Impact of Reperfusion Strategy on Erectile Dysfunction After ST-Elevation Myocardial Infarction

Running Title: *Reperfusion Strategy and Erectile Dysfunction Post-STEMI.*

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Abstract

Background: Patients with acute ST-elevation myocardial infarction (STEMI) face high rates of mortality and morbidity. Development of erectile dysfunction (ED) after STEMI is a common adverse effect. The study aimed to evaluate the effect of reperfusion strategy (primary percutaneous coronary intervention (PPCI) or fibrinolytic therapy (FT)) on erectile function in STEMI patients.

Patients and Methods: This observational study included 300 male patients with recent STEMI treated with either FT (FT-treated group, 128 patients) or PPCI (PPCI-treated group, 172 patients). Erectile function was evaluated using the International Index of Erectile Function 5-item (IIEF-5) during the patient's hospital stay to assess erectile function in the past three months and then 6 months after STEMI.

Results: There was a significant reduction in the post-STEMI IIEF-5 score in patients of the FT-treated group than those of the PPCI-treated group ($p < 0.001$), and this was confirmed by the distribution of IIEF-5 categories ($p = 0.037$). Reperfusion strategy, age, smoking, heart rate on admission, left ventricular internal diameter end-systole, and hypertension were independent predictors of post-STEMI IIEF-5 score.

Conclusion: PPCI was associated with a lower prevalence of ED following STEMI compared to FT. Furthermore, older age, smoking, hypertension, elevated heart rate on admission, and enlarged LVIDs were associated with deterioration of erectile function after STEMI.

Keywords: Erectile dysfunction, fibrinolytic therapy, IIEF-5, primary percutaneous coronary intervention, ST-elevation myocardial infarction.

Introduction:

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to achieve and/or maintain penile erection sufficient for satisfactory sexual performance (1). The overall prevalence of ED was 13.1–71.2%, according to the International Index of Erectile Function (IIEF), with a trend of increase ing ED prevalence with increasing age (2).

The prevalence of ED is almost high in men with coronary artery disease (CAD), and its severity depends on the extent of CAD (3-5). The incidence of cardiovascular disease (CVD) events (sudden cardiac death, myocardial infarction, or stroke) increased significantly from 5.1 per 1000 person-years in men with normal erection to 10.1 in men with reduced erectile rigidity to 19 in men with severely reduced erectile rigidity (6).

It was reported that ST-elevation myocardial infarction (STEMI) survivors experienced lower health-related quality of life in general health, physical health, daily activity, and mental health compared to the general population (7). In addition, previous studies revealed that STEMI was directly related to the occurrence of ED (8, 9). Two main reperfusion strategies for the treatment of STEMI were recommended: primary percutaneous coronary intervention (PPCI) and fibrinolytic therapy (FT) (10). In many ways, PPCI is superior to FT in terms of mortality and re-infarction rates (11). However, there is inadequate data relating to the effects of these reperfusion strategies on ED.

This study aimed to evaluate the erectile function in patients presenting with STEMI by comparing those treated with PPCI with those receiving FT.

Patients and Methods

Study Population

The present observational study included patients with recent STEMI treated with either FT or PPCI. Patients with STEMI who underwent PPCI with a final TIMI flow grade III (received care at the Assiut University Heart Hospital) or FT with successful fibrinolysis (received care at the Assiut Police Hospital) were included. The fourth universal definition of myocardial infarction, which is based on typical electrocardiographic abnormalities as well as clinical symptoms combined with elevations in cardiac biomarkers, was used to diagnose STEMI (12). Successful fibrinolysis was characterized by the occurrence of at least two of the following: the disappearance of chest pain within 90 minutes of initiating the fibrinolytic infusion, the reduction of ST-segment elevation by more than 50% following initiating the fibrinolytic infusion in the lead with maximum elevation on baseline ECG, or a sudden initial rise in cardiac enzyme levels within the first 24 hours following the onset of symptoms (13).

Exclusion criteria were defined as follows: Patients with non-ST elevation myocardial infarction, previous history of myocardial infarction or surgical revascularization, congenital heart disease, severe valvular heart disease, renal disease, liver cirrhosis, thyroid disease, history of using medications that affect erectile function (phosphodiesterase-5 inhibitors, amphetamines, antidepressant, and antipsychotic drugs), or history of urethral, penile or prostate surgery. In addition, those who had failed reperfusion after FT and those who did not achieve TIMI-III flow after PPCI in the infarct-related artery were excluded.

Sample Size Calculation

The sample size was calculated using the EPI info 2000 statistical package. The calculation used the expected frequencies from previous studies using a 95% confidence interval, 80% power of the study, 11% prevalence of coronary heart disease (according to The National Canter For Biotechnology Information), and the worst acceptable result, 5%. The calculated sample was 110 patients, which was increased to 300 to avoid missed data from the non-response rate.

Study Design

The studied patients were classified into 2 groups according to reperfusion strategy; the PPCI-treated group was treated with PPCI, and the FT-treated group received FT (1.5 million units of streptokinase given intravenously over 30-60 min).

Erectile function was assessed by an andrology consultant, who was unaware of the patient's treatment strategy, using the International Index of Erectile Function 5-item version questionnaire (IIEF-5) (Table 1) (14). Based on IIEF-5, the score range from 5 to 25, and ED was categorized into no (22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe (5–7) (Table 1). The Arabic version of IIEF-5 was reliable and validated with high specificity and sensitivity among the Egyptian population (15). The patients were asked to complete the IIEF-5 form during their hospital stay to evaluate erectile functions in the past three months before STEMI and a second IIEF

evaluation 6 months after STEMI. No treatment for ED was given before the second IIEF evaluation.

Ethical Approval

The present study was reviewed and approved by the ethical and medical research committee, Faculty of Medicine, Assiut University (approval number: 04-2022-20010), and complies with the Declaration of Helsinki. Following an explanation of all the study's processes, written informed consent was obtained from each participant. All participants were informed that the collected data was confidential and only used for scientific study. Participants could quit the study at any time without any negative impact on their medical treatment.

Statistical Analysis

Data were analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics: Means, standard deviations, medians, ranges, frequency, and percentages were calculated. The normality of continuous variables was tested using Kolmogorov–Smirnov test/Shapiro–Wilk test as appropriate. Test of significances: Chi-square/Fisher's exact test was used to compare the distribution of frequencies among different groups as appropriate. The McNemar test was used to compare differences in frequency within the group. Student t-test analysis was carried out to compare the means of dichotomous parametric data. Mann Whitney U test analysis was carried out to compare the medians of dichotomous non-parametric data. Repeated measure two-way ANOVA (RM-ANOVA) test was calculated to test the mean differences of the data that followed a normal distribution and had repeated measures (between groups, within groups, and overall difference). The multivariable linear regression model was created to obtain significant independent predictors of post-STEMI IIEF-5 score. A significant p-value was considered when it was < 0.05.

Results

The current study included 300 male patients classified into 2 groups according to the reperfusion strategy: The PPCI-treated group (172 patients) and the FT-treated group (128 patients).

Both groups were matched for age, body mass index, smoking, diabetes mellitus, dyslipidemia, and ECG location of STEMI, with the anterior STEMI being the commonest type in both groups (Table 2). Hypertension was significantly more frequent in the FT-treated group compared to the PPCI-treated group ($p < 0.001$). Contrarily, PPCI-treated group patients had a higher prevalence of family history of CAD than patients in the FT-treated group (14.5% vs 6.3%, $p = 0.023$). Moreover, it was found that patients in the FT-treated group suffered from higher systolic blood pressure ($p = 0.002$), diastolic blood pressure ($p = 0.002$), and hence pulse pressure ($p=0.012$) than those in the PPCI-treated group on admission (Table 2). Both groups were comparable in Total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol levels. However, cardiac enzyme levels (CK-MB and Troponin I) were significantly elevated in the FT-treated group compared with the PPCI-treated group ($p < 0.001$ and 0.002, respectively).

Both groups had no significant differences in the pre-STEMI IIEF-5 score ($p = 0.259$) (Table 3). However, there was a reduction in the post-STEMI IIEF-5 score in both groups compared with the pre-STEMI IIEF-5 score. Still, a statistically significant reduction in post-STEMI IIEF-5 score was observed in the FT-treated group compared with the PPCI-treated group (15.38 ± 3.3 vs 17.07 ± 2.7, $p < 0.001$) (Figure 1). This was confirmed by the distribution of IIEF-5 categories ($p = 0.037$) (Table 3), i.e., mild to moderate, moderate, and severe ED was less frequent in the PPCI-treated group compared with the FT-treated group (Figure 2).

Independent predictors of post-STEMI IIEF-5 score are shown in Table 4. The final linear regression model contained seven predictors. In other words, the intercept (post-STEMI IIEF-5 score) was 17 (12-24) after adjusting for all correlates ($p < 0.001$). Moreover, patients in the PPCI-treated group

increased their post-STEMI IIEF-5 score by 1.2 points (1.1–5.9 points, p=0.047). On the other hand, with a one-year increase in age, there was a 0.65 point (0.02-0.88 points, p=0.031) decrease in the post-STEMI IIEF-5 score. Also, smokers decreased the post-STEMI IIEF-5 score by 2.1 points (0.76–3.4 points, p=0.021). Also, with a one beat/minute increase in heart rate (HR) on admission, there was a 0.41-point (0.11–0.91 points, p=0.034) reduction in the post-STEMI IIEF-5 score. Further, with a one-cm increase in left ventricular internal diameter end-systole (LVIDs), there was 1.2 points (0.5–1.9 points, p=0.001) decrease in the post-STEMI IIEF-5 score. Likely, hypertensive patients had a decrease in the post-STEMI IIEF-5 score by 1.9 points (0.1–2.3 points, p=0.028).

Tables

Table 1: International index of erectile function 5-item version questionnaire (IIEF-5) and erectile dysfunction categories (14).

Question	Answer	Score
1. How do you rate your confidence that you could get and keep an erection?	• Very low	1
	• Low	2
	• Moderate	3
	• High	4
	• Very high	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	• Almost never or Never	1
	• A few times (much less than half the time)	2
	• Sometimes (about half the time)	3
	• Most times (much more than half the time)	4
	• Almost always or always	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	• Almost never or Never	1
	• A few times (much less than half the time)	2
	• Sometimes (about half the time)	3
	• Most times (much more than half the time)	4
	• Almost always or always	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	• Extremely difficult	1
	• Very difficult	2
	• Difficult	3
	• Slightly difficult	4
	• Not difficult	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	• Almost never or Never	1
	• A few times (much less than half the time)	2
	• Sometimes (about half the time)	3
	• Most times (much more than half the time)	4
	• Almost always or always	5
The IIEF-5 score is the sum of the responses to the 5 questions and ED is categorized into: • No ED: 22 – 25 • Mild ED: 17 – 21 • Mild to moderate ED: 12 – 16 • Moderate ED: 8 – 11 • Severe ED: 5 – 7		

Table 2: Patients' baseline charateristics on admission.

	PPCI-treated group (172 patients)	**FT-treated group (128 patients)**	***p-value***
Age (years)	54.8 ± 11.8	53.95 ± 10.7	0.469
BMI (kg/m^2)	29.84 ± 2.4	29.33 ± 4.2	0.181
Smoking	145 (84.3)	101 (78.9)	0.229
Hypertension	37 (21.5)	52 (40.6)	< 0.001
Diabetes mellitus	49 (28.5)	27 (21.1)	0.145
Dyslipidemia	17 (9.4)	6 (4.7)	0.094
Family history of CAD	25 (14.5)	8 (6.3)	0.023
Heart Rate (beat/minute)	84.88 ± 15.1	81.76 ± 14.7	0.074
Systolic BP (mmHg)	128.08 ± 21.4	137.34 ± 26.9	0.002
Diastolic BP (mmHg)	79.24 ± 13.1	83.91 ± 14.1	0.002
Pulse pressure (mmHg)	49.30 ± 4.2	53.44 ± 4.9	0.012
EF (%)	50.89 ± 10.3	48.13 ± 9.5	0.018
ECG localization of STEMI			
Anterior STEMI	115 (69.9)	95(74.2)	0.29
Inferior STEMI	48 (27.8)	33 (25.8)	
Posterior STEMI	2 (1.2)	0 (0)	
Lateral STEMI	7 (4.1)	0 (0)	
Total Cholesterol (mg/dl)	228.58 ± 43.8	227.44 ± 44.7	0.864
Total Triglyceride (mg/dl)	207.79 ± 42.4	206.80 ± 47.1	0.897
HDL-C (mg/dl)	30.39 ± 4.1	30.50 ± 2.4	0.865
LDL-C (mg/dl)	140.05 ± 19.7	144.65 ± 19.4	0.178
CK-MB (ng/ml)	79.25 ± 72.1	126.37 ± 124.9	< 0.001
Troponin I (ng/ml)	13.81 ± 10.7	18.53 ± 14.7	0.002

Data are expressed as mean ± SD or frequency (%).
BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CK-MB: creatine kinase-myocardial band; ECG: electrocardiogram; EF: ejection fraction; FT: fibrinolytic therapy; HDL-C: high density lipoprotein; LDL-C: low density lipoprotein cholesterol; PPCI: primary percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

Table 3: Effect of treatment strategy on erectile function using IIEF-5

	PPCI-treated group (172 patients)	**FT-treated group (128 patients)**	**P-value**
IIEF-5 score			
Pre-STEMI IIEF	17.43 ± 3.5	17.93 ± 3.9	0.259*
Post-STEMI IIEF	17.07 ± 2.7	15.38 ± 3.3	< 0.001**
P-value**	0.344	< 0.001	< 0.001***
IIEF-5 category			
Pre-STEMI IIEF			
No ED	31 (18.0)	24 (18.7)	0. 0.576[$]
Mild ED	62 (36.1)	44 (34.4)	
Mild to moderate ED	36 (20.9)	26 (20.3)	
Moderate ED	29 (16.9)	21 (16.4)	
Severe ED	14 (8.1)	13 (10.2)	
Post-STEMI IIEF			
No ED	22 (12.8)	10 (7.8)	0.037[$]
Mild ED	57 (33.1)	21 (16.4)	
Mild to moderate ED	38 (22.1)	43 (33.6)	
Moderate ED	36 (20.9)	35 (27.4)	
Severe ED	19 (11.1)	19 (14.8)	
P-value[#]	0.482	< 0.001	

Data are expressed as mean ± SD or frequency (%).
Two-way RM-ANOVA *Between groups **Within the group ***Interaction.
[$]Chi-square test was used to compare differences in frequency between groups.
[#]McNemar test was used to compare differences in frequency within the group.

ED: erectile dysfunction; FT: fibrinolytic therapy; IIEF: international index of erectile function; PPCI: primary percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

Table 4: Multivariable linear regression analyses of the IIEF-5 score predictors after STEMI.

	Estimate	SE**	t-stat***	P-value
Intercept	17.1 (12.26 to 23.84) *	1.93	10.78	< 0.001
• Group (PPCI-treated group)	1.21 (1.05 to 5.92)	0.67	4.59	0.047
• Age	-0.65 (-0.88 to -0.02)	0.12	-2.98	0.031
• Smoking	-2.1 (-3.4 to -0.76)	1.6	-5.12	0.021
• Heart rate on admission	-0.41 (-0.91 to -0.11)	0.41	-2.05	0.034
• LVIDs (cm)	-1.19 (-1.89 to -0.48)	0.36	-3.31	0.001
• Hypertension	-1.19 (-2.25 to -0.13)	0.54	-2.21	0.028

*CI= Confidence Interval, **SE=Standard Error, ***T-stat=T-test value

IIEF: international index of erectile function; LVIDs: left ventricular internal diameter end-systole; PPCI: primary percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

Figure Legends

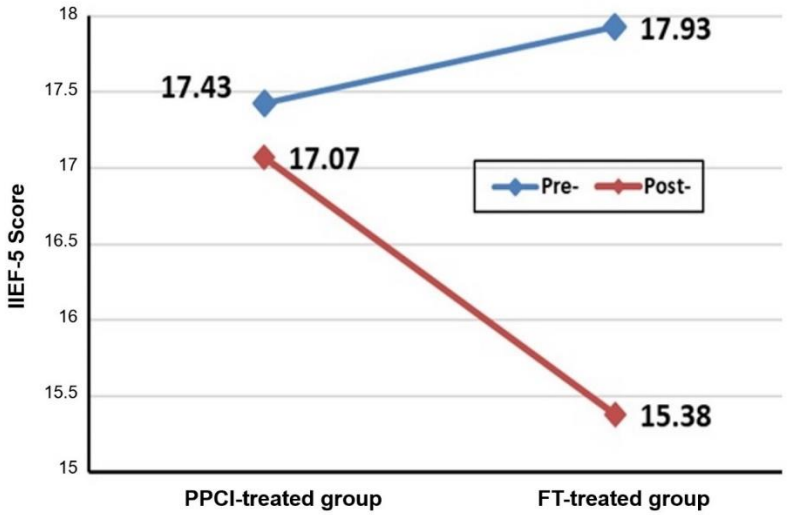

Figure 1: IIEF-5 score change pre- and post-STEMI in both groups.

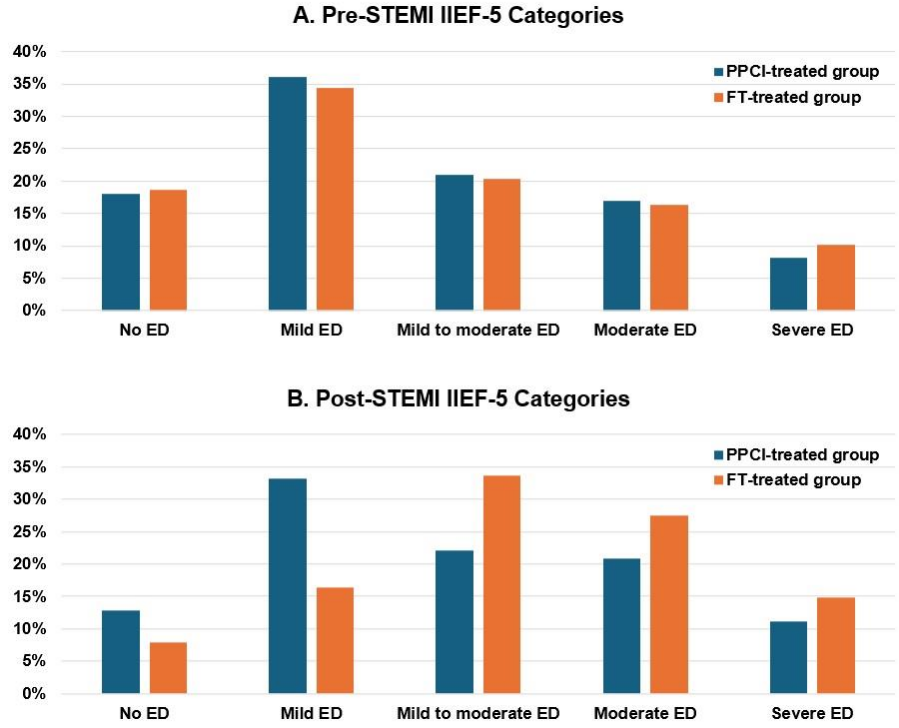

Figure 2: IIEF-5 categories change pre- (A) and post-STEMI (B) in both groups.

Discussion

ED is a common health problem among patients with CAD, and there is a correlation between the severity of CAD and ED (4, 16). ED preceded approximately 34 months before CAD symptoms, thus suggesting a temporal association between ED and CAD (17). Previous studies reported that the existence of ED is associated with a two-fold increase in the risk of STEMI among men (18, 19). Rinkūnienė et al. reported that the overall prevalence of ED after STEMI was 62% and is often present before the cardiac event (20). Previous randomized trials and meta-analyses demonstrated that PPCI in acute STEMI reduces mortality rates, re-infarction, recurrent ischemia, and stroke compared with FT (11, 21, 22). Therefore, PPCI is the recommended reperfusion strategy in patients with acute STEMI within 12 hours of the beginning of symptoms, provided it can be performed immediately (i.e., within 120 minutes from STEMI diagnosis) by a qualified team (10). To our knowledge, few studies have investigated the choice of reperfusion strategy for ED after STEMI. The current study revealed the effect of treatment modality on the ED according to the IIEF-5 score as the pre-treatment score in both groups was comparable, and at 6 months post-treatment, the score was reduced in both groups. Still, it was significantly better in patients of the PPCI-treated group than those of the FT-treated group, which deteriorated more.

Moreover, the current study was the first to demonstrate the changes in the distribution of IIEF-5 categories (no, mild, mild to moderate, moderate, and severe ED) post-STEMI. We observed a significant deterioration in erectile function categories in FT-treated patients in contrast to PPCI-treated patients (Figure 2). These data from the current study were similar to those previously reported by Akdemir et al., who showed that PPCI is superior to FT in reducing the prevalence of ED after STEMI (23). The small number of patients (71 patients) and using the IIEF-15 questionnaire, which is complicated and confusing for the patients, were the main limitations of Akdemir's study. However, our study included a large number of patients (300 patients) and used the IIEF-5 questionnaire, which is simple and easily understandable for the patients. Effective reperfusion achieved by PPCI reduces the extent of myocardial damage, which is supported by our finding regarding levels of cardiac enzymes such as Troponin I was significantly elevated in the FT-treated group compared with the PPCI-treated group (24).

Moreover, LV EF was higher in the PPCI-treated group than in the FT-treated group (25). Preservation of LV function by reducing the extent of myocardial damage using PPCI leads to improving cardiac output and blood flow to penial tissue, which is necessary for achieving and maintaining an erection. This finding is supported by Eren et al., who demonstrated impaired LV systolic functions using the speckle-tracking echocardiography method in patients with ED (26). The PPCI likely improved microcirculation perfusion, decreasing vasoactive substance release from the myocardium and safeguarding the function of microcirculation in other vulnerable organs such as penial tissue. However, additional studies are required to clarify this link and identify the underlying mechanisms.

The present study's intercept (IIEF-5 score) was 17 after adjusting for all correlates. Moreover, six adjusted predictors for ED were identified, i.e., treatment modality, age, smoking, hypertension, HR on admission, and LVIDs. This was in agreement with Akdemir et al., who reported that comparing the covariant variables, the post-STEMI IIEF-5 score and the regression analysis revealed the superiority of PPCI over FT as a reperfusion strategy (23). In addition, they showed that early reperfusion therapy preserves erectile function,

regardless of the type of reperfusion strategy used (23).

ED becomes more common with aging because of the natural decline in testosterone levels over time. By age 40, nearly 40% of males experience some degree of ED (5% with severe ED), and this number increases to about 70% by age 70 (15% with severe ED) (27). This agrees with our results, which showed that age was an independent predictor of ED. Moreover, Dostálová et al. reported that, in young myocardial infarction survivors, mild ED occurs in 26% and severe in 7%, while in the older survivors, mild ED occurred in 52% and severe in 38% (8).

It is not surprising to find that smoking is a predictor of ED post-STEMI as it is one of the most famous cardiovascular risk factors. Smoking can affect many regulatory systems crucial for erectile function (28). Smoking disrupts the normal autonomic function through activation of the sympathetic nervous system and decreases parasympathetic activity, which can disrupt erectile function. Smoking reduces the availability of nitric oxide via endothelial injury, which potentially contributes to ED. Tobacco and nicotine increase inflammatory markers (superoxide free radicals and endothelin-1) and activation of pro-inflammatory processes, which are implicated in the pathogenesis of ED. Cigarette smoking affects the testosterone level, which has a major role in sexual desire and function. A meta-analysis of 62 population-based studies (240882 men) found that cigarette smoking was an important independent risk factor for ED (29).

Hypertension is one of the most well-known cardiovascular risk factors. Therefore, it is expected that hypertension is an independent predictor of ED after STEMI. Because ED is a vascular disease, hypertension can cause ED, and ED may be an early warning sign of hypertension (30, 31). Many pathophysiological mechanisms suggested linked hypertension and ED. Such as hypertension affects the blood flow to the penis due to atherosclerosis, a crucial step in the process of achieving and keeping an erection (32). Hypertension is associated with an increase in the release of vasoconstrictors (angiotensin II, endothelin 1, and aldosterone), leads to endothelial dysfunction, which affects vascular nitric oxide levels, the corpus cavernosum, the vascular system, and erection (33). In penile tissue, endothelial dysfunction is a hallmark of the development of ED. Hypertension was evaluated as a risk factor for ED in a meta-analysis that included 40 studies with 121641 patients that showed that hypertension was closely related to ED (OR = 1.74, $p < 0.01$) (34). Moreover, hypertension was identified as a risk factor for ED in different regions of the world (Africa, OR = 3.35, $p < 0.01$; America, OR = 1.97, $p < 0.01$; Asia, OR = 1.97, $p < 0.01$; Europe, OR = 1.83, $p < 0.01$).

While HR on admission is a significant predictor of outcomes in patients with STEMI and worse prognosis (35), the specific role of admission HR as a predictor of ED in STEMI patients isn't as clearly defined in the literature. Elevated admission HR indicates a high level of stress and more severe myocardial damage, which exacerbates ED. Moreover, the stress and damage to the cardiovascular system during STEMI could impair blood flow and be implicated in endothelial dysfunction and inflammation, resulting in ED (36). Although there is no evidence in the literature linking LVIDs and ED in patients with STEMI, an indirect implication could be found. LVIDs is an important parameter in assessing left ventricular systolic function (37) and its abnormalities can indicate impaired left ventricular function, a common consequence of STEMI. Thus, reduced cardiac output and impaired blood flow can further contribute to ED by limiting the blood supply necessary for achieving and maintaining an erection.

The current study certainly has a few limitations. This study was a single-center study with a short period of follow-up. Therefore, the generalization of the findings to broader populations cannot be applied. However, it enrolled many patients, which is

in contrast to the other studies. Moreover, penial artery ultrasound, testosterone level, and other hidden organic causes of ED were not investigated.

Conclusions

PPCI has a positive impact in reducing the prevalence of ED after STEMI compared to FT. Furthermore, older age, smoking, hypertension, elevated heart rate on admission, and enlarged LVIDs were associated with deterioration of erectile function after STEMI.

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Conflicts of Interest

The authors declare that they have no competing interests.

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