Comparison of Left Ventricular Diastolic Parameters Between Patients With and Without Significant Mitral Regurgitation

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Mitral regurgitation (MR) can affect left ventricular diastolic parameters because of interference with regurgitation flow. This study compared left ventricular diastolic parameters between patients with and without significant MR. The MR group included 57 consecutive patients with significant MR. Fifty-seven age-, sex- and Tei index-matched patients without significant MR were selected as the reference group. Baseline characteristics and Tei index and its components were comparable between the MR and reference groups. The MR group had higher left atrial volume index, transmitral E wave velocity (E), ratio of E to transmitral A wave velocity, early diastolic mitral annular velocity (Ea), E/Ea, and ratio of E to isovolumic relaxation flow propagation velocity (IRFPV) ($p \leq 0.025$), and lower E-wave deceleration time ($p = 0.019$) and late diastolic mitral annular velocity ($p < 0.001$). However, the two groups had similar IRFPV ($p = 0.844$). In conclusion, MR apparently affects E and Ea, but not IRFPV. IRFPV could potentially be a reliable relaxation parameter in patients with significant MR, but further confirmation by invasive studies is needed.

Key Words: early diastolic mitral annular velocity, isovolumic relaxation flow propagation velocity, left ventricular diastolic function, mitral regurgitation

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Left ventricular (LV) systolic function is preserved in about half of all heart failure patients [1]. Although clinical characteristics vary widely, diastolic heart failure is associated with markedly increased morbidity and all-cause mortality [2]. Doppler echocardiography is currently the preferred tool for assessing LV diastolic function. Although variables derived from Doppler mitral inflow velocity are considered key indicators of diastolic function, they are easily influenced by physiological factors, such as filling pressure [3]. Reliable and noninvasive indices of ventricular relaxation are needed for repeated measurements during patient follow-up and for management of disease progression. Doppler parameters of relaxation should be independent of preload alterations. The early diastolic mitral annular velocity (Ea) was initially shown to be independent of preload alterations [4]. However, subsequent studies have revealed that Ea can be altered by marked preload changes induced by hemodialysis [5–7]. Ie et al reported that volume overload before hemodialysis can falsely elevate Ea [5]. Ea is measured

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after opening the mitral valve. Hence, the use of Ea to evaluate LV diastolic function in patients with significant mitral regurgitation (MR) might be affected by MR flow, which is a condition similar to preload increase. In fact, Olson et al demonstrated that measuring LV diastolic function by Ea alone can overestimate LV diastolic function in patients with severe MR [8].

We recently proposed isovolumic relaxation flow propagation velocity (IRFPV) as a promising new load-independent parameter of LV relaxation function [9,10]. IRFPV describes hemodynamic events during the isovolumic relaxation phase and before the LV filling phase. Therefore, it might be unaffected by MR flow.

The Tei index, a proposed indicator of combined ventricular systolic and diastolic function, is defined as the ratio of the sum of isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) to ejection time (ET) [11,12]. Previous studies have indicated that the Tei index and its components are unaffected by surgical correction of MR, which implies that they are unaffected by MR flow [13,14].

This study compared LV diastolic parameters between age-, sex-, and Tei index-matched patients with and without significant MR.

Methods

Study subjects

The subjects in this study were patients referred to Kaohsiung Municipal Hsiao-Kang Hospital for echocardiographic examination. Patients with significant aortic valve disease, significant mitral stenosis, atrial fibrillation, and inadequate image visualization were excluded. The MR group comprised 57 consecutive patients with significant MR, and the reference group comprised 57 age-, sex-, and Tei index-matched patients without significant MR. All patients had sinus rhythm. The study protocol was approved by the Institutional Review Board of this hospital. Before enrollment in the study, all patients gave written informed consent to participate.

Echocardiographic assessment

Transthoracic echocardiography (Vivid 7; GE Medical Systems, Horten, Norway) was performed with the participant breathing quietly in the left decubitus position. Two-dimensional guided M-mode images were recorded from the standardized views. The Doppler sample volume was placed at the tips of the mitral leaflets to obtain LV inflow waveforms from the apical four-chamber view. All sample volumes were positioned with the ultrasonic beam aligned to the flow. Tissue Doppler imaging was obtained with the sample volume placed at the lateral corner of the mitral annulus from the apical four-chamber view. The wall filter settings were adjusted to exclude high-frequency signals, and gain was minimized. LV ejection fraction was measured by the modified Simpson method. For tissue Doppler imaging, IVCTa was measured from the end of diastolic mitral annular velocity pattern to the onset of the systolic mitral annular velocity pattern, ETa was measured from the onset to the end of the systolic mitral annular velocity pattern, and IVRTa was measured from the end of the systolic mitral annular velocity pattern to the onset of the diastolic mitral annular velocity pattern [15,16]. Left atrial (LA) volume was measured using the biplane area–length method [17]. Apical four- and two-chamber views were obtained to determine LA area and length (as measured from the middle of the plane of the mitral annulus to the posterior wall). Maximal LA chamber area and minimal length were measured before mitral valve opening, excluding the LA appendage and pulmonary veins. LA volume was calculated and indexed to body surface area. IRFPV was measured similarly to E-wave propagation velocity, as described previously [18]. During Doppler color flow mapping, color gain was set at subsaturation levels in all subjects. Fine adjustments were made to obtain the longest column of color flow of the LV inflow. An M-mode cursor was then positioned through the center of the inflow with the cursor line parallel to the inflow jet. The maximum detectable mean velocity that moved toward the transducer was gradually reduced until the first isovelocity line of the isovolumic relaxation flow wavefront was clearly identifiable. For maximum resolution of the isovolumic relaxation flow wavefront, the maximal velocity limit was usually set as low as 25 cm/s. IRFPV was then measured as the slope of this isovelocity line segment. The Doppler data for three consecutive beats were averaged to obtain the mean values for further analysis. The raw ultrasonic data were recorded and analyzed offline by a cardiologist using the EchoPac software package (GE Medical Systems).

MR was assessed by mapping color jet expansion in the left atrium in four- and two-chamber views at end systole for three separate cardiac cycles. MR was considered significant if the regurgitant jet area exceeded 20% of the LA area [19,20].

Statistical analysis

Data are expressed as means ± standard deviation. SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous and categorical variables were compared by independent sample t test and χ^2 test. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Table 1 compares the clinical characteristics between the MR and reference groups. The MR group included 15 patients with coronary artery disease, 13 with dilated cardiomyopathy, and 31 with heart failure. The respective numbers of patients in the reference group were 15, 11 and 25. Age, sex, body mass index, systolic and diastolic blood pressures, heart rate, prevalence of diabetes mellitus and hypertension, and antihypertensive drug use did not significantly differ between the two groups.

Table 2 compares the echocardiographic characteristics between the MR and reference groups. IVCTa, ETa, IVRTa, and Tei index did not differ significantly. However, LA volume index (LAVI), transmitral E wave velocity (E), the ratio of E to transmitral A wave velocity (A), Ea, E/Ea, and E/IRFPV were higher in the MR group than in the reference group. The E-wave deceleration time (EDT) was shorter, and late diastolic mitral annular velocity was lower in the MR group than in the reference group. The two groups had comparable IRFPV ($p = 0.844$).

Figure 1 shows the E, Ea and IRFPV for two representative cases. Case 1 was a 37-year-old woman without significant MR. Her Tei index, E, Ea and IRFPV were 0.87, 52 cm/s, 5.6 cm/s, and 13 cm/s, respectively. Case 2 was a 39-year-old woman with significant MR. Compared with case 1, case 2 had a similar Tei index (0.86) and IRFPV (14 cm/s) but relatively higher E (94 cm/s) and Ea (14.0 cm/s).

Figure 2 compares the individual data points for E, Ea and IRFPV between the two groups.

Discussion

In patients with significant MR, E can be elevated as a result of increased LA pressure and Ea might or might not be normal, even though it is thought to be a less load-dependent index [4,5]. E/Ea is reportedly unreliable for predicting LV filling pressure in patients with severe MR [8]. LAVI is also considered an unreliable marker for evaluating LV diastolic function or filling pressure in patients with significant MR [21]. Therefore, a more accurate noninvasive index of LV diastolic function, which is suitable for repetitive follow-up of disease progression and for managing patients with significant MR, would be welcome. The present study

Table 1. Comparison of clinical characteristics in study subjects

	MR group ($n = 57$)	Reference group ($n = 57$)	p
Age (yr)	63 ± 14	61 ± 13	0.457
Sex, male:female	32:25	39:18	0.176
Body mass index (kg/m^2)	25 ± 4	26 ± 4	0.053
Diabetes mellitus (%)	32	37	0.554
Hypertension (%)	65	60	0.562
Coronary artery disease (%)	26	26	1.000
Heart failure (%)	54	44	0.261
Dilated cardiomyopathy (%)	23	19	0.646
ACEIs (%)	25	19	0.497
ARBs (%)	42	35	0.442
CCBs (%)	21	19	0.815
β-Blockers (%)	39	39	1.000
Heart rate (beats/min)	76 ± 16	78 ± 15	0.409
Systolic BP (mmHg)	141 ± 27	139 ± 20	0.698
Diastolic BP (mmHg)	82 ± 14	81 ± 14	0.802

MR = Mitral regurgitation; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor antagonists; CCBs = calcium channel blockers; BP = blood pressure.

Table 2. Comparison of echocardiogrpahic characteristics in study subjects

	MR group ($n = 57$)	Reference group ($n = 57$)	p
LAVI (mL/m^2)	57 ± 20	41 ± 14	< 0.001
LVEDV (mL)	156 ± 53	149 ± 65	0.524
LVESV (mL)	99 ± 56	97 ± 62	0.885
E (cm/s)	104 ± 27	73 ± 24	< 0.001
A (cm/s)	75 ± 30	82 ± 24	0.231
E/A	1.73 ± 1.08	1.02 ± 0.58	< 0.001
EDT (ms)	151 ± 64	182 ± 72	0.019
Ea (cm/s)	7.51 ± 2.92	6.36 ± 2.50	0.025
E/Ea	16.2 ± 8.3	13.2 ± 5.8	0.025
Aa (cm/s)	7.1 ± 2.8	9.1 ± 3.1	< 0.001
IVCTa (ms)	114 ± 40	108 ± 36	0.416
IVRTa (ms)	103 ± 37	113 ± 57	0.263
ETa (ms)	254 ± 54	258 ± 44	0.706
Tei index	0.92 ± 0.37	0.90 ± 0.42	0.878
LVEF (%)	41 ± 20	40 ± 19	0.790
IRFPV (cm/s)	37 ± 49	39 ± 44	0.849
E/IRFPV	7.7 ± 7.2	4.7 ± 3.8	0.007

A = Transmitral A wave velocity; Aa = late diastolic mitral annular velocity; E = transmitral E wave velocity; Ea = early diastolic mitral annular velocity; EDT = E-wave deceleration time; Eta = ejection time from tissue Doppler echocardiography; IVCTa = isovolumic contraction time from tissue Doppler echocardiography; IVRTa = isovolumic relation time from tissue Doppler echocardiography; IRFPV = isovolumic relaxation flow propagation velocity; LAVI = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation.

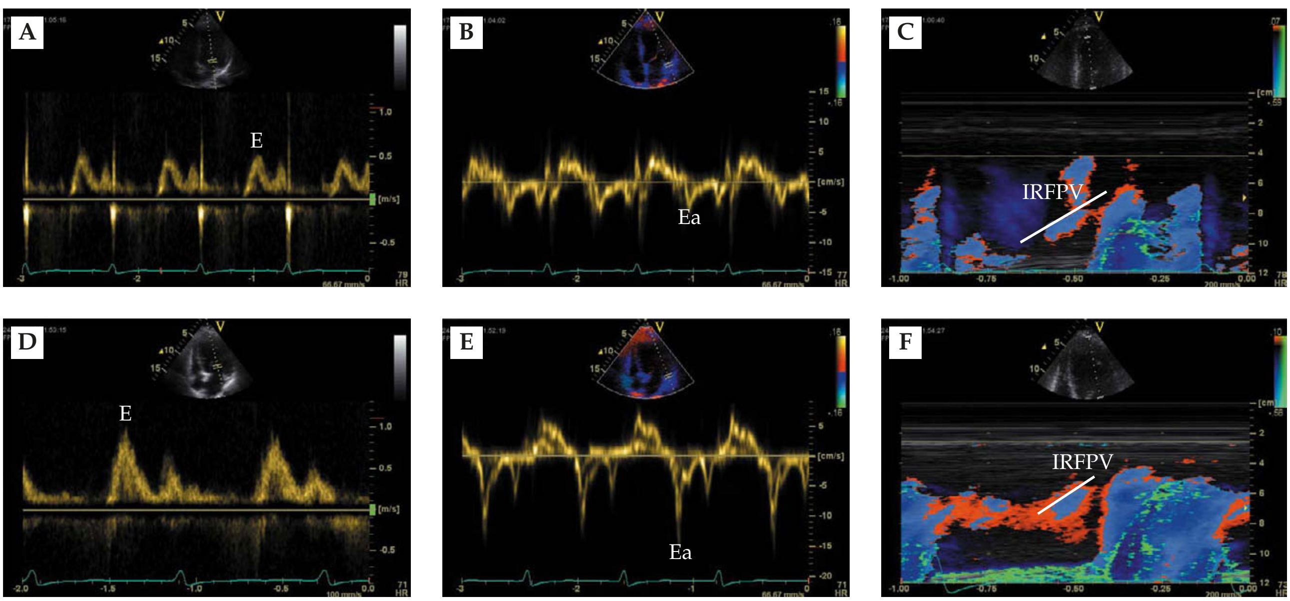

Figure 1. *Transmitral E-wave velocity (E), early diastolic mitral annular velocity (Ea), and isovolumic relaxation flow propagation velocity (IRFPV) obtained in two representative cases. (A–C) A 37-year-old woman without significant mitral regurgitation. (D–F) A 39-year-old woman with significant mitral regurgitation.*

evaluated the impact of MR on echocardiographic parameters and demonstrated that, in patients with similar global LV function, patients with significant MR had higher E, E/A, Ea, E/Ea, E/IRFPV and LAVI, shorter EDT, and lower late diastolic mitral annular velocity compared to those without significant MR. However, IRFPV was comparable in patients with and without significant MR, which suggests that regurgitation flow of significant MR affects E, Ea and LAVI but not IRFPV. Therefore, IRFPV might be a relatively

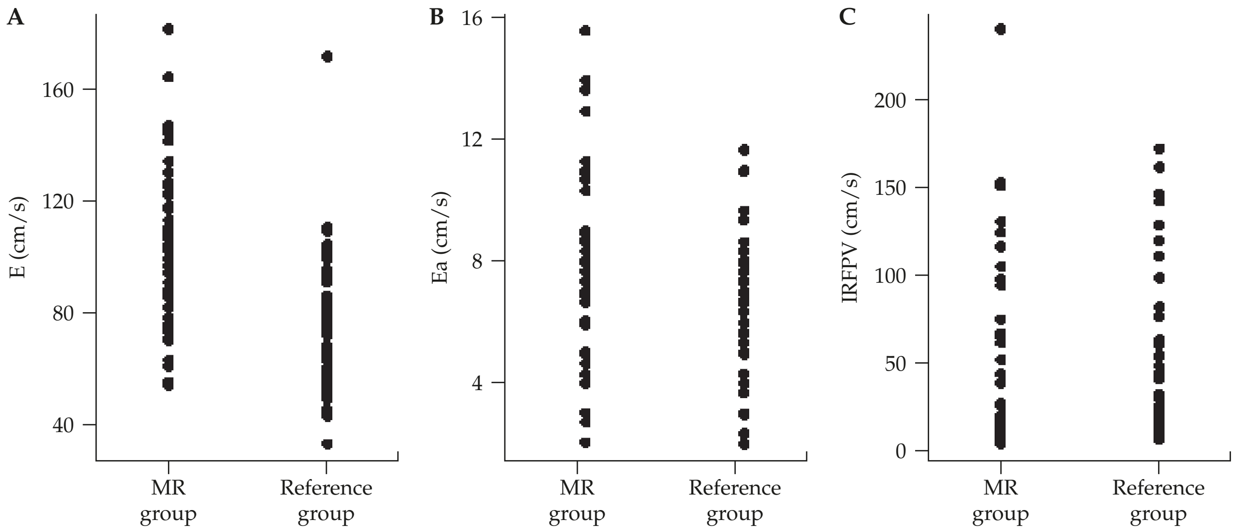

Figure 2. *Individual data points for (A) transmitral E-wave velocity (E); (B) early diastolic mitral annular velocity (Ea); and (C) isovolumic relaxation flow propagation velocity (IRFPV) between mitral regurgitation (MR) and reference groups.*

adequate parameter for assessing LV diastolic function in patients with significant MR.

Mabrouk-Zerguini et al [13] found that Tei index was not significantly altered by surgical correction of MR in 23 patients who had undergone mitral valve replacement, which implies that MR flow might not significantly affect Tei index. In the present study, Tei index and its components were comparable in the MR and reference groups, which suggested that the groups had similar global LV function, including LV systolic and diastolic functions.

Pulse–wave Doppler recordings of LV inflow velocities across the mitral valve are used to assess LV filling and diastolic function [22]. Significant MR increases the rate and proportion of early LV filling because of changes in the pressure gradient between the left atrium and left ventricle [23]. Therefore, E is increased and EDT is shortened in patients with significant MR [24]. The changes in LV inflow waveforms observed in the current study are consistent with those in the literature. Without measuring other diastolic parameters, the diastolic function of MR patients with a relatively high E and short EDT cannot be determined reliably. Therefore, reliable echocardiographic parameters that are unaffected by MR flow are needed to assess LV diastolic function in patients with significant MR.

In patients without significant MR, Ea is reportedly negatively correlated with the time constant of LV isovolumic pressure decrease [4,25,26]. However, Ie et al [5] demonstrated that Ea is a preload-dependent diastolic parameter in hemodialysis patients, and is falsely elevated before hemodialysis, which is a state of fluid overload. Another study of LV diastolic parameters in 20 patients with severe MR by Olson et al [8] found that Ea might overestimate diastolic function. Therefore, pseudonormalization of Ea might occur at fluid overload. Additionally, Ea is measured after opening of the mitral valve, and thus might be influenced by the MR flow; a similar situation of fluid overload. In the current study, although the MR and reference groups did not significantly differ for Tei index or its components, the MR group had higher Ea. Therefore, Ea apparently overestimated LV diastolic function in the MR group. However, IRFPV measured at the isovolumic relaxation phase, which was before the LV filling phase, was comparable in the two groups. Hence, MR flow might not significantly affect IRFPV.

Previous studies have indicated that E/Ea and E/IRFPV are good predictors of LV filling pressure in patients without significant MR [27,28]. However, the present study shows that E and Ea could be affected by MR flow. Thus the value of E/Ea and E/IRFPV for evaluating LV filling pressure in patients with significant MR needs confirmation in further studies.

The current study had several limitations. The subjects were patients at Kaohsiung Municipal Hsiao-Kang Hospital, where there was no cardiovascular surgeon available. As a result of high surgical risk or patient preference, many patients with significant MR and depressed LV systolic function were treated medically at this hospital. Thus, although the MR and reference groups had comparable LV ejection fraction, our patients had a relatively low LV ejection fraction. Tei index and its components are reportedly unaffected by MR, therefore, they were used instead of invasive parameters to compare global LV function, including LV systolic and diastolic function, between the MR and reference groups. Therefore, this finding requires further confirmation in invasive studies. Finally, most patients had chronic conditions that required regular administration of antihypertensive medication. For ethical reasons, medication was not withdrawn. Although medication was comparable in the MR and reference groups, we could not exclude the influence of antihypertensive agents on the present findings.

In conclusion, although Tei index and its components were comparable in the MR and reference groups, several diastolic parameters, including E, Ea, E/Ea, E/IRFPV and LAVI were higher in the MR group. In contrast, the two groups had similar IRFPV. Thus MR flow might significantly affect E and Ea, but not IRFPV. IRFPV could have the potential to be a reliable relaxation parameter in patients with significant MR, but further confirmation by invasive studies is needed.

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比較合併有意義二尖瓣逆流和沒有合併有意義二尖瓣逆流的病人之間的左心室舒張參數

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因為二尖瓣逆流血流的關係，左心室舒張參數可能會受其影響。本研究的目的就是在探討左心室舒張參數，在合併二尖瓣逆流和沒有合併二尖瓣逆流的病人之間的異同。57 位合併有意義二尖瓣逆流的病人被連續地收做二尖瓣逆流組；另外 57 位年齡、性別和 Tei 指數均互相配合且沒有合併二尖瓣逆流的病人為對照組。雖然基本資料、Tei 指數和 Tei 指數的成分均相似，但是左心房容積、早期舒張期左心室入口波的傳遞速度、早期比晚期舒張期左心室入口波的傳遞速度的比值、早期舒張期二尖瓣環的組織速度、早期舒張期左心室入口波的傳遞速度比上早期舒張期二尖瓣環的組織速度的比值、早期舒張期左心室入口波的傳遞速度比上等舒張期波的傳遞速度的比值、E 波速度的遞減時間和晚期舒張期二尖瓣環的組織速度，在這二組病人之間均有明顯差異。相對地，等舒張期波的傳遞速度在二組之間卻相似（$p = 0.844$）。因此，我們可以推論二尖瓣逆流可能對早期舒張期左心室入口波的傳遞速度和早期舒張期二尖瓣環的組織速度有影響，但可能對等舒張期波的傳遞速度沒有影響。所以，等舒張期波的傳遞速度，對二尖瓣逆流的病人而言，可能是一個較可靠的舒張指數。但此種論點可能須要侵襲性的研究再進一步証實。

關鍵詞：早期舒張期二尖瓣環的組織速度，等舒張期波的傳遞速度，左心室舒張功能，二尖瓣逆流

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