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Percutaneous Coronary Intervention

Impact of Prolonged Door-to-Balloon Times on the Diastolic Function in Acute ST-Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention

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Background: Emerging evidence indicates that diastolic left ventricular (LV) function is a powerful outcome predictor after acute ST-elevation myocardial infarction (STEMI). We hypothesized that shorter door-to-balloon (D2B) times with early restoration of coronary perfusion may preserve diastolic LV function in STEMI patients undergoing primary percutaneous coronary intervention (PPCI).

Methods: This study enrolled 340 consecutive STEMI patients who underwent PPCI with D2B times of < 90 min in 232 patients and D2B times ≥ 90 min in 108 patients, who all received subsequent echocardiographic examination within 48 hours of hospitalization.

Results: Although the LV ejection fraction was similar (50.92% vs. 51.66%, p = 0.573), the proportion of E/E' ratio > 15 was greater in patients with D2B times ≥ 90 min compared to those with D2B times < 90 min (44.4% vs. 30.6%, p = 0.013). Logistic regression analysis revealed that D2B time ≥ 90 min [odds ratio (OR): 1.82, 95% confidence interval (CI): 1.04-3.17, p = 0.035] was an independent predictor for LV diastolic dysfunction. The effect was more prominent in patients ≥ 65 years of age (OR: 2.77, 95% CI: 1.09-7.00, p = 0.032), in whom the fraction of LV diastolic dysfunction increased proportionally with prolonged D2B times.

Conclusions: Prolonged D2B time of greater than 90 min predicted LV diastolic dysfunction, particularly in aged subjects. D2B times shortening is important to preserve diastolic heart function after PPCI.

Key Words: Acute myocardial infarction • Diastolic dysfunction • Door-to-balloon time • Primary percutaneous coronary intervention

INTRODUCTION

Acute myocardial infarction (AMI) is a leading factor associated with heart failure, despite significant treatment advancements in recent years.[1] Development of new-onset heart failure in patients with AMI is a poor prognostic factor with higher in-hospital mortality.[2] A number of studies have indicated that both mortality and morbidity rates can be reduced in ST-elevation myocardial infarction (STEMI) patients who receive primary percutaneous coronary intervention (PPCI), particularly if the door-to-balloon (D2B) time, that is, the time interval between patients' arrival in the emergency department and the first intracoronary balloon inflation, can be reduced to less than 90 minutes (min).[3,4] Shortened revascularization time or D2B time has been shown to

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save more myocardium and preserve left ventricular (LV) systolic heart function, which plays a crucial role in reducing mortality and morbidity.[5,6] Thus, the current guidelines strongly recommend that D2B time should be 90 min or less to improve patient outcomes.[7,8]

Although the systolic LV function is a well-known prognostic factor in patients with AMI, a growing body of evidence indicates that diastolic LV function, as assessed by Doppler echocardiography, is an important predictor of patient outcomes after AMI.[9-11] The mechanisms underlying post-infarction LV diastolic dysfunction are complex and remain incompletely understood. Impaired active relaxation of the myocardium along with increased LV chamber stiffness secondary to myocardial ischemia and/or other pathophysiological factors following AMI are thought to be responsible for post-infarction LV diastolic dysfunction.[11-15] Clinically, in STEMI patients successfully treated with PPCI, the diastolic function grade by Doppler echocardiography has been demonstrated to be independently correlated with infarct size measured by cardiac magnetic resonance imaging.[16] Previous studies using aspartate transaminase or resting Thallium-201 tomography to estimate infarct size also demonstrated an association between diastolic function and infarct size after AMI.[17,18] To limit the infarct size, it has been shown that the timing of reperfusion to restore normal TIMI 3 flow is a principal determinant of infarct size after AMI.[19,20] Therefore, it is reasonable to assume that shorter D2B times with early restoration of the coronary perfusion may improve LV diastolic function through the reduction of infarct size and/or other mechanisms. In this study, we sought to investigate the association between D2B times and diastolic heart function in STEMI patients undergoing PPCI as reperfusion therapy in a high-volume PPCI-experienced center.[21]

METHODS

Study patients enrollment

This study retrospectively analyzed STEMI patients who received PPCI and echocardiographic examination in our center from January 2008 to June 2010. Our institution is a 2,000-bed tertiary care university medical center located in Taichung City in central Taiwan. Approximately 160 STEMI patients are treated per year in this hospital with PPCI as the reperfusion therapy. All patients $\geq$ 18 years of age who presented in the emergency department within 12 hours of the onset of ischemic chest pain, fulfilled the diagnostic criteria of acute STEMI by electrocardiography (ECG), underwent emergency cardiac catheterization, and received subsequent echocardiography examination within 48 hours of hospitalization were enrolled for analysis. All patients received standard pharmacological therapy including dual antiplatelets (aspirin and clopidogrel), statins, beta-blockers and angiotensin-converting enzymes inhibitors or angiotensin II receptor antagonists unless contraindicated after PPCI. STEMI was defined as ECG ST-segment elevation of > 1 mm in 2 contiguous limb leads or 2 mm in pre-cordial leads, or the presence of new onset left bundle branch block. Exclusion criteria of the study included the following: (1) prior use of thrombolytic agents, (2) D2B time > 90 min with documented patient-related reasons for delay, such as prolonged cardiopulmonary resuscitation in the emergency department, refusal of PPCI due to social or religious concerns, (3) enrollment in other clinical trials, (4) ST elevation on ECG without obvious coronary artery diseases such as acute myocarditis, early repolarization, or Takotsubo cardiomyopathy, (5) symptom-to-door time > 12 hours but receipt of PPCI based on clinical judgment, (6) failure to receive echocardiography examination within 48 hours of hospitalization, (7) atrial fibrillation at the time of echocardiography examination, and (8) failure to obtain written informed consent. The clinical and echocardiographic data were obtained from the study subjects' electronic medical records database. In-hospital outcome measures consisted of hospitalization days and major adverse cardiovascular events (MACE), including death, recurrent AMI, stroke, or target lesion revascularization.

Conventional and tissue Doppler imaging

The echocardiography was performed in the left lateral decubitus position using Vivid 7 cardiac ultrasound machine (General Electric, Milwaukee, WI, USA) with a 3.5 MHz transducer. Standard echocardiographic examinations[22] that included left ventricular ejection fraction (LVEF), pulsed-wave Doppler echocardiography, and tissue Doppler imaging at the septal mitral annulus margin were performed in each patient. LVEF was measured by the M-mode method from the parasternal short-axis view. Pulsed-wave Doppler echocardiography to assess the diastolic mitral inflow velocities was performed from the apical four-chamber view with a 3 mm sample volume at the tip of the mitral leaflets. The E/A ratio was calculated by the ratio of the peak early (E) to late (A) diastolic mitral inflow velocities. From the apical four-chamber view, the systolic (S'), early diastolic (E'), and late diastolic (A') peak mitral annular velocities were detected by tissue Doppler imaging at the septal mitral annulus location. The E/E' ratio was calculated by the ratio of the peak early mitral inflow E to peak early diastolic mitral annulus velocity E' (Figure 1). An E/E' ratio greater than 15, indicating an elevated LV filling pressure, was defined as LV diastolic dysfunction.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation (SD) for normally distributed variables. Differences between proportions were assessed by chi-square tests, and differences between two groups were tested by Student's t tests. Logistic regression was used for multivariate analysis of D2B time on the occurrence of E/E′ > 15, adjusted for age, sex, and other covariates. Adjusted odds ratio (OR) and 95% confidence interval calculated from multiple logistic regression were presented for each explanatory variable. In addition, subgroup analysis using logistic regression was used to explore the association between the occurrence of E/E′ > 15 and D2B time by different age groups. A 2-tailed p value < 0.05 was considered statistically significant, and all analyses were performed using the SAS 9.1 statistical package (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 340 consecutive STEMI patients receiving PPCI as the reperfusion therapy constituted the study population after excluding 66 patients due to a variety of reasons (12 with patient-related delays, 8 with symptom-to-door time > 12 hours, 3 with ST elevation on ECG but no significant angiographic coronary artery disease, and 43 with echocardiography data obtained after 48 hours of admission). Eligible subjects were divided into 2 groups. Group A consisted of 232 patients with D2B < 90 min, and Group B was composed of 108 patients with D2B ≥ 90 min. Basic demographic, clinical, and echocardiographic data are shown in Table 1. There were no significant differences with regard to age distribution (≥ 65 vs. < 65) and the male-to-female ratio between the two groups. The majority of the studied patients achieved TIMI 3 flow after PPCI in each group (92.67% vs. 87.04%, p = 0.093). The proportion of disease severity on presentation as reflected by the Killip class or left anterior descending artery occlusion did not differ between the two groups. The mean LVEF measured within 48 hours after successful PPCI was similar between the two groups (51.66% vs. 50.92%, p = 0.573). There was a trend towards a reduction of the peak troponin I level in patients with D2B time < 90 min, but the difference was not statistically significant (106.90 ± 91.86 vs. 134.80 ± 91.79 ng/ml, p = 0.227). Hypertension was the most common risk factor for the STEMI patients in this study.

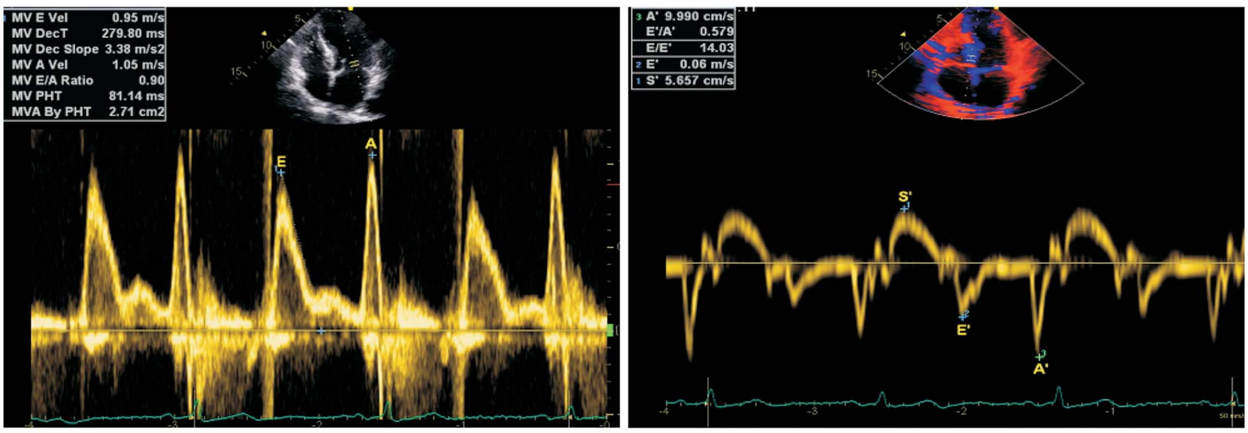

Figure 1. *Measurement of conventional mitral inflow (left) and tissue Doppler imaging at the septal mitral annulus (right).*

Table 1. Demographic, clinical, and echocardiographic characteristics

Variables	N = 340		p-value
	D2B < 90 (n = 232)	D2B ≥ 90 (n = 108)	
Age (years)			0.341
< 65	152 (65.52)	65 (60.19)	
≥ 65	80 (34.48)	43 (39.81)	
Sex			0.367
Female	36 (15.52)	21 (19.44)	
Male	196 (84.48)	87 (80.56)	
Killip			0.524
I + II	173 (74.57)	77 (71.3)	
III + IV	59 (25.43)	31 (28.7)	
LAD occlusion			0.672
No	134 (57.76)	65 (60.19)	
Yes	98 (42.24)	43 (39.81)	
TIMI 3 flow			0.093
No	17 (7.33)	14 (12.96)	
Yes	215 (92.67)	94 (87.04)	
LV mass*	170.42 (78.00-555.90)	151.82 (44.00-414.24)	0.153
Grade 2-4 MR			0.255
No	202 (87.07)	89 (82.41)	
Yes	30 (12.93)	19 (17.59)	
Hypertension			0.495
No	108 (46.55)	46 (42.59)	
Yes	124 (53.45)	62 (57.41)	
Diabetes mellitus			0.350
No	158 (68.10)	68 (62.96)	
Yes	74 (31.90)	40 (37.04)	
Hyperlipidemia			0.379
No	141 (60.78)	71 (65.74)	
Yes	91 (39.22)	37 (34.26)	
E/E′			0.013
≤ 15	161 (69.40)	60 (55.56)	
> 15	71 (30.60)	48 (44.44)	
E′ (cm/sec)			0.531
≥ 5	145 (62.50)	70 (66.04)	
< 5	87 (37.50)	36 (33.96)	
LAVI (ml/m^2)			0.220
≤ 32	134 (72.04)	17 (60.71)	
> 32	52 (27.96)	11 (39.29)	
Deceleration time (ms)			0.589
≤ 140	33 (14.80)	12 (12.50)	
> 140	190 (85.20)	84 (87.50)	
E/A	1.01 ± 0.46	1.09 ± 0.48	0.170
E (cm/sec)	73.69 ± 21.20	77.29 ± 20.65	0.145
A (cm/sec)	78.00 ± 21.01	78.62 ± 23.13	0.810
LVEF (%)	51.66 ± 10.75	50.92 ± 11.71	0.573
CKMB (ng/ml)	114.30 ± 104.40	110.10 ± 86.86	0.697
TnI (ng/ml)	106.90 ± 91.86	134.80 ± 91.79	0.227

All values are expressed as mean ± standard deviation or n (%). *, LV mass value is expressed as median (minimal-maximal). A, the peak late velocity of diastolic mitral flow; CKMB, creatine kinase MB fraction; D2B, door-to-balloon time; E, the peak early velocity of diastolic mitral flow; E′, the peak mitral annular velocity at early diastole detected by tissue Doppler imaging; E/E′, the ratio of E wave to E′ wave; E/A, the ratio of E wave to A wave; LAD, left anterior descending coronary artery; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TnI, troponin I.

The percentage of patients carrying risk factors including hypertension, diabetes, and hyperlipidemia was similar between the two groups. Conventional and tissue Doppler-echocardiography measurements revealed no significant differences in the LV mass, the fraction of decreased E' (< 5), the E/A ratio, the E wave value, and the A wave value between the two groups. The percentage of left atrial volume index > 32 mL/m^2 and the fraction of deceleration time ≤ 140 ms were also equivalent between the two groups. However, the proportion of E/E' ratio > 15, indicating the presence of restrictive LV filling and diastolic dysfunction, was significantly higher in patients with D2B times ≥ 90 min compared to those with D2B times < 90 min (44.4% vs. 30.6%, p = 0.013).

Table 2 shows logistic regression analysis for LV diastolic dysfunction with age, sex, Killip class, infarction-

Table 2. Risk factors associated with LV diastolic dysfunction

Variables	E/E' (N = 340)		Adjusted OR (95% CI)	p-value
	≤ 15 (n = 221)	> 15 (n = 119)		
D2B				
< 90	161 (72.85)	71 (59.66)	1 (ref.)	
≥ 90	60 (27.15)	48 (40.34)	1.82 (1.04-3.17)	0.035
Age (years)				
< 65	171 (77.38)	46 (38.66)	1 (ref.)	
≥ 65	50 (22.62)	73 (61.34)	3.99 (2.25-7.07)	< 0.0001
Sex				
Male	200 (90.5)	83 (69.75)	1 (ref.)	
Female	21 (9.5)	36 (30.25)	2.83 (1.38-5.81)	0.005
Killip				
I + II	183 (82.81)	67 (56.3)	1 (ref.)	
III + IV	38 (17.19)	52 (43.7)	2.73 (1.50-4.95)	0.001
LAD occlusion				
No	133 (60.18)	66 (55.46)	1 (ref.)	
Yes	88 (39.82)	53 (44.54)	0.95 (0.55-1.65)	0.865
Hypertension				
No	117 (52.94)	37 (31.09)	1 (ref.)	
Yes	104 (47.06)	82 (68.91)	1.66 (0.95-2.92)	0.077
Diabetes mellitus				
No	159 (71.95)	67 (56.3)	1 (ref.)	
Yes	62 (28.05)	52 (43.7)	1.45 (0.81-2.58)	0.212
Hyperlipidemia				
No	129 (58.37)	83 (69.75)	1 (ref.)	
Yes	92 (41.63)	36 (30.25)	1.22 (0.68-2.19)	0.510
LVEF (%)				
≥ 40	190 (88.79)	100 (85.47)	1 (ref.)	
< 40	24 (11.21)	17 (14.53)	0.82 (0.36-1.85)	0.626
TIMI 3 flow				
No	17 (7.69)	14 (11.76)	1 (ref.)	
Yes	204 (92.31)	105 (88.24)	0.70 (0.29-1.73)	0.443
Grade 2-4 MR				
No	196 (88.69)	95 (79.83)	1 (ref.)	
Yes	25 (11.31)	24 (20.17)	0.80 (0.37-1.72)	0.561
LV mass	166.28 (77.87-365.92)	169.00 (44.00-555.90)	1.00 (0.999-1.009)	0.080

All values are expressed as median (minimal-maximal) or n (%).
CI, confidence interval; D2B, door-to-balloon; E/E, the ratio of E wave to E wave; LAD, left anterior descending; LV, left ventricular; LVEF, left ventricular ejection fraction; OR, odd ratio; ref., reference.
Other abbreviations as in Table 1.

related arteries, hypertension, diabetes, hyperlipidemia, LVEF, TIMI 3 flow status, presence of significant mitral regurgitation, and LV mass as covariates. Among the 340 study patients, D2B time $\geq$ 90 min (adjusted OR 1.82, p = 0.035), age $\geq$ 65 (adjusted OR 3.99, p < 0.0001), female sex (adjusted OR 2.83, p = 0.005), and Killip III or IV status (adjusted OR 2.73, p = 0.001) were independent risk factors for LV diastolic dysfunction. Other factors, including left anterior descending coronary artery (LAD) occlusion, hypertension, diabetes, hyperlipidemia, the proportion of LVEF < 40, the percentage of TIMI 3 flow, significant mitral regurgitation, and LV mass were not significantly associated with LV diastolic dysfunction. While analyzing the risk factors associated with LV diastolic dysfunction according to different age subgroups, Table 3 shows that prolonged D2B times (adjusted OR 2.77, p = 0.032) and higher Killip classes (adjusted OR 3.48, p = 0.010) were the only two independent predictors for LV diastolic dysfunction in patients $\geq$ 65 years of age. On the other hand, in patients younger than 65 years old, female sex (adjusted OR 5.85, p = 0.001) and increased LV mass (adjusted OR 1.01, p = 0.045) were both a significant risk factor for LV diastolic dysfunction. Further analysis revealed that in the older age subgroup, the percentage of LV diastolic dysfunction increased proportionally and significantly with prolonged D2B times compared to the younger age subgroup (Figure 2).

DISCUSSION

The results of this study clearly demonstrate that prolonged D2B time $\geq$ 90 min along with other variables, including age $\geq$ 65, female sex, Killip III or IV status, and hypertension, are independent predictors for LV diastolic dysfunction in STEMI patients undergoing successful PPCI in a single-center setting. The negative impact of prolonged D2B time on LV diastolic function is particularly significant in patients $\geq$ 65 years of age. To the best of our knowledge, this is the first study that identifies D2B time as an independent risk factor for post-infarction LV diastolic dysfunction. Our results emphasize the importance of D2B time shortening in relation to the preservation of the diastolic heart function in STEMI patients undergoing PPCI.

LV diastolic dysfunction by Doppler echocardiography predicts poor post-infarction outcome

Advanced LV diastolic dysfunction characterized by restrictive LV filling is a poor prognostic marker after AMI.[23-25] Both invasive cardiac catheterization and non-invasive echocardiographic index have been utilized to assess diastolic LV function in AMI patients.[26-30] Although direct measurements of the right heart or LV end-diastolic pressure are important predictors of adverse outcome after AMI in certain patients,[26,31] the inconvenience and risk of complications preclude routine use of indwelling catheters in all AMI patients. Alternatively, non-invasive measures of diastolic function using Doppler echocardiographic techniques to assess LV filling dynamics have gained wide acceptance in predicting outcome in patients with AMI. Naqvi et al.[27] reported that in 59 AMI patients receiving PPCI, patients with in-hospital cardiac events had significantly higher E/E' ratio and decreased early mitral inflow deceleration time (DT). In uncomplicated AMI patients, Temporelli et al.[28] used early mitral DT $\leq$ 130 ms as the surrogate marker for restrictive LV filling and reported that patients with persistent baseline and pre-discharge restrictive LV filling had the highest risk of 6-month LV remodeling and 4-year mortality. Sinagra et al.[32] further demonstrated that in post-MI patients with severe restrictive LV filling, as defined by E/A ratio $\geq$ 2 and DT < 115 ms, post-mortem pathological examination exhibited a higher rate of myocyte apoptosis, which may partly explain the adverse outcomes associated with LV diastolic dysfunction after AMI.

E/E' ratio is a reliable indicator to identify restrictive LV filling

Although the DT of early transmitral flow is a simple and powerful predictor of outcome after AMI,[24,25,33,34] the correlation between DT and LV filling pressure is relatively poor in patients with preserved systolic function.[35] To address this limitation, Doppler tissue imaging of mitral annulus motion has been shown to be a useful technique in assessing LV diastolic function.[35,36] Mitral annulus velocity is related to myocardial relaxation as it reflects the rate of change in LV long-axis dimension and volume. Impaired LV relaxation results in a reduced early mitral annulus velocity (E'), which is independent of the preload status.[37] The ratio of early transmitral flow ve-

Table 3. Subgroup analysis of risk factors associated with LV diastolic dysfunction separated by age

Variables	Age < 65 (n = 217)				Age = 65 (n = 123)			
	E/E′ ≤ 15 (n = 171)	E/E′ > 15 (n = 46)	Adjusted OR (95% C.I.)	p-value	E/E′ ≤ 15 (n = 50)	E/E′ > 15 (n = 73)	Adjusted OR (95% C.I.)	p-value
D2B (min)								
< 90	121 (70.76)	31 (67.39)	1 (ref.)		40 (80)	40 (54.79)	1 (ref.)	
≥ 90	50 (29.24)	15 (32.61)	1.17 (0.54-2.54)	0.683	10 (20)	33 (45.21)	2.77 (1.09-7.00)	0.032
Sex								
Male	161 (94.15)	36 (78.26)	1 (ref.)		39 (78)	47 (64.38)	1 (ref.)	
Female	10 (5.85)	10 (21.74)	5.85 (2.02-16.90)	0.001	11 (22)	26 (35.62)	1.64 (0.57-4.69)	0.357
Killip								
I + II	143 (83.63)	34 (73.91)	1 (ref.)		40 (80)	33 (45.21)	1 (ref.)	
III + IV	28 (16.37)	12 (26.09)	1.79 (0.76-4.26)	0.185	10 (20)	40 (54.79)	3.48 (1.36-8.95)	0.010
LAD occlusion								
No	108 (63.16)	23 (50)	1 (ref.)		25 (50)	43 (58.9)	1 (ref.)	
Yes	63 (36.84)	23 (50)	1.24 (0.60-2.57)	0.558	25 (50)	30 (41.1)	0.61 (0.24-1.53)	0.289
Hypertension								
No	98 (57.31)	20 (43.48)	1 (ref.)		19 (38)	17 (23.29)	1 (ref.)	
Yes	73 (42.69)	26 (56.52)	1.54 (0.73-3.25)	0.254	31 (62)	56 (76.71)	1.66 (0.62-4.43)	0.310
Diabetes mellitus								
No	121 (70.76)	28 (60.87)	1 (ref.)		38 (76)	39 (53.42)	1 (ref.)	
Yes	50 (29.24)	18 (39.13)	1.53 (0.72-3.25)	0.270	12 (24)	34 (46.58)	1.63 (0.59-4.48)	0.347
Hyperlipidemia								
No	91 (53.22)	23 (50)	1 (ref.)		38 (76)	60 (82.19)	1 (ref.)	
Yes	80 (46.78)	23 (50)	1.53 (0.74-3.17)	0.252	12 (24)	13 (17.81)	1.07 (0.35-3.32)	0.907
LVEF (%)								
≥ 40	146 (89.02)	41 (91.11)	1 (ref.)		44 (88.00)	59 (81.94)	1 (ref.)	
< 40	18 (10.98)	4 (8.89)	0.59 (0.16-2.18)	0.425	6 (12.00)	13 (18.06)	1.04 (0.31-3.49)	0.956
TIMI 3 flow								
No	14 (8.19)	6 (13.04)	1 (ref.)		3 (6.00)	8 (10.96)	1 (ref.)	
Yes	157 (91.81)	40 (86.96)	0.70 (0.22-2.20)	0.536	47 (94.00)	65 (89.04)	0.49 (0.09-2.71)	0.411
Grade 2-4 MR								
No	155 (90.64)	43 (93.48)	1 (ref.)		41 (82.00)	52 (71.23)	1 (ref.)	
Yes	16 (9.36)	3 (6.52)	0.41 (0.10-1.73)	0.223	9 (18.00)	21 (28.77)	1.33 (0.44-4.02)	0.614
LV mass	162.87 (77.87-352.87)	172.00 (92.00-555.90)	1.01 (1.00-1.01)	0.045	170.37 (78.42-365.92)	162.00 (44.00-414.24)	1.00 (0.99-1.01)	0.742

All values are expressed as median (minimal-maximal) or n (%). Abbreviations are in Tables 1 and 2.
Cl, confidence interval; D2B, door-to-balloon; LAD, left anterior descending; LV, left ventricular; LVEF, left ventricular ejection fraction; OR, odd ratio.

locity (E) to early diastolic septal mitral annulus velocity (E/E′) has been shown to correlate well with LV end diastolic pressure and predict survival after AMI.[38] This relationship between E/E′ ratio and LV filling pressure has been validated in the presence of preserved or depressed LV systolic function.[35]

In our study, we used E/E′ > 15 as the echocardiographic surrogate marker for significant LV diastolic dysfunction for several reasons. First, compared to E/A ratio, E/E′ ratio is relatively preload-independent and is

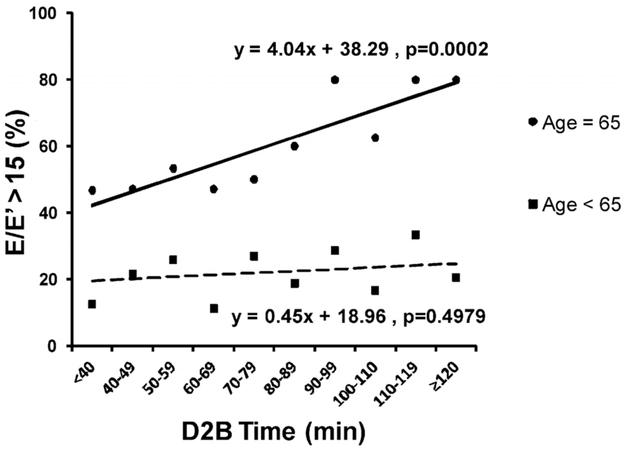

Figure 2. *Correlation between proportions of E/E' > 15 and D2B time categories according to different age groups. Among patients aged ≥ 65 (circle), the fraction of E/E' > 15 increases proportionally and significantly with prolonged D2B times, compared to the younger age subgroup (square). D2B, door-to-balloon.*

less affected by other confounding factors, such as LV relaxation rate or compliance.[9,38] Second, the majority of our patients (mean LVEF 51%) had preserved LV systolic function and the E/E' ratio has been shown to correlate well with LV diastolic parameters acquired by pressure-volume loop methods irrespective of LV systolic function.[35,39] Third, E/E' ratio can be applied to estimate the LV filling pressure both in sinus tachycardia and atrial fibrillation,[40] which are not uncommonly observed in AMI. In this study, although conventional Doppler-derived parameters, including DT, E wave, A wave, and E/A ratio are similar among patients with longer (≥ 90 min) or shorter (< 90 min) D2B times, the proportion of E/E' ratio > 15 is significantly greater in patients with prolonged D2B time than those with D2B less than 90 min. It is possible that the conventional Doppler index may not be sufficiently sensitive to detect the elevated LV filling pressure in the acute phase of AMI in this study (≤ 48 hrs). The importance of E/E' ratio as the index of choice to screen for LV diastolic dysfunction is further confirmed by its powerful role in predicting in-hospital MACE rates and hospital stay in STEMI patients after receiving successful PPCI in this study.

Prolonged D2B time, a new risk factor for post-MI LV diastolic dysfunction

A number of risk factors that may contribute to LV diastolic dysfunction including age, hypertension, coronary artery disease, diabetes, aortic stenosis, hypertrophic cardiomyopathy, and restrictive cardiomyopathy are well-known.[41] In this study, after accounting for confounding factors, we found that age ≥ 65, female sex, high Killip class (III or IV), and prolonged D2B time are all independent risk factors for LV diastolic dysfunction in STEMI patients treated with PPCI. Among the risk factors identified, old age is a conventional predictor for diastolic dysfunction;[41] high Killip class indicating large infarct size has been associated with post-infarction diastolic dysfunction;[16,42] and female sex has been identified as an independent predictor of all-cause mortality after AMI.[43] Prolonged D2B time is identified for the first time as a new and reversible risk factor that is linked to LV diastolic dysfunction characterized by E/E' > 15 in STEMI patients after successful PPCI treatment. Because the peak troponin I level was only modestly reduced in patients with shorter D2B times (107 vs. 135 ng/ml) in this study, the exact mechanism underlying the association of longer D2B times and diastolic dysfunction is not fully explained by infarct size reduction per se. The LV diastolic dysfunction is correlated with impaired myocardial relaxation and increased LV stiffness. The former is determined by myocardial inactivation, preload, afterload, and dyssyhronization. On the other hand, myocardial stiffness is determined by myocardial cell, interstitial matrix fibrosis, or chamber geometry.[44] While the E/E' ratio is usually applied to predict the LV filling pressure, which is the main physiological sequence of LV diastolic dysfunction, the E' velocity usually decreased with impaired LV relaxation.[45] In our study, the proportion of E/E' ratio > 15 was greater in patients with D2B times ≥ 90 min compared to those with D2B times < 90 min, but there was no difference in E' between different D2B time groups. It is possible that myocardial elasticity normalizes with the early and sustained reperfusion obtained after PPCI for AMI, leading to a reduction in left ventricular stiffness and filling pressures, which, in turn, contributes to preservation of LV diastolic function after AMI.[46-49] The impact of D2B time on the LV diastolic function is particularly important in patients ≥ 65 years of age in whom D2B time ≥ 90 min and Killip III or IV are the only two independent predictors of diastolic dysfunction after AMI. Furthermore, the length of D2B time positively correlates with the proportion of LV diastolic dysfunction in older subjects but not in younger patients. It is conceivable that the myocardium in older patients may be more vulnerable to ischemic events and prone to become stiff thereafter. Consequently, the aged myocardium may be less tolerable to reperfusion delay due to longer D2B times, as indicated by this study.

Study limitations

There were several limitations in this study. First, the study was a single-center observational study with a relatively small sample size. Future multi-center, large-scale studies are necessary to replicate our experience. Second, although we clearly demonstrated that D2B time ≥ 90 min is an independent risk factor for LV diastolic dysfunction in STEMI patients after PPCI therapy, as defined by mitral septal E/e’ > 15, it should be noted that the average E/e’ > 13 may be a better indicator to study LV diastolic dysfunction in these patients. Third, LV diastolic phase is composed of isovolumic relaxation, rapid filling, diastasis, and atrial contraction. In this study, we did not characterize which component was responsible for the observed diastolic dysfunction. However, dysfunction in each phase will eventually lead to increased LV filling pressure, which correlates well with the ratio of E/e’. We believe that the ratio of E/e’ is still a useful parameter for post-MI heart function evaluation. Fourth, in our study, we only used the M-mode method to measure LVEF, which may not be as accurate as the biplane method in AMI patients. Fifth, long-term follow-up is needed to determine whether prolonged D2B times in this patient subset has a negative impact on patient outcomes or mortality. Finally, the symptom-to-door time is not included for analysis in this study because this time variable was not available or uncertain in a significant portion of the study patients. Because the symptom-to-door time is important to estimate the actual time interval from ischemia to reperfusion and affects STEMI patient outcomes,[50] it is also essential to study the correlation between symptom-to-door time or symptom-to-balloon time and LV diastolic function preservation in STEMI patients.

CONCLUSIONS

Prolonged D2B time of greater than 90 min in STEMI patients after PPCI is an independent predictor of LV diastolic dysfunction, particularly in older patients. Our results reinforce that a dedicated approach to shorten D2B time to less than 90 min is important to preserve diastolic heart function in STEMI patients undergoing PPCI.

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CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

Contributor statement

K.-C.C. designed research; Y.-C.W., H.-P.W., H.-Y.L., and K.-C.C. analyzed the data; P.-H.L. and Y.-C.W. performed primary PCI and data collection; Y.-C.W. and K.-C.C. wrote the paper.

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