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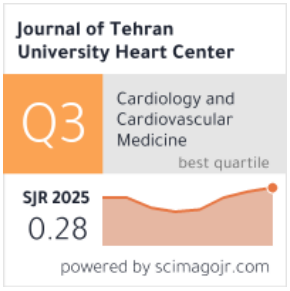
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Original Article

Delayed Percutaneous Coronary Intervention Regulates MMP-9, NOX2, and TGF-β1 After ST-Segment Elevation Myocardial Infarction: A Quasi-Experimental Study

Suryono Suryono [1*], Achmad Ilham Tohari [2,3], Muhammad Rijal Fahrudin Hidayat [3], Muhammad Irsyad Amien [3], Muhammad Farhan Hibatulloh [3], Muhammad Naufal Hibatullah [3], Hazbina Fauqi Ramadhan [4]

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Highlights

- In the real world, after being transferred to the PCI center, many patients have missed the optimal PCI time (<12 h).
- In this pilot quasi-experimental study of stable late-onset STEMI patients, delayed PCI performed 12 to 48 hours after symptom onset was associated with lower circulating levels of MMP-9, NOX2, and TGF-β1 at both 24 hours and day 5 compared with OMT.
- In the current study, delayed PCI performed 12 to 48 hours after symptom onset was associated with a more favorable early profile of remodeling-related biomarkers in stable STEMI patients and may be regarded as complementary to current recommendations.
- It does not alter the central role of very early reperfusion but suggests that, in carefully selected late-onset stable STEMI patients, revascularization may also modulate molecular pathways relevant to subsequent ventricular remodeling.

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ABSTRACT

Background: Primary percutaneous coronary intervention (PCI) remains the main treatment for patients with ST-segment elevation myocardial infarction (STEMI). Nonetheless, many patients still miss the primary PCI golden period or refuse it, especially in developing countries, such as Indonesia. This study compared the effects of delayed PCI (12–48 hours after STEMI onset) and optimal medical therapy (OMT) on cardiac remodeling biomarkers matrix metalloproteinase-9 (MMP-9), nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2), and transforming growth factor-β1 (TGF-β1).

Methods: This quasi-experimental study enrolled 55 patients with STEMI. Initially, all participants were advised to undergo delayed PCI. Patients who agreed to receive delayed PCI plus OMT were included in group 1 (n=24), and those who refused delayed PCI were included in group 2 and received OMT only. Blood samples were drawn at 24 hours and on day 5 after the intervention. MMP-9, NOX2, and TGF-β1 levels were measured using enzyme-linked immunosorbent assay. Data were analyzed using Stata, version 17.

Results: Group 1 showed significant reductions at 24 hours and day 5 in MMP-9 (Cohen d: −0.97, P<0.01 and −0.91, P<0.01, respectively), TGF-β1 (Cohen d: −0.64, P=.01 and −0.73, P<0.01, respectively), and NOX2 (Cohen d: −0.68, P=0.04 and −0.37, P=0.04, respectively) compared with group 2. No significant difference was observed between 24 hours and day 5 within each intervention group.

Conclusion: Delayed PCI performed within 12–48 hours was associated with significantly lower circulating levels of MMP 9, NOX2, and TGF β1 at 24 hours and 5 days compared with OMT alone in STEMI patients with stable conditions.

Keywords: Matrix Metalloproteinase-9 (MMP-9); Nicotinamide Adenine Dinucleotide Phosphate Oxidase 2 (NOX2); Primary percutaneous coronary intervention (PCI); ST-Segment Elevation Myocardial Infarction (STEMI); Transforming Growth Factor-β1 (TGF-β1)

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RHYTHM
Research in Heart Yield and Translational Medicine

Introduction

ST-elevation myocardial infarction (STEMI) occurs when myocardial ischemia progresses to injury or necrosis due to the occlusion of 1 or more coronary arteries that supply blood to the heart.[1] Primary percutaneous coronary intervention (PCI) is an important treatment for STEMI. The latest guidelines established early reperfusion to the infarct-related artery.[2] Following an acute MI, salvaging the myocardium at the earliest time is critical. Primary PCI can reopen the infarct-related artery, reducing the infarct area and residual stenosis, improving left ventricular function, and preventing reocclusion.

In the real world, after being transferred to the PCI center, many patients have missed the optimal PCI time (<12 h). In developed countries, approximately one-third of eligible patients received primary PCI, while the remaining two-thirds received either delayed PCI or conservative therapy.[3,4] In Indonesia, many patients with STEMI do not receive primary PCI for many reasons, such as denial of chest pain sensation, poor access to the PCI center, poor economic condition, and refusal of the primary PCI procedures.

Some studies have shown that optimal medical therapy (OMT) has the same results as delayed PCI in stable patients, whereas other studies have shown that delayed PCI can effectively preserve cardiac function and alleviate electrophysiological abnormalities.[5–7] On the other hand, cardiac remodeling occurs in patients experiencing STEMI. Cardiac remodeling can affect the left ventricle through dilatation, hypertrophy, and restriction of cardiomyocytes and can also decrease contractility, thereby accelerating heart failure.[8]

Several biomarkers, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (eg, NOX2), matrix metalloproteinase-9 (MMP-9), and transforming growth factor-β1 (TGF-β1), have been developed to investigate cardiac remodeling.[9]

The present study aims to determine whether delayed PCI within 12 to 48 hours is superior to OMT only in reducing MMP-9, NOX2, and TGF-β1 after STEMI.

Methods

Ethics Approval and Consent to Participate

This research was approved by the Health Research Ethics Committee of Saiful Anwar General Hospital (registration number: 400/235/K.3/302/2020). All patients included in this study provided informed consent before undergoing the procedure.

Study and Population

This research was a pilot quasi-experimental study conducted in 3 hospitals in East Java, Indonesia (Saiful Anwar, Soebandi, and Iskak Hospitals) from June - December 2022. MMP-9, NOX-2, and TGF-β1 were measured in the Laboratory of Physiology, Animal Structure and Development, Molecular Biology Building, Faculty of Mathematics and Natural Sciences, Brawijaya University, Indonesia. All patients who met the inclusion criteria for this research were recruited (total sampling). Initially, all participants were advised to undergo delayed PCI. Patients who agreed to receive delayed PCI plus OMT were included in group 1 (n=24), and those who refused delayed PCI were included in group 2 which and received OMT only. Group 1 received delayed PCI by an interventional cardiologist at 12 to 48 hours after the onset of chest pain and OMT for STEMI, including statins, aspirin, P2Y12 inhibitors, beta-blockers, low-molecular-weight heparin, nitrates, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, based on guidelines and the patient's condition. Group 2 received OMT only.

Inclusion and Exclusion Criteria

The inclusion criteria were patients who presented with STEMI more than 12 hours after the onset of chest pain, were aged 40 to 70 years, and provided informed consent. Informed consent was obtained from patients before undergoing delayed PCI in group 1. Participants included in group 2 were those who refused coronary intervention.

The main exclusion criteria were age younger than 40 years or older than 70 years; comorbid diseases such as infection, inflammation, malignancy, severe renal failure (estimated

glomerular filtration rate < 30), a history of hepatic cirrhosis, acute exacerbation of hepatitis, or severe liver disease; alcohol use disorder; cardiac arrest; ventricular fibrillation or cardiogenic shock; hemodynamic instability; heart failure; and lethal arrhythmia.

The protocol (Figure 1) was approved by the institutional review boards and was implemented in accordance with the provisions of the Declaration of Helsinki.

Data Extraction

Blood samples were collected to measure MMP-9, NOX2, and TGF-β1 via enzyme-linked immunosorbent assay (ELISA; BT Laboratory). Blood collection was performed in the ICCU 24 hours after delayed PCI in group 1 and 24 hours after admission to the ICCU in group 2. A total of 40 µL of blood sample and 10 µL of antibody (anti-MMP-9, anti-NOX2, and anti–TGF-β1) were added to the plate for each marker. Subsequently, 50 µL of streptavidin–horseradish peroxidase was added to each plate. Next, 50 µL of substrate A, 50 µL of substrate B, and 50 µL of stop solution were added to each plate. Absorbance was measured using a spectrofluorometer at 450 nm. Five days later, a second blood collection for MMP-9, NOX2, and TGF-β1 was performed in each group.

End Point

The primary end point was the effect of delayed PCI on MMP-9, NOX2, and TGF-β1 levels.

Statistical Analysis

Data were analyzed using Stata, version 17. Descriptive data-including age, sex, risk factors, comorbidities, and infarct location-are presented as numbers and percentages. The χ^2 and Fisher exact tests were used to compare differences in baseline characteristics between groups. MMP-9, NOX2, and TGF-β1 levels are expressed as median (interquartile range [IQR]). The Mann–Whitney U test was employed to compare MMP-9, NOX2, and TGF-β1 levels at 24 hours and day 5 between group 1 and group 2. Within each group, the Wilcoxon matched-pairs signed-rank test was utilized to compare outcomes at 24 hours and day 5. Effect size was measured using the Cohen *d*. A P value of less than 0.05 was considered statistically significant.

Results

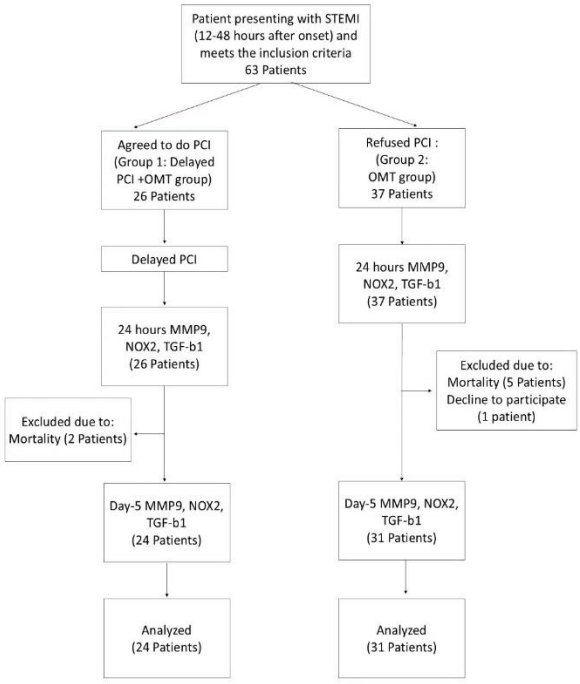


Figure 1. The flow chart of the present study

Total sampling was employed to recruit all patients who met the inclusion criteria. Initially, 63 patients were recruited for this study. Twenty-six participants who agreed to receive delayed PCI were included in group 1, and 37 patients who refused delayed PCI were included in group 2. During the 5 days of monitoring in the ICCU, 2 deaths occurred in group 1 and 5 in group 2. One patient was discharged against medical advice and declined to continue participation in the study. Ultimately, 24 patients were included in group 1 and 31 in group 2.

Demographic Characteristics

The mean (SD) age of all patients in this study was 57 (48–66) years, and 36 of the patients were male. A total of 28 patients had hypertension, 15 had diabetes, 8 had dyslipidemia, 34 were smokers or ex-smokers, and 27 had large infarcts. There was a significant difference in diabetes between group 1 and group 2 (Table 1).

Table 1. Demographic data of the study population

Characteristic	Category	Group 1 Delayed PCI + OMT No (%) (n=24)	Group 2 OMT Only No (%) (n=31)	Total (n=55)	*P*
Age, y (SD)	-	56.08 (8.02)	54.32 (6.87)		0.569[a]
Sex	Male	18 (75.0%)	18 (58.06%)	36 (65.45%)	0.123[b]
	Female	6 (25.0%)	13 (41.93%)	19 (34.54%)	
Hypertension	Yes	12 (50.0%)	16 (51.61%)	28 (50.90%)	0.906[b]
	No	12 (50.0%)	15 (48.38%)	27 (40.09%)	
Diabetes	Yes	2 (8.33%)	13 (41.93%)	15 (27.27%)	0.006[c]*
	No	22 (91.66%)	18 (58.06%)	40 (72.72%)	
Dyslipidemia	Yes	3 (12.5%)	5 (16.12%)	8 (14.54%)	0.705[b]
	No	21 (87.5%)	26 (83.87%)	47 (85.45%)	
Smoking / Ex-smoker	Yes	17 (70.83%)	17 (54.83%)	34 (61.81%)	0.226[b]
	No	7 (29.16%)	14 (45.16%)	21 (38.18%)	
Location of Infract	Anterior	5 (20.83%)	8 (25.80%)	13 (23.63%)	
	Anteroseptal	4 (16.66%)	5 (16.12%)	9 (16.36%)	
	Anterolateral	0 (0%)	0 (0%)	0 (0%)	
	Anterior Extensive	6 (25.0%)	1 (3.22%)	7 (12.72%)	0.201[b]
	Inferior	9 (37.5%)	17 (54.83%)	26 (42.27%)	

[a] Mann-Whitney U test; [b] χ^2 test; [c] Fisher exact test
Large infarct: anterior, anteroseptal, anterolateral, and anterior extensive (interpreted from electrocardiography and echocardiography)
Small infract: inferior (interpreted from electrocardiography and echocardiography)
Primary end point

(Table 2) reports the median (IQR) levels of MMP-9, NOX2, and TGF-β1 in each group. Group 1 showed significant reductions in MMP-9 (effect size: −0.97; P<0.01), TGF-β1 (effect size: −0.64; P=0.01), and NOX2 (effect size: −0.68; P=0.04) compared with group 2 at 24 hours. Outcomes on day 5 also demonstrated decreases in MMP-9 (effect size: −0.91; P<0.01), TGF-β1 (effect size: −0.73; P<0.01), and NOX2 (effect size: −0.37; P=0.04) in group 1 compared with group 2. Nevertheless, these differences were not significant within each group following the intervention.

Group 1 showed no significant difference between 24 hours and day 5 in MMP-9 (effect size: 0.32; P=0.60), TGF-β1 (effect size: 0.38; P=0.22), and NOX2 (effect size: −0.22; P=0.85). Group 2 also demonstrated no significant difference in MMP-9 (effect size: 0.05; P=0.59), TGF-β1 (effect size: 0.46; P=0.14), and NOX2 (effect size: −0.23; P=0.62).

Table 2. MMP- 9, NOX2, and TGF-β1 in each group

Outcome	Group 1 Delayed PCI + OMT Median (IQR)	Group 2 OMT Only Median (IQR)	P	Effect Size
MMP-9				
24 h	2.50 (0.86)	3.51 (3.26)	<0.01[a]*	-0.97[c]
Day 5	2.54 (1.68)	3.44 (2.49)	<0.01[a]*	-0.91[c]
P	0.60[b]	0.59[b]		
Effect size	0.32[c]	0.05[c]		
TGF-β1				
24 h	3.28 (0.99)	4.35 (2.01)	0.01[a]*	-0.64[c]
Day 5	3.08 (1.36)	3.73 (1.72)	<0.01[a]*	-0.73[c]
P	0.22[b]	0.14[b]		
Effect size	0.38[c]	0.46[c]		
NOX2				
24 h	1.97 (1.32)	2.59 (1.32)	0.04[a]*	-0.68[c]
Day 5	1.91 (1.62)	2.88 (2.09)	0.04[a]*	-0.37[c]
P	0.85[b]	0.62[b]		
Effect size	-0.22[c]	-0.23[c]		

[a] Mann-Whitney U test, [b] Wilcoxon matched pair signed rank test, [c] Cohen d test
*P<0.05

Discussion

In this pilot quasi-experimental study of stable late-onset STEMI patients, delayed PCI performed 12 to 48 hours after symptom onset was associated with lower circulating levels of MMP-9, NOX2, and TGF-β1 at both 24 hours and day 5 compared with OMT only. These findings suggest that opening the infarct-related artery during this time window may modulate key molecular pathways implicated in early postinfarction remodeling, even when primary PCI within the recommended 12-hour window has been missed. Our results showed no sustained biomarker reduction over time between 24 hours and day 5.

MMP-9 is a key matrix metalloproteinase involved in degradation of the extracellular matrix scaffold, leukocyte recruitment, and modulation of cytokine activity in the infarct border zone. Experimental models have shown that MMP-9 activity increases early after MI and that perturbation of MMP-9 signaling can substantially influence infarct expansion, left ventricular dilation, and systolic function.[10] Recent studies further support a relationship between higher circulating MMP-9 concentrations and adverse left ventricular remodeling or heart failure progression and highlight MMP-9 as a candidate biomarker of remodeling severity and prognosis.[10–12] In this context, the lower MMP-9 levels observed in group 1 at both 24 hours and day 5 may reflect attenuation of early extracellular matrix degradation and inflammatory activation in the repercussed myocardium.

NOX2, a major catalytic subunit of nicotinamide adenine dinucleotide phosphate oxidase in cardiomyocytes and immune cells, is a prominent source of reactive oxygen species (ROS) after MI and has been linked to oxidative stress–driven hypertrophy, interstitial fibrosis, and left ventricular dysfunction. Experimental data indicate that NOX2 expression and activity increase after coronary occlusion and that genetic deletion or pharmacologic inhibition of NOX2 can attenuate post-MI remodeling by reducing ROS burden and mitochondrial injury.[13] Higher systemic indices of oxidative stress have also been associated with worse clinical outcomes.[14] The lower NOX2 levels observed in group 1 may, therefore, represent reduced NOX2-dependent ROS generation in the peri-infarct and remote myocardium following revascularization, potentially limiting downstream activation of redox-sensitive pathways involved in matrix degradation and neurohormonal activation.

TGF-β1 is a central profibrotic mediator that orchestrates the transition from inflammation to scar formation and contributes to chronic interstitial fibrosis and diastolic dysfunction in the post-MI heart. Contemporary reviews emphasize that TGF-β signaling is rapidly activated in infarcted and remodeling myocardium, where it promotes myofibroblast differentiation, collagen synthesis, and suppression of matrix degradation while also exerting complex cell-specific effects on cardiomyocytes and immune cells.[15] Elevated TGF-β1 has been linked to more extensive fibrosis and adverse left ventricular remodeling in both experimental and clinical settings and modulation of TGF-β signaling is being explored as a potential antifibrotic strategy in heart failure.[16] The lower TGF-β1 levels observed in patients undergoing delayed PCI in our study may indicate attenuation of early profibrotic signaling, which is biologically plausible because reperfusion can limit infarct size, reduce neurohormonal activation, and alter mechanical stress in the border zone. Still, without serial imaging of left ventricular volumes or fibrosis, we cannot confirm whether these biochemical differences translate into meaningful structural or functional benefits.

From a clinical perspective, these biomarker findings should be interpreted within the framework of contemporary acute coronary syndrome guidelines. The 2023 European Society of Cardiology (ESC) Guidelines for the Management of Acute Coronary Syndromes identify primary PCI within 12 hours of symptom onset as the preferred strategy and recommend an invasive approach beyond 12 hours mainly for patients with ongoing ischemia, heart failure, cardiogenic shock, or malignant arrhythmias, while advising an individualized strategy in stable late-onset STEMI patients without evidence of ongoing ischemia.[7] In the current study, delayed PCI performed 12 to 48 hours after symptom onset was associated with a more favorable early profile of remodeling-related biomarkers in stable STEMI patients and may be regarded as complementary to current recommendations. It does not alter the central role of very early reperfusion but suggests that, in carefully selected late-onset stable STEMI patients, revascularization may also modulate

molecular pathways relevant to subsequent ventricular remodeling and warrants further study in larger, outcome-driven cohorts.

The results of the present study warrant cautious interpretation. First, this was a small, nonrandomized, quasi-experimental pilot study conducted across 3 centers in which group allocation was based on patients' acceptance or refusal of delayed PCI. This design introduces potential selection bias and unmeasured confounding because patients who declined PCI may differ systematically in clinical status, comorbidities, or socioeconomic factors from those who consented. Baseline characteristics were broadly similar across groups. However, the OMT-only group had a higher prevalence of diabetes, a factor known to influence oxidative stress, fibrosis, and remodeling risk, which could partly account for the biomarker differences.

Second, biomarkers were assessed at only 2 early time points (approximately 24 hours and day 5), which do not capture the full temporal dynamics of MMP-9, NOX2, and TGF-β1 or their relation to later structural changes and clinical events.

Third, the study did not include imaging-based measures of left ventricular volumes, function, or scar burden, nor did it collect long-term clinical outcomes such as heart failure hospitalizations or mortality, precluding direct conclusions regarding remodeling reversal or prognostic benefit.

Fourth, there may be time-related measurement bias insofar as group 1 had blood collection 24 hours after the PCI procedure and group 2 had blood collection 24 hours after admission to the ICCU; the time difference was approximately 1 hour due to the PCI procedure.

Conclusions

In this pilot quasi-experimental study of stable patients with STEMI presenting more than 12 hours after symptom onset, delayed PCI performed within 12 to 48 hours was associated with significantly lower circulating levels of MMP-9, NOX2, and TGF-β1 at 24 hours and 5 days compared with OMT alone. These findings suggest that, beyond symptom relief and epicardial reperfusion, delayed PCI may favorably influence early molecular pathways associated with adverse left ventricular remodeling in patients with late presentation. Nonetheless, the present data do not establish causality or confirm structural or prognostic benefit. Larger, preferably randomized, studies integrating multimodality imaging, extended biomarker assessment, and long-term clinical outcomes are needed to determine whether modulation of these remodeling biomarkers by delayed PCI translates into improved left ventricular structure, function, and prognosis in this high-risk population.

Declarations:

Ethical Approval

This research was approved by the Health Research Ethics Committee of Saiful Anwar General Hospital (registration number: 400/235/K.3/302/2020).

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Conflict of Interest

The authors report no conflict of interest.

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