

Wire Crossing Time Correlates with Left Ventricular End-Diastolic Pressure in Patients with ST Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Abstract

Background: Mortality and morbidity in acute myocardial infarction depend on the extent of the infarct area. Rapid recovery of coronary artery blood flow with primary percutaneous coronary intervention (PPCI) can limit the extent of infarction and improve left ventricular function. Acute myocardial infarction reduce diastolic function, which in the early stage of diastolic dysfunction, there is an increase in left ventricular end-diastolic pressure (LVEDP). The non-invasive marker of E/e' ratio is an accurate parameter of increased LVEDP.

Methods: This was a cross-sectional study enrolled consecutive patients with ST Segment Elevation Myocardial Infarction (STEMI) who underwent PPCI at Dr. Sardjito Hospital. The wire crossing time was calculated from the onset of chest pain until the guidewire crossed the infarct-related artery during the pPCI procedure. The E/e' ratio was determined by transthoracic echocardiography which performed within 48 hours after the primary PCI. Correlation between the wire crossing time and the E/e' ratio was assessed by the Pearson correlation test. The value of $p < 0.05$ was considered statistically significant.

Results: A total of 40 patients were enrolled in this study. The mean wire crossing time was 12.73 ± 5.22 hours. The median value of the E/e' ratio was 8.36 (range: 4.71-22.00). There was a moderate strength and significant correlation between the wire crossing time and the E/e' ratio ($r = 0.572$; $p < 0.001$). Patients with E/e' ratio > 15 had significantly longer wire crossing time than in patient with E/e' ratio ≤ 15 (20.21 ± 2.5 hours vs. 11.41 ± 4.39 hours; $p < 0.001$; respectively). The wire crossing time was independently associated the E/e' ratio ($r = 0.463$; $p = 0.003$).

Conclusion: There was a moderate strength and significant positive correlation between the wire crossing time and increased LVEDP, an earlier marker of diastolic dysfunction, measured by E/e' ratio using TTE in patients with STEMI underwent pPCI.

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Keywords: STEMI, Primary PCI, wire crossing time, LVEDP, E/e' ratio

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Introduction

An ST-Segment Elevation Myocardial Infarction (STEMI) characterised by a total occlusion of coronary artery which cause the myocardia supplied by the artery become ischemic and injured.¹ After occlusion of the coronary arteries, the myocardia can survive up to about 20 minutes from severe ischemia without experiencing irreversible injury. But after 20-30 minutes in a state of severe ischemia, irreversible myocardial injury begins. In the next 3-4 hours, myocardial injury continues in a wave pattern from the sub-endocardial region into the sub-epicardial region.² The earlier recovery of coronary artery blood flow, one of the treatment choices is primary percutaneous coronary intervention (PPCI), is expected to limit the extent of myocardial infarction.³

Acute myocardial infarction results in contractile muscle loss which reduces both systolic and diastolic function. The two physiological phases of diastolic namely active relaxation and passive filling are influenced by the myocardial ischemia and infarction. Active relaxation is disrupted in the event of myocardial infarction, as well as left ventricular stiffness, according to the area of infarction and beginning of remodeling process.⁴ Left ventricle diastolic dysfunction predict unfavorable outcome following STEMI.⁴ Specifically, increased left ventricle end diastolic pressure (LVEDP), is the only increased intracardiac pressure in the earlier phase of diastolic dysfunction.⁵ The E/e' ratio is the most accurate non-invasive predictor of increasing LVEDP, which can be achieved by bedside transthoracic echocardiography (TTE), where the ratio $E/e' > 15$ shows high LVEDP (> 15 mmHg) with a specificity of 86% .⁵ This E/e' ratio also shows a strong positive correlation with LVEDP ($r = 0.8; p < 0.0001$) .⁶

The aims of this study are: to investigate the correlation between wire-crossing time with LVEDP assessed by non-invasive TTE with E/e' parameter in patients with STEMI undergo pPCI in Dr. Sardjito Hospital Yogyakarta and to evaluate the performance of pPCI in Dr. Sardjito Hospital Yogyakarta in term of the rapidity of response and its impact on morbidity.

Methods

This study was an observational study with a cross-sectional design. The subjects were enrolled by

consecutive sampling technique. The subjects were patients with STEMI who underwent pPCI at Dr. Sardjito Hospital, Yogyakarta, Indonesia between 1 December 2018 - 15 January 2019 who met the research criteria. This study was approved by the ethics committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta.

The inclusion criteria in this study were: (1) patients diagnosed with STEMI for the first time, (2) the time of anginal chest pain was known, (3) ages ≤ 75 years, and (4) underwent reperfusion therapy with pPCI at Dr. Sardjito Hospital with a balloon angioplasty with or without stenting. Exclusion criteria in this study were: (1) history of previous coronary heart disease, (2) history of heart failure, (3) history of diastolic dysfunction from previous echocardiography examination, if available, (4) significant left heart valve disease, (5) changes in left ventricular geometry, (6) treated with fibrinolytic previously, (7) severe unstable hemodynamics, (8) the diastolic function with echocardiography can not be interpreted, and (9) inadequate echocardiographic images. All subjects were provided signed informed consent to participate in this study.

The wire crossing time was calculated in hours, starting from the first anginal chest pain until wire crossing was performed on infarct-related lesions of the infarct-related artery during the pPCI procedure. The decision to choose reperfusion therapy with pPCI was not influenced by this study and carried out in accordance with the standard procedures at Dr. Sardjito Hospital, Yogyakarta. The LVEDP was estimated non-invasively by TTE using the E/e' ratio measurement. The E/e' ratio was the ratio between E wave velocity from mitral flow doppler echocardiography and e' wave velocity from TDI mitral annulus examination. The e' wave value used is the e' value of the average of e' medial and e' lateral examination results.⁷ The TTE examination was conducted within 48 hours after pPCI according to the standard procedure in the CVCU of our hospital. The measurement technique and sample volume placement for the calculation of the E/e' ratio refers to the recommendation of ASE and EACI 2016.⁸ The TTE was performed with the VIVID S6 (GE, USA) by 2 trained examiners who were blind to wire crossing time data from the subjects measured. Both examiners were tested for conformity using intraclass correlation (ICC) analysis, which result of correlation

score 0.848 indicated strong conformity between two examiners. The results of the examination were then validated by a cardiologist.

For statistics analysis, the normality test was performed for continuous data with the Shapiro-Wilk test. The correlation analysis between two continuous data was assessed with the Pearson or Spearman correlation test, based on the data distribution. Based on the E/e' ratio, subjects were divided between those with E/e' >15 and E/e' ≤15. Comparative analysis between group was assessed with Student T-test. The effect of confounding factors on the E/e' ratio was analyzed bivariately and if the *p* value < 0.25, it will be followed by

multivariate linear regression analysis. The results were deemed to be statistically significant if *p* < 0.05.

Results

Within the study period, a total of 91 STEMI patients were admitted to the emergency room and were treated at the CVCU of our hospital. Among them, 58 patients underwent pPCI. Of those 58 patients, 40 patients met the research criteria as subjects in this study (Figure 1).

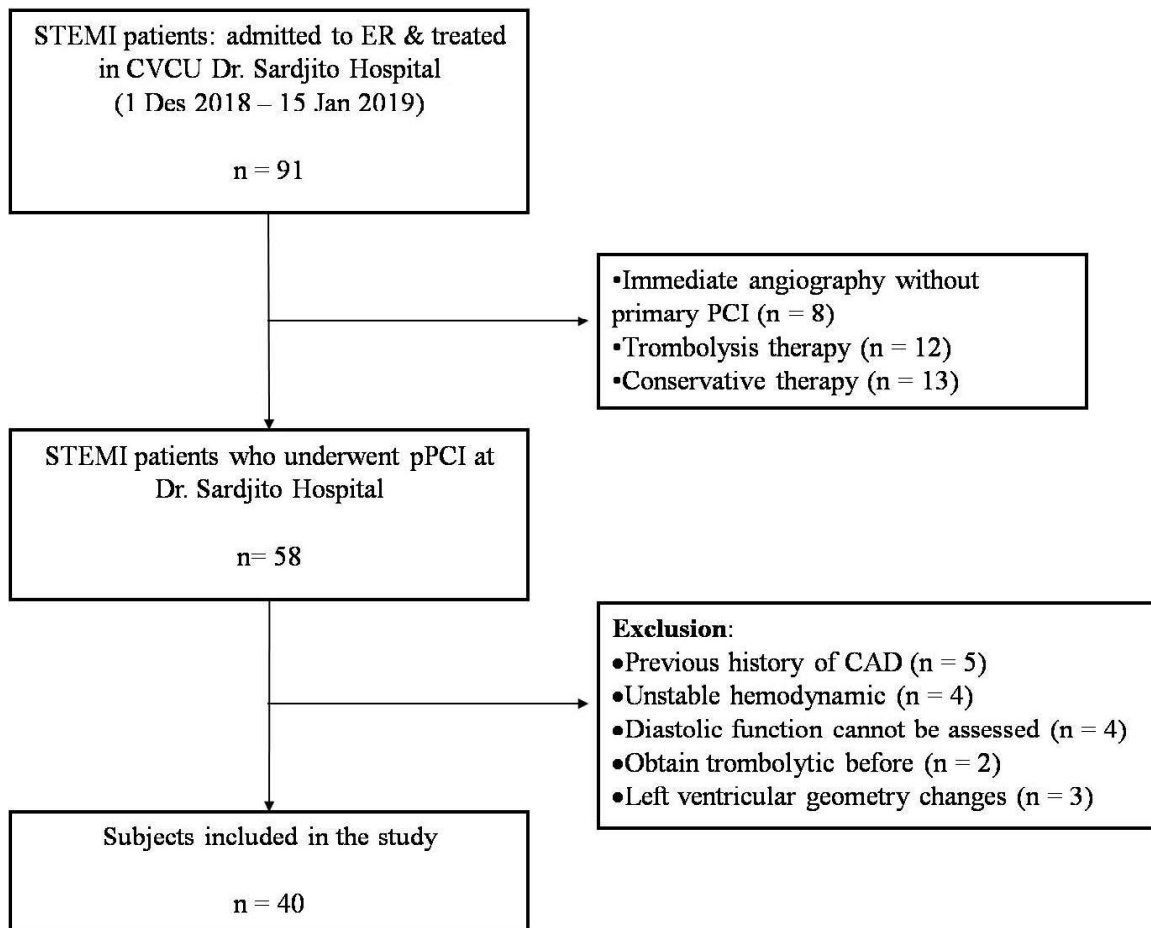


Figure 1. Flow of subjects recruitment.

The baseline characteristics of the subjects were shown in Table 1. The subjects were 34 male (85%) and 6 female (15%) with a mean age of 58.03±11.04 years. Based on the description of ST segment elevation on the ECG, 19 (47.5%) subjects were diagnosed with anterior

STEMI and 21 (52.5%) subjects with inferior STEMI. Some subjects had risk factors such as 14 with diabetes mellitus (35%), 26 with hypertension (65%), 27 with dyslipidemia(67.5%), and 30 with smoking/history of smoking (75%).

Table 1 Baseline characteristics of subjects with STEMI underwent pPCI

Characteristics	Value (n = 40)
Male; n (%)	34 (85.0)
Age (years); mean ± SD	58.03±11.04
Diagnosis:	
- Anterior STEMI; n (%)	19 (47.5)
- Inferior STEMI; n (%)	21 (52.5)
Killip class:	
- Killip I; n (%)	29 (72.5)
- Killip II; n (%)	8 (20.0)
- Killip III; n (%)	3 (7.5)
Risk factors:	
- Diabetes mellitus; n (%)	14 (35.0)
- Hypertension; n (%)	26 (65.0)
- Dislipidemia; n (%)	27 (67.5)
- Smoking; n (%)	30 (75.0)
Therapy given before TTE examination:	
- ACE inhibitor; n (%)	25 (62.5)
- Beta blocker; n (%)	15 (37.5)
- Nitrat; n (%)	19 (47.5)
Time parameter:	
- Onset (hour); median (min–max)	9.0 (2.5 – 20)
- Diagnosis until wire crossing (minute); mean±SD	145.97±45.92
- Wire crossing time (hour)*; mean±SD	12.73±5.22
- Time from wire crossing** to TTE (hour); mean±SD	18.04±9.48
The transthoracic echocardiography parameter:	
- LVIDd (mm); mean±SD	45.05±6.48
- Ejection Fraction (%); mean±SD	42.50±9.26
- E/A ratio; median (min–max)	0.82 (0.32–2.80)
- E/e' ratio; median (min–max)	8.36 (4.71–22.0)
Number of coronary artery blocked:	
- 1 artery; n (%)	16 (40.0)
- 2 arteries; n (%)	13 (32.5)
- 3 arteries; n (%)	11 (27.5)
Blood flow after Primary PCI:	
- TIMI 3 flow; n (%)	33 (82.5)
- TIMI 2 flow; n (%)	6 (15.0)
- TIMI 1 flow; n (%)	1 (2.5)
Laboratory parameter	
- hs-Troponin I (ng/L); median (min–max)	4,121.60 (64.1 – 40,000.0)

STEMI: acute myocardial infarction with ST segment elevation; LVIDd: left ventricular inner diameter diastolic; ACE: angiotensin-converting-enzyme; TIMI: Thrombolysis in Myocardial Infarction; SD: standard deviation; min: minimum; max: maximum.

*Wire crossing time: the time span of the patient begins to feel the first anginal chest pain until wire crossing is performed on infarct-related lesions in the infarct-related artery during the primary PCI procedure.

**Wire crossing: when the guide-wire penetrates an occlusive lesion in an infarct-related artery.

Subjects with the clinical presentation of Killip class I were 29 (72.5%), Killip class II were 8 (20%) and Killip class III were 3 (7.5%). Based on the results of coronary angiography preceded the pPCI, subjects with stenosis in 1 coronary artery were 16 (40%), stenosis in 2 coronary arteries were 13 (32.5%), and stenosis in 3 coronary arteries were 11 (27.5%). From evaluation angiography after primary PCI, there were 33 (82.5%) subjects with coronary blood flow TIMI 3 flow, 6 (15%) subjects with TIMI 2 flow, and 1 (2.5%) subject with TIMI 1 flow.

The median onset of anginal chest pain was 9 hours (range: 2.5 hours - 20 hours). The mean time since the patients were diagnosed with STEMI at the ER until the pPCI was performed was 145.97 ± 45.92 minutes. The mean wire crossing time was 12.73 ± 5.22 hours. The mean time span from wire crossing until the TTE

examination at the CVCU was 18.04 ± 9.48 hours.

The results of TTE showed a mean LVIDd was 45.05 ± 6.48 mm, the mean LV ejection fraction (Simpsons method) was $42.5 \pm 9.26\%$, mean TAPSE was 17.80 ± 5.21 mm, median ratio of E/A was 0.82 (range: 0.32 - 2.80), and median ratio E/e' was 8.36 (range: 4.71 - 22.00). From the results of laboratory tests, the median value of hs-Troponin I was 4,121.60 ng/L (range: 64.1 ng/L - 40,000 ng/L).

Correlation analysis between wire crossing time and E/e' ratio found a positive correlation between the two variables with a moderate strength and was statistically significant, indicated by the correlation coefficient $r=0.572$ and $p<0.001$. Scatter-plot of the correlation between wire crossing time and E/e' ratio was depicted in Figure 2.

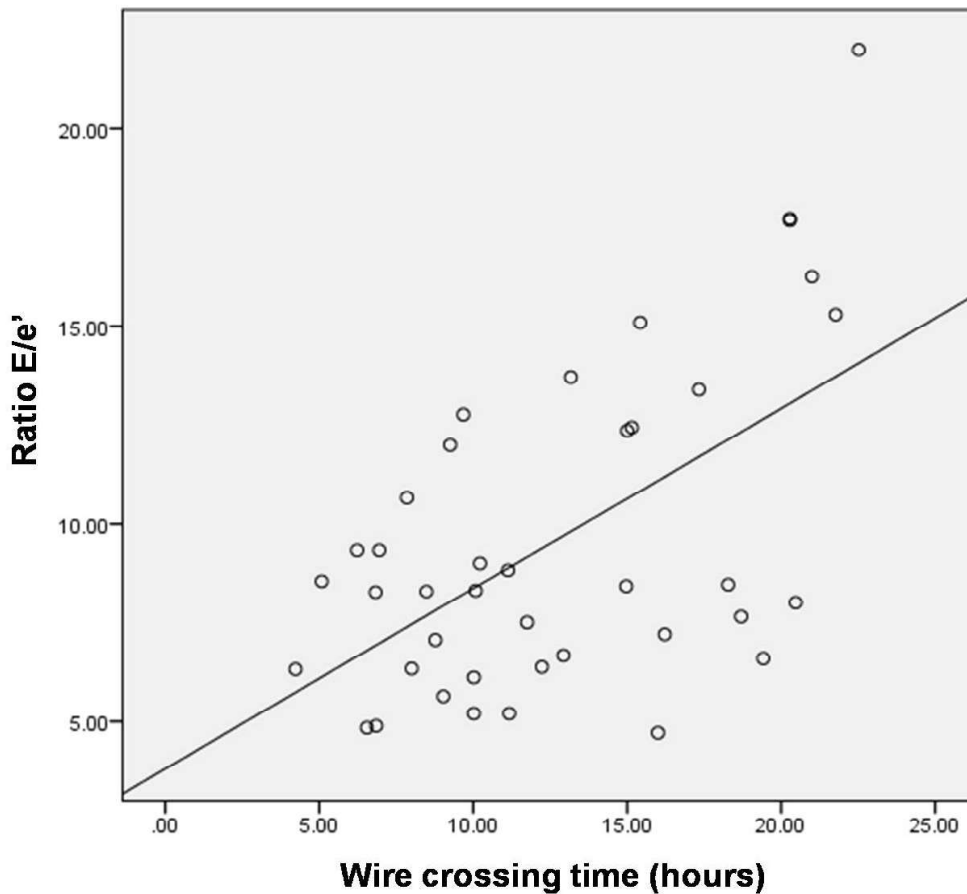


Figure 2. Scatter-plot of correlation between wire crossing time and E/e' ratio in STEMI patients who pPrimary PCI ($r=0.572$; $p<0.001$)

In this study, a sub-analysis by dividing subjects into 2 groups, groups of subjects with an E/e' ratio ≤ 15 and >15 . There was a significant difference in mean wire crossing time between subjects with $E/e' \leq 15$ and >15 , (11.41 ± 4.39 hours vs. 20.21 ± 2.5 hours; $p < 0.001$, respectively). Box-plot graph that describe the mean value of wire crossing time in both groups is shown in Figure 3.

Bivariate analysis with several variables which were estimated to influence the value of the E/e' ratio can be seen in Table 2. From the results of the bivariate test, confounding variables were entered to multivariate

linear regression analysis (Table 3). From multivariable analysis, it was known that the wire crossing time was a variable that independently influence the E/e' ratio ($r = 0.463$; $p = 0.003$).

The wire crossing time in this study exceeded the wire crossing time recommended by guideline. We conducted the investigation to assess the variables that affect the wire crossing time in our hospital. Most patients arrived in our ER not in working day or working hour. The time of activation and preparation of cath-lab team was the most consumed time. The variables that affect wire crossing time are shown in Table 4.

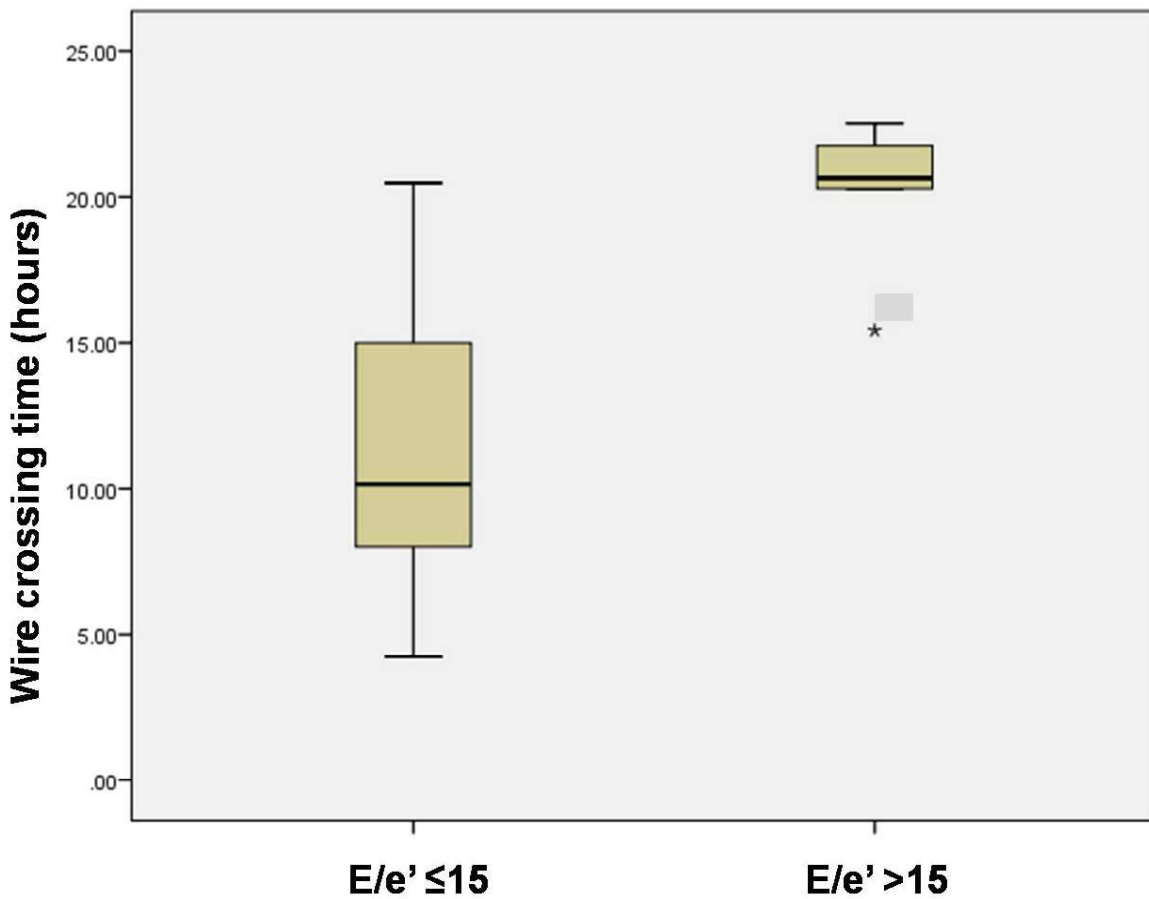


Figure 3. Box-plot graph of mean wire crossing time in subjects with $E/e' \leq 15$ (11.41 ± 4.39 hours) and subjects with an $E/e' > 15$ (20.21 ± 2.5 hours). The difference in mean wire crossing time between the two groups was statistically significant ($p < 0.001$)

Table 2. Bivariate analysis of factors affecting the E/e' ratio in STEMI patients underwent pPCI

Variables	r value	p-value
Age (years)	0.186	0.249*
Infarct location (anterior/inferior)	0.144	0.377
Diabetes mellitus	0.019	0.907
Hypertension	0.130	0.424
ACE-inhibitor therapy	0.133	0.414
Beta blocker therapy	0.163	0.316
Nitrat therapy	0.143	0.380
Wire crossing time (hour)	0.572	<0.001*
Number of artery(s) blocked	0.158	0.331
TIMI flow after pPCI	-0.417	0.007*
hs-Troponin I (ng/L)	0.015	0.926

ACE: angiotensin-converting-enzyme; TIMI: Thrombolysis in Myocardial Infarction; pPCI: primary percutaneous coronary intervention
*Bivariate analysis value that continue with multivariate linear regression analysis

Table 3. Multivariate analysis of the factors that influence E/e' ratio on STEMI patients underwent pPCI

Variables	r	p-value
Age	0.105	0.434
Wire crossing time (hour)	0.463	0.003
TIMI flow after pPCI	-0.235	0.108

TIMI: Thrombolysis in Myocardial Infarction; pPCI: primary percutaneous coronary intervention

Table 4. Wire crossing time variables of STEMI patients underwent pPCI at Dr. Sardjito Hospital

Variables	value
Onset (hour); median (min-max)	9.0 (2.5–20)
Door to ECG time (minute); median (min-max)	10.0 (3–35)
Time of consultation with doctor in charge (minute); median (min-max)	7.5 (2–92)
Time of calling the interventionist (minute); median (min-max)	6.5 (1–72)
Time of activation and preparation of cath-lab team (minute); median (min-max)	49.0 (10–170)
Transport time from ER–cath-lab (minute); median (min-max)	18.3 (6–59)
Patients preparation to puncture time (minute); median (min-max)	15.5 (6–45)
Time from puncture to wire crossing (minute); median (min-max)	23.3 (6–70)
Patient arrived:	
- During working day and work hour; n (%)	15 (37.5%)
- Not in working day or work hour; n (%)	25 (62.5%)

SD: standard deviation; Min: minimum; Max: maximum; cath-lab: catheterization laboratory

Discussion

This study indicated that the longer wire crossing time was correlated with increased LVEDP, an earlier marker of diastolic dysfunction, measured by E/e' ratio using TTE in patients with STEMI underwent pPCI. Furthermore, the wire crossing time was independently predict E/e' ratio. In our hospital, the mean wire crossing time was surpassed the expected time frame based on current guideline. Factors that influence the longer wire crossing time were patients arriving in ER not during

working days/working hours and the cath-lab activation and preparation.

In this study, the mean age of subjects was those in fifth decade of life majority of male patients. We found that smoking was the most conventional cardiovascular risk factor, while the risk factors for dyslipidemia, hypertension and diabetes mellitus were also high. The number of subjects who admitted to the ER with the initial clinical presentation of Killip class I was predominant. Various registry data and studies show patients with high Killip classes have a worse clinical

profile compared than patients with low Killip classes. The high Killip classes is also an independent predictor of mortality in STEMI. The results of laboratory tests showed that hs-troponin I showed positive correlation with onset of anginal chest pain. A previous study showed a strong negative correlation between serum troponin I concentration and the left ventricular ejection fraction after the first acute myocardial infarction.⁹ Another study found that the hs-troponin during admission in STEMI patients who underwent pPCI was strongly associated with major cardiovascular events in 30 days and 1 year.¹⁰

Based on the results of coronary angiography before the pPCI, subjects with stenosis in 1 coronary artery were predominant, however 40% of subjects had multivessel involvement. This result was in accordance with previous study which estimated 40-65% of STEMI patients have multivessel stenosis.¹¹ This multivessel disease in ACS is independently associate with worse clinical outcomes compare to STEMI patients who only have stenosis in 1 coronary artery.¹⁴ The mean wire crossing time, which means the time from onset of subjective anginal chest pain until intervention, reached 12.73 ± 5.22 hours. The delay in doing reperfusion action is related to wider infarct size and higher mortality rates.¹² Previous studies showed that a longer time span from the onset of symptoms to pPCI was associated with higher mortality.^{13,14}

In this study the mean E/e' ratio was 9.61 ± 4.15 with a median value of 8.36 (min– max: 4.71-22.0). The subjects with an E/e' ratio value >15 were 6 (15%) subjects. In the study of Saha *et al.* (2015) found that patients with an E/e' ratio >15 have a longer duration of hospital care and a higher incidence of heart failure, arrhythmia and mortality than patients with an E/e' ratio ≤ 15 .¹⁵ An E/e' ratio >15 also correlated with Killip class on admission, and demonstrated to be a superior predictor regarding major cardiovascular events and mortality, compared to conventional parameters of LV systolic function, such as left ventricular ejection fraction and Wall Motion Score Index.¹⁶ The E/e' ratio had a moderate strength and significant positive correlation with wire crossing time. The results of this study is in accordance with the previous study, which showed that long reperfusion time is an independent predictor of increasing E/e' ratio. In this study, patients with longer reperfusion time had a higher E/e' ratio

with a higher rate of diastolic dysfunction.¹⁷ Similar result was found in other study, where the proportion of patients with E/e' ratio >15 is significantly higher in patients with door-to-balloon time >90 minutes.¹⁰ It also found that door-to-balloon time >90 minutes is an independent predictor of LV diastolic dysfunction.¹⁰

Total coronary artery occlusion that occurs in STEMI causes necrosis and a decrease in contractile function of myocardia. The delay in performing reperfusion action is related to a wider size of infarction.¹² In STEMI, in addition to reduced systolic function, the diastolic function also disrupted.¹² In the early stages of diastolic dysfunction there is an increase in LVEDP which can be assessed non-invasively using the E/e' ratio parameter, where the E/e' ratio >15 shows high LVEDP (>15 mmHg).^{7,8} In this study, a group of subjects with an E/e' >15 only minority (15%), while then majority was subjects with $E/e' \leq 15$ (85%). Between the groups, there was a significant difference of mean wire crossing time. These results are consistent with the previous studies which showed longer reperfusion time is an independent predictor of increasing E/e' ratio.^{10,17,18} The multivariate analysis found that age was not an independent variable that can affect the E/e' ratio. This result is different from previous studies where the prevalence of diastolic dysfunction in the elderly population reaches 81-86%. This number is even higher in populations age >75 years accompanied by comorbid hypertension and diabetes mellitus.^{19,20} Hypertension patients had increased LVEDP which reflects diastolic dysfunction, therefore patients with antecedent hypertension during STEMI and even with pPCI still had increased risk to develop ventricular remodeling and heart failure.²¹ However, our data indicated that hypertension did not associate with E/e' ratio.

The multivariate analysis found that the variable that can independently influence the value of the E/e' ratio was the wire crossing time, where longer wire crossing time was related to the higher E/e' ratio. This can be explained because the total occlusion of the coronary arteries in STEMI will cause necrosis of myocardial cells, and the delay in reperfusion is associated with a wider size of infarction.¹² The wider size of the infarction cause an increase in ventricular wall stiffness and impaired active relaxation and passive filling during the diastolic phase characterized by an increase in the E/e' ratio in echocardiography examination.

Door-to-balloon time is one indicator of the quality of pPCI procedure and is one of the predictor for clinical outcomes in STEMI. A number of studies have shown that door-to-balloon time >90 minutes is associated with greater cardiovascular events and higher mortality during hospital and post-treatment.^{22,23} However, in our hospital during this study, time span between diagnosed in ER until wire crossing in cath-lab was still >90 minutes, which was 145.97 ± 45.92 minutes. Most patients arrived in ER not in working days or hours, when the cath-lab team was not in working shift. Therefore, there was a time delay for cath-lab activation. The time needed for activation and preparation of the cathlab team was one component that causes longer time from diagnosis to wire crossing.

This study had several limitations. Firstly, the number of samples in this study was not too large, with total sample of 40 subjects. However, this study had a research power of 98.98% with type II errors of 1.02%, and $Z\beta = 2.32$. Secondly, the baseline E/e' ratio value was unknown in each study subject before being diagnosed with STEMI which could confound the results of the study. Third limitation was the serial evaluation of echocardiography was not carried out to assess short and long term changes of echocardiographic parameters after pPCI procedure, ideally longer follow up period is needed to assess the LVEDP evolution post STEMI or pPCI.

Conclusion

There was a moderate strength and significant positive correlation between the wire crossing time and increased LVEDP, an earlier marker of diastolic dysfunction, measured by E/e' ratio using TTE in patients with STEMI underwent pPCI. The longer wire crossing time associate independently with the increased LVEDP.

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