in diastole

	LV non-RFP (n = 50)	LV-RFP (n = 55)	p Value
Age (years)	64.27 ± 1.82	60.90 ± 1.88	0.201
Sex (male: female)	35:20 (64%; 36%)	34:16 (68%; 32%)	0.638
NYHA class			
I	5 (9.1%)	8 (16.0%)	$X^2 = 8.4$
II	27 (49.1%)	7 (14.0%)	0.0004
III	22 (40.0%)	31 (62.0%)	
IV	1 (1.8%)	4 (8.0%)	
HR (beats/min)	76.39 ± 1.92	85.78 ± 2.49	0.004
PASP (mmHg)	29.00 ± 1.97	40.73 ± 2.31	<0.001
LV-EDD (cm)	6.51 ± 0.17	6.41 ± 0.13	0.641
FS (%)	18.34 ± 0.53	15.38 ± 0.68	0.001
EF (%)	37.18 ± 0.99	32.02 ± 1.23	0.001
LA (cm)	4.07 ± 0.10	4.23 ± 0.10	0.257
MV-E wave (cm/s)	47.01 ± 2.14	70.85 ± 2.59	<0.001
A wave (cm/s)	65.96 ± 2.23	39.49 ± 2.30	<0.001
E/A ratio	0.70 ± 0.03	2.04 ± 0.13	<0.001
DT (ms)	201.99 ± 10.41	105.95 ± 2.94	<0.001
LV-IVRT (ms)	133.12 ± 6.49	125.58 ± 7.92	0.460
TV-E wave (cm/s)	42.72 ± 1.28	45.45 ± 1.66	0.191
A wave (cm/s)	45.56 ± 1.50	39.33 ± 1.71	0.008
E/A ratio	0.95 ± 0.04	1.11 ± 0.06	0.042
DT (ms)	201.98 ± 8.72	153.80 ± 7.05	<0.001
RV-IVRT (ms)	95.68 ± 6.61	101.59 ± 6.23	0.518

Abbreviations as in Table I.

0.016) (Table IV). By multiple linear regression analysis, the presence of RV diastolic dysfunction was the only significant factor that predicted nonfatal cardiac morbidity (odds ratio 2.29, p = 0.025, Table V). The other clinical and echocardiographic parameters were all insignificant.

TABLE III The correlation between (A) the presence of restrictive filling pattern of left ventricle (LV-RFP), and (B) the presence of LV-RFP with poor systolic function (EF = 25%) and cardiac mortality by chi-square test

(A) $X^2 = 6.14$, $p = 0.013$

	LV Non-RFP	LV-RFP
Survived	42 (44.7%)	27 (28.7%)
Died	8 (8.5%)	17 (18.1%)

(B) $X^2 = 11.72$, $p = 0.003$

	EF > 25% & LV non-RFP	EF > 25% & LV-RFP	EF = 25% & LV-RFP
Survived	39 (42.8%)	24 (26.4%)	3 (3.3%)
Died	8 (8.8%)	10 (11.0%)	7 (7.8%)

Abbreviations as in Table I.

Change in Pattern of Diastolic Dysfunction at Follow-Up Echocardiography in Survivors

A follow-up echocardiogram was performed at the end of 1 year in the survivors (n = 69). In one patient, pulse Doppler study was technically inadequate. Comparing baseline with follow-up echocardiography, there were significant changes in LV diastolic parameters (Table VI). The LV diastolic pattern became less restrictive as indicated by a prolongation of

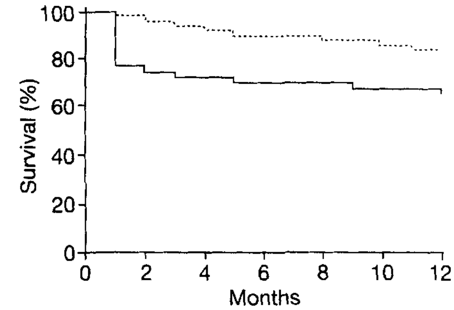

FIG. 1 Kaplan-Meier analysis of survival illustrating effect of left ventricular restrictive filling pattern (LV-RFP) on mortality. ---- = LV non-RFP, — = LV-RFP.

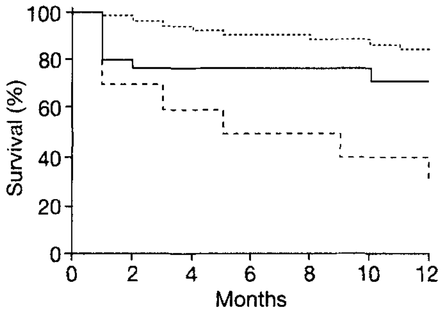

FIG. 2 Kaplan-Meier analysis of survival illustrating the combined effect of a left ventricular restrictive filling pattern (LV-RFP) and reduced ejection fraction (EF) on mortality. ---- = LV non-RFP and EF >25%, — = LV-RFP and EF >25%, - - - - = LV-RFP and EF ≤25%.

TABLE IV The correlation between (A) the presence of restrictive filling pattern of left ventricle (LV-RFP), and (B) the presence of right ventricular (RV) diastolic dysfunction and nonfatal hospital admission for heart failure or unstable angina by chi-square test

(A) $X^2 = 0.06, p = 0.804$

Cardiac morbidity	LV non-RFP	LV-RFP
No	45 (45.9%)	39 (39.9%)
Yes	7 (7.1%)	7 (7.1%)

(B) $X^2 = 5.76, p = 0.016$

	RV diastolic dysfunction	
Cardiac morbidity	No	Yes
No	71 (72.4%)	13 (13.3%)
Yes	8 (8.2%)	6 (6.1%)

MV-DT and a decrease in peak MV-E. The MV-E/A ratio also decreased significantly. The number (and percentage) of patients in the three LV diastolic pattern groups at baseline versus follow-up echocardiography were: "normal"—11 (16%) vs. 18 (26%); ARP—31 (45%) vs. 40 (59%); and RFP—27 (39%) vs. 10 (15%), respectively ($X^2 = 10.6, p = 0.005$). In the right ventricle, the TV-DT was also less short. The prevalence of RV diastolic dysfunction was significantly improved. Respective baseline and follow-up results were: normal—55 (80%) vs. 65 (96%) and abnormal—14 (20%) vs. 3 (4%) ($X^2 = 7.94, p = 0.005$).

The survivors also showed significant improvement in LV systolic function (Table VI). Both EF and FS were increased and the LV end-diastolic diameter was decreased. In these patients, it was found that 51% (n = 35) still had their initial LV diastolic pattern (RFP = 7, ARP = 22 and "normal" = 6). In the remaining 20 patients, the pattern shifted from an initial LV-RFP to a nonrestrictive pattern. Only three patients developed a restrictive filling pattern. In order to determine whether the changes in follow-up echocardiographic parameters were largely due to changes in the patients with an initial RFP, these were divided into subgroups: persistent LV-RFP (n = 7) and those who reverted to nonrestrictive pattern from an initial LV-RFP (n = 20). Their baseline and follow-up echocardiographic results were compared separately by paired *t*-test (Table VII). Those with a persistent LV-RFP showed no evidence of improvement of cardiac function. Instead, there was evidence for deterioration, with decrease in peak MV-A velocity and borderline increase in MV-E/A, and the LV enlarged further (Table VII). On the other hand, patients who shifted from a restrictive to a nonrestrictive LV diastolic pattern showed significant improvement in both diastolic and systolic function, with a decrease in MV-E velocity, increase in MV-A, decrease in MV-E/A, and normalization of MV-DT (Table VII). This was associated with an increase in EF and FS. The left ventricle became less dilated; in the right ventricle, TV-DT became longer, heart rate decreased, and more patients were in NYHA class I/II at follow-up.

With respect to RV diastolic dysfunction, all 14 survivors with initial RV diastolic dysfunction improved. When comparing follow-up results with the baseline in this group, LV EDD decreased (6.55 ± 0.27 cm vs. 6.06 ± 0.31 cm, p = 0.045) and NYHA functional class improved (2.6 ± 0.1 vs. 2.1 ± 0.2, p = 0.029). There was a trend toward improving LV FS and EF, but it was not significant statistically (FS: 16.36 ± 1.02% vs. 20.21 ± 1.88%, p = 0.087; EF: 33.86 ± 1.80% vs. 40.29 ± 3.29%, p = 0.095). The heart rate slowed (93.51 ± 3.79 beats/min vs. 70.28 ± 2.24 beats/min, p < 0.001). Right ventricular diastolic parameters also improved with an increase in TV-E/A ratio (0.78 ± 0.04 vs. 0.99 ± 0.06, p = 0.009) and the TV-DT normalized (120.68 ± 3.8 ms vs. 235.07 ± 12.64 ms, p < 0.001). There was normalization of MV-DT (119.50 ± 12.79 ms vs. 215.24 ± 18.5 ms, p = 0.001) and decrease in MV-E velocity (59.21 ± 6.65 cm/s vs. 40.14 ± 2.73 cm/s, p = 0.015), indicating a change from an LV-RFP toward a non-RFP.

TABLE V Multiple linear regression showing the relationship between nonfatal cardiac morbidity and clinical as well as echocardiographic parameters

Variable	Beta-coefficient	p Value	Odds ratio
RV diastolic dysfunction	0.252	0.025	2.29
Age	−0.071	0.530	−0.63
Sex	0.147	0.184	1.34
NYHA class	0.195	0.083	0.76
Heart rate	0.022	0.855	0.18
PASP	−0.019	0.878	−0.16
LV-EDD	0.167	0.131	1.53
LV-FS	−0.099	0.391	−0.86
LV-EF	−0.094	0.415	−0.82
LV-RFP	0.030	0.800	0.25
MV-DT	−0.103	0.382	−0.88
TV-DT	−0.053	0.686	−0.41

Abbreviations as in Table I.

TABLE VI Comparison of baseline and follow-up clinical and echocardiographic characteristics of 69 survivors by paired *t*-test.

	Baseline	1-Year follow-up	p Value
NYHA class			
I	12 (17.4%)	14 (20.3%)	$X^2 = 8.3$
II	24 (34.8%)	38 (55.1%)	0.005
III	33 (47.8%)	16 (23.2%)	
IV	0 (0%)	1 (1.4%)	
HR (beats/min)	78.93 ± 2.12	70.62 ± 1.57	<0.001
PASP (mmHg)	32.43 ± 1.85	34.73 ± 1.19	0.229
LV-EDD (cm)	6.60 ± 0.14	6.24 ± 0.14	<0.001
FS (%)	17.75 ± 0.53	21.43 ± 1.02	<0.001
EF (%)	36.27 ± 0.93	42.05 ± 1.71	<0.001
LA (cm)	4.21 ± 0.09	4.06 ± 0.10	0.257
MV-E wave (cm/s)	57.15 ± 2.62	50.20 ± 2.49	0.024
A wave (cm/s)	53.79 ± 2.33	55.90 ± 1.94	0.394
E/A ratio	1.23 ± 0.11	0.99 ± 0.09	0.033
DT (ms)	166.68 ± 9.67	213.31 ± 8.35	<0.001
LV-IVRT (ms)	133.44 ± 6.41	115.30 ± 4.80	0.041
TV-E wave (cm/s)	45.69 ± 1.27	43.91 ± 1.20	0.305
A wave (cm/s)	43.58 ± 1.55	41.36 ± 1.35	0.303
E/A ratio	1.06 ± 0.05	1.06 ± 0.04	0.970
DT (ms)	184.59 ± 7.46	217.55 ± 6.18	0.001
RV-IVRT (ms)	94.02 ± 5.82	84.67 ± 7.25	0.336

Abbreviations as in Table I.

TABLE VII Comparison of baseline and follow-up clinical and echocardiographic characteristics of patients who changed from a left ventricular restrictive filling pattern (LV-RFP) to a nonrestrictive pattern (non-RFP), or with a persistent LV-RFP, respectively, by paired *t*-test

	Patients changed from LV-RFP to non-RFP (n=20)			Patients with persistent LV-RFP (n=7)		
	Baseline	1-Year follow-up	p Value	Baseline	1-Year follow-up	p Value
NYHA class						
I	4 (20%)	2 (10%)	$X^2 = 6.5$	4 (47%)	3 (43%)	$X^2 = 1.4$
II	5 (25%)	13 (65%)	0.039	0 (0%)	3 (43%)	0.237
III	11 (55%)	5 (25%)		3 (43%)	1 (14%)	
HR (beats/min)	84.39 ± 4.58	69.66 ± 2.22	0.004	83.07 ± 6.47	72.93 ± 6.04	0.160
PASP (mmHg)	36.58 ± 3.29	34.90 ± 2.12	0.658	38.57 ± 5.80	35.57 ± 4.43	0.620
LV-EDD (cm)	6.23 ± 0.13	5.66 ± 0.17	<0.001	7.13 ± 0.48	7.47 ± 0.56	0.045
FS (%)	17.15 ± 1.01	23.83 ± 1.77	0.002	16.86 ± 1.63	18.57 ± 1.19	0.441
EF (%)	35.44 ± 1.73	46.75 ± 3.10	0.003	34.93 ± 2.56	36.86 ± 2.14	0.610
LA (cm)	4.17 ± 0.14	4.05 ± 0.21	0.619	4.56 ± 0.32	4.11 ± 0.28	0.330
MV-E wave (cm/s)	72.03 ± 4.53	46.20 ± 3.78	<0.001	73.09 ± 7.14	70.21 ± 8.45	0.673
A wave (cm/s)	40.66 ± 3.28	58.97 ± 2.76	<0.001	36.04 ± 3.44	26.64 ± 3.36	0.002
E/A ratio	2.03 ± 0.21	0.81 ± 0.09	<0.001	2.20 ± 0.35	2.78 ± 0.23	0.099
DT (ms)	109.16 ± 3.50	209.87 ± 13.67	<0.001	113.86 ± 9.96	134.57 ± 14.38	0.018
LV-IVRT (ms)	139.94 ± 17.67	123.38 ± 7.34	0.354	110.86 ± 12.17	71.79 ± 9.21	0.075
TV-E wave (cm/s)	48.85 ± 2.48	42.64 ± 2.00	0.041	49.11 ± 4.24	48.13 ± 3.52	0.781
A wave (cm/s)	39.27 ± 2.23	40.39 ± 2.35	0.770	43.15 ± 3.27	42.82 ± 2.98	0.940
E/A ratio	1.21 ± 0.10	1.07 ± 0.07	0.324	1.09 ± 0.12	1.06 ± 0.03	0.788
DT (ms)	161.58 ± 13.33	214.32 ± 11.23	0.006	167.38 ± 13.94	214.45 ± 22.38	0.153
RV-IVRT (ms)	83.37 ± 6.70	85.10 ± 15.39	0.918	108.33 ± 22.55	76.92 ± 10.38	0.241

Abbreviations as in Table I.

Discussion

First, this study confirms that despite maximum medical therapy, heart failure in our community still has a poor prognosis, and second, that LV diastolic dysfunction is common with a restrictive filling pattern occurring in 48% of patients, similar to that reported by others (37 to 58%).[1, 7, 12–14, 16–21] The restrictive filling pattern is associated with worse systolic function, higher NYHA functional class,[1, 12–14, 22] and higher atrial and brain natriuretic peptide levels (which are markers of high left atrial and ventricular filling pressures).[23] Abnormalities of diastolic performance may also be the most important cause of exercise intolerance in patients with chronic heart failure.[24, 25] Previous studies have mostly focused on LV diastolic function, although many cardiac diseases affect both the left and right ventricles. Recently we have shown that there is also a high prevalence of RV diastolic dysfunction in patients with systolic heart failure and that this is not related to elevated pulmonary systolic pressure alone.[15] However, there is no published information on the impact of RV diastolic dysfunction on morbidity or mortality, although RV systolic function appears to be a powerful predictor of survival,[26] and it is possible, therefore, that RV diastolic function is also important.

Right Ventricular Diastolic Dysfunction and Prognosis

We were unable to demonstrate any independent association between mortality and RV diastolic dysfunction. The relative lower incidence of RV diastolic dysfunction compared with an LV-RFP may be one of the reasons and have a greater impact on LV systolic and diastolic dysfunction. However, we found that RV diastolic dysfunction is the single most important factor that predicted nonfatal hospital admission for congestive heart failure or unstable angina. In part, this may be a reflection of pulmonary hypertension, and thus the severity of LV disease.[15] In addition, the filling pressure of the right ventricle may be elevated because of increased stiffness of the RV secondary to myocardial fibrosis, as is found in idiopathic dilated cardiomyopathy and in the noninfarcted right ventricle secondary to anterior myocardial infarction,[27] as well as in patients with ischemic cardiomyopathy.[28] High ventricular pressures during early filling will rapidly equalize the pressure gradient across the tricuspid annulus causing a short TV-DT. In addition, the increase in circulating volume in heart failure may cause a dominant atrial filling wave during right atrial contraction. The prolongation of RV-IVRT probably reflects either the elevated pulmonary artery pressure or delayed relaxation of the ventricle, which can be related to myocardial structural changes, ventricular interdependence,[29] or pericardial restraint in the dilated heart. There is a suggestion that in patients with dilated cardiomyopathy, RV filling time is limited by prolonged tricuspid regurgitation or a prolonged RV-IVRT.[30] Although some factors affect diastolic performance in both ventricles simultaneously, the differing prognostic implications imply that either different pathophysiologic factors may operate or, more likely, the impact of LV disease is so much greater. It is interesting to speculate why RV diastolic dysfunction should be associated with an increased risk of unstable angina. One hypothesis is that RV diastolic dysfunction is more likely with, and may be a marker of more severe ischemic heart disease.

Left Ventricular Diastolic Dysfunction and Prognosis

In this study, we have confirmed that the presence of an LV restrictive filling pattern during diastole is an independent predictor of short-term cardiac mortality.[13] The survival decreased from 84% in the nonrestrictive group to 61% in the restrictive group. Pinamonti *et al.* found that deceleration time was the strongest predictor of survival.[12] However, we were unable to demonstrate any association between individual diastolic parameters and mortality. The age in their study group was much younger (mean 39 years) and the only diagnostic group studied was that with dilated cardiomyopathy, which may partially account for the difference. Rihal *et al.*, in another retrospective cohort study, found that patients with LV deceleration time < 130 ms and LV ejection fraction < 25% had a worst survival at 34.8%, which is similar to our finding although the definition of RFP was slightly different.[1]

Although it is generally recognized that low EF is a poor prognostic factor,[19, 31, 32] it is not a consistent finding.[33] In our study, we found that patients with LV-RFP and coexisting poor systolic function (EF < 25%) had a markedly decreased 1-year survival of only 30%. This relationship persisted in Cox multivariate regression analysis. This is important clinically, as combined severe LV systolic and diastolic dysfunction appears to predict the natural progression reliably to end stage heart failure which is invariably fatal, and this group of patients may benefit most from aggressive medical therapy and early cardiac transplantation.

Changes of Diastolic Patterns

In the survivors, there were changes in both diastolic and systolic function, with less LV restrictive filling patterns, less RV diastolic dysfunction, as well as better systolic function. We also assessed the changes in echocardiographic parameters within the subgroup with an initial LV-RFP. It is important that we found that patients with persistent LV-RFP had no evidence of improvement of systolic and diastolic parameters. Instead, there was deterioration of cardiac status with further dilatation of the LV, and possibly progressive atrial failure as denoted by the significant decrease in peak MV-A velocity. On the other hand, those who reverted from a restrictive to a nonrestrictive filling pattern not only had significant improvement in their LV diastolic parameters, but also better systolic function and decrease in heart size. There was also a favorable change in RV diastolic filling with prolongation of the TV-DT. Moreover, the functional status improved with more patients in NYHA class I/II. It is likely that improvement in loading conditions with longer-term treatment (especially ACE inhibitors) and possibly structural changes in the myocardium cause the change from a restrictive to a nonrestrictive pattern. Those with a persistent LV-RFP probably have irreversible changes in the myocardium, therefore a restrictive filling pattern continues despite any hemodynamic improvements that occur with long-term treatment. In this situation, the DT (the main determinant of the RFP) becomes a reasonably good measure of LV stiffness. Little *et al.*,[34] in an elegant study using an animal model, were able to confirm that actual chamber stiffness closely correlated with predicted LV chamber stiffness based on measured early deceleration time. In the right ventricle, the incidence of RV diastolic dysfunction also decreased significantly from 20 to 4% in the survivors. In the subgroup, in whom abnormal RV diastolic function changed to normal, cardiac status improved as indicated by a lower NYHA class and slower heart rate. In addition, this was associated with improved LV diastolic performance which tended to be less restrictive.

It is well known that Doppler-derived echocardiographic parameters are affected by a number of factors including age, heart rate, location of Doppler sampling window, respiration, as well as loading condition.[35–40] In our study, the echocardiogram was performed after initiation of diuretic drugs and other anti-heart failure therapy when the hemodynamic status was stabilized, but a slower symptomatic improvement clearly occurred in many patients over 1 year. The effect of respiration was minimized by averaging the measurement of at least three cardiac cycles during inspiratory and expiratory phases. This is especially important in the right ventricle. Our study is relatively short term but comparable to other published studies; the longer-term effects of persistent diastolic dysfunction on prognosis remain to be determined.

Conclusion

Left ventricular diastolic dysfunction is common in patients with systolic heart failure; the LV restrictive filling pattern is a predictor of cardiac mortality at 1 year, especially in those with the lowest ejection fraction (25%); and RV diastolic dysfunction does not independently relate to mortality but is associated with nonfatal hospital admission for heart failure or unstable angina. We also demonstrated that, in the survivors, there were favorable changes in both LV and RV diastolic patterns, which are associated with improvement in symptoms as well as in systolic function. However, the presence of a persistent LV restrictive filling pattern is associated with worse systolic and diastolic function and represents the subgroup with the poorest long-term prognosis.

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