Original Article

Microvascular reperfusion of fibrinolysis followed by percutaneous coronary intervention versus primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction

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Background: Primary percutaneous coronary intervention (PPCI) has been widely recognized as the preferred treatment for ST-segment-elevation myocardial infarction (STEMI). However, substantial numbers of STEMI patients cannot receive timely PPCI. Early fibrinolysis followed by routine percutaneous coronary intervention (FPCI) has been proposed as an effective and safe alternative for eligible patients. To date, few studies have compared FPCI with PPCI in terms of microvascular reperfusion. This study aimed to evaluate the microvascular function of FPCI and PPCI.

Methods: STEMI patients at the Peking University First Hospital and Miyun Hospital were enrolled in this retrospective study between January 2015 to December 2020. Microvascular function documented by the coronary angiography-derived index of microvascular resistance (caIMR) was measured at the final angiogram after revascularization. The primary end point was the caIMR of the culprit vessels. The secondary end points were in-hospital and follow-up major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal recurrent myocardial infarction, target-vessel revascularization (TVR), and non-fatal stroke/transient ischemic attacks (TIA). Details of the adverse clinical events were obtained from telephone interviews and electronic medical record systems until January 2022.

Results: In total, 496 STEMI patients were enrolled in this cross-sectional retrospective study. Of these patients, 81 underwent FPCI, and 415 underwent PPCI. At the baseline, the PPCI patients had a higher-risk profile than the FPCI patients. The time from symptom onset to reperfusion therapy was significantly shorter in the FPCI group than the PPCI group (median 3.0 *vs.* 4.5 hours; P<0.001). The caIMR was significantly lower in the FPCI group than the PPCI group (median 20.34 *vs.* 40.33; P<0.001). The median follow-up duration was 4.1 years. During the follow-up period, the rate of MACE was lower in the FPCI group than the PPCI group [7 (10.1%) *vs.* 82 (20.8%), P=0.048]. After propensity score matching to adjust for the imbalances at the baseline, the caIMR remained significant and the clinical outcomes did not differ significantly between the two groups.

Conclusions: In eligible STEMI patients, clinically successful FPCI may be associated with better

microvascular reperfusion and comparable clinical outcomes as compared with PPCI.

Keywords: Microvascular reperfusion; fibrinolysis; primary percutaneous coronary intervention (PPCI)

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Introduction

Despite great developments in its management in recent years, ST-segment-elevation myocardial infarction (STEMI) continues to be a prominent contributor to global mortality (1). Guidelines recommend primary percutaneous coronary intervention (PPCI) as the preferred reperfusion strategy for STEMI patients within 12 hours of symptom onset, with a performance goal of ≤90 minutes from the first medical contact (FMC) (2). However, in practice, PPCI is only performed within 120 and 60 minutes after FMC in 61.8% and 20% of patients, respectively (3). The extent to which the time delay associated with percutaneous coronary intervention (PCI) undermines the advantages it has over fibrinolysis has been widely affirmed (4). The pharmaco-invasive strategy of early fibrinolysis followed by routine percutaneous coronary intervention (FPCI) has proven to be an acceptable alternative reperfusion strategy. In the FAST-MI study (4), patients who received this pharmaco-invasive strategy had better survival outcomes compared to those who received PPCI late and comparable outcomes compared to those who received timely PPCI during the 5-year follow-up period. Moreover, in a large Canadian STEMI study (5), a dedicated pharmaco-invasive strategy resulted in superior reperfusion and a better 1-year outcome than PPCI.

Despite the restored patency of epicardial coronary circulation after PPCI, myocardial tissue hypoperfusion remains in large numbers of patients. Microvascular dysfunction is the principal cause of this phenomenon, which contributes to a poor long-term recovery and outcomes (6,7). The index of microvascular resistance (IMR) has clinical utility in evaluating microvascular dysfunction. Previous studies have shown that the IMR value at the time of PPCI is related to infarct size and the recovery of left ventricular function (8,9). Moreover, the IMR is a strong independent prognosticator of long-term clinical outcomes (10). However, the routine clinical adoption of the IMR in PPCI remains limited due to its additional procedural time and cost. Instead of relying on invasive pressure-wire measurement and hyperemic stimulus, the coronary angiography-derived index of microvascular resistance (caIMR) uses the wire-derived IMR as the gold-standard reference to overcome these limitations and has been shown to have exceptional diagnostic accuracy (11,12).

To date, few, studies have assessed the effect of FPCI compared with PPCI in terms of microvascular function using the caIMR. Accordingly, we sought to evaluate the microvascular function of patients with STEMI undergoing these reperfusion strategies using the caIMR, and its relationship to the clinical outcomes. We present this article in accordance with the STROBE reporting checklist (13) (available at https://qims.amegroups.com/article/view/10.21037/qims-23-666/rc).

Methods

Study population and data collection

This cross-sectional retrospective study was conducted at the Peking University First Hospital and Miyun Hospital using the data of patients with a diagnosis of STEMI based on the fourth universal definition of myocardial infarction (MI) (14) between January 2015 and December 31, 2020. This study was approved by the Institutional Review Board of the Peking University First Hospital, and the requirement of individual consent for this retrospective analysis was waived. The Peking University First Hospital and Miyun Hospital were informed of the study and agreed to its being conducted. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patients with STEMI who underwent either FPCI or PPCI were enrolled in this study. PPCI emerged as the favored reperfusion strategy for patients presenting within 12 hours of symptom onset or >12 hours with evidence of ongoing ischemia, and was promptly executed by a proficient team. Fibrinolysis was initiated when there were delays in achieving timely metrics. The routine early PCI strategy was performed after successful

fibrinolysis, otherwise, immediate angiography and rescue PCI was indicated in cases of failed fibrinolysis. In this study, successful fibrinolysis was defined as the disappearance of symptoms, a ST-segment resolution >50% at 60–90 minutes, typical reperfusion arrhythmia, and pre-procedure thrombolysis in myocardial infarction (TIMI) flow ≥2.

The fibrinolysis drugs were administered according to the instructions. Three types of thrombolytic agents were used in this study. First, 15 mg of alteplase was administered by bolus injection over 1 to 2 minutes, followed by 0.75 mg/kg (maximum 50 mg) over 30 minutes, and then 0.5 mg/kg (maximum 35 mg) over the next 60 minutes. Second, 10 U of reteplase was administered by bolus injection over 2 minutes, and then 10 U was administered at 30 minutes. Third, tenecteplase was administered by a single bolus injection over 5 to 10 s based on body weight as follows: 30 mg for patients <60 kg, 35 mg for patients 60–69 kg, 40 mg for patients 70–79 kg, 45 mg for patients 80–89 kg, and 50 mg for patients ≥90 kg. Additionally, 20 mg of recombinant human prourokinase was administered by bolus injection over 3 minutes, and then 30 mg was administered in 30 minutes.

Patients were excluded from the study if they had any contraindications to reperfusion therapy; were scheduled to undergo coronary artery bypass grafting (CABG) or received medical treatment alone after coronary angiography; had angiographic imaging that could not be used to quantify the caIMR in the culprit vessels. The clinical data were extracted from the electronic medical records by proficient physicians using a standardized form for meticulous data collection. The caIMR was measured at the final angiogram after revascularization.

caIMR measurement

The caIMR is a novel physiological parameter based on coronary angiograms and the aortic pressure wave (12). It is expressed as follows:

$$CaIMR = (P_d)hyp \frac{L}{K \cdot V_{diatole}} \quad [1]$$

where $(P_d)hyp$ refers to the mean pressure (unit: mmHg) at the distal position when the maximal hyperemia is reached; L is a constant (L=75) mimicking 75 mm downstream from the inlet of the coronary arterial tree; $V_{diastole}$ is the mean flow velocity (unit: mm/s) at the distal position at the diastole; and K is a constant (K=2.1) (15). The caIMR is characterized as the microvascular resistance in the unit volume of the myocardium distal to the L position. The caIMR was computed using the above equation by researchers at an independent institution, who were completely blinded to the patients' clinical data.

Schematic of the caIMR system (see Figure S1, FlashAngio console, FlashAngio software, and FlashPressure pressure transducer). (I) Three-dimensional reconstruction of the right coronary artery (RCA) based on angiograms from two projections separated by ≥30°; (II) the aortic pressure wave obtained from the FlashPressure sensor; (III) determination of resting flow velocity based on the RCA length and contrast passing time; and (IV) caIMR display in the FlashAngio software. The coronary angiography-derived fractional flow reserve (caFFR) system followed a similar method to the above procedures.

Outcomes

The primary outcome of the study was the caIMR of the culprit vessels. The secondary end points were in-hospital and follow-up major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal recurrent MI, target-vessel revascularization (TVR), and non-fatal stroke/transient ischemic attacks (TIA). The definitions of the cardiovascular outcomes were based on the uniform standard (16). Cardiovascular death was defined as any death resulting from cardiovascular causes. Non-fatal recurrent MI was determined based on the presence of myocardial necrosis in conjunction with indicative manifestations of myocardial ischemia. TVR was defined as a repeat PCI or bypass surgery of the target vessel. Non-fatal stroke/TIA was defined as episodes of neurological dysfunction resulting from cerebrovascular injury, with or without acute infarction. The safety endpoint was bleeding events, which were categorized as Bleeding Academic Research Consortium (BARC) types 2, 3, or 5 (17). Follow-up clinical outcomes were obtained through electronic medical record systems and telephone interviews until January 2022. The clinical and safety end points were duly validated by a discerning blinded adjudication physician.

Statistical analysis

The normally distributed continuous variables are presented as the mean ± standard deviation (SD) and were compared using the Student's t test. The non-normally distributed continuous variables are presented as the

median (interquartile range) and were compared using the Wilcoxon rank sum test. The categorical variables are reported as the number and percentage and were compared using the χ^2 test or Fisher's exact test. The relationship between the reperfusion strategies and the composite MACE outcome was estimated by employing cause-specific hazards models in which non-cardiac death was treated as a competing event. To determine the independent predictors of the caIMR, a multivariate linear regression analysis was conducted. The parameters demonstrating clinical significance and exhibiting significant statistical associations (P<0.05) with the caIMR in the univariable analysis were incorporated into the multivariable model. Given that potential bias existed at the baseline between the FPCI and PPCI strategies, a propensity score matched analysis was conducted. A greedy matching protocol (1:4 nearest neighbor matching without replacement) with a caliper width of 0.1 of the SD was used. After matching, standardized differences for all the covariates <10% indicated good balance between the matched groups. A two-sided alpha level of 0.05 was considered statistically significant. All the statistical analyses were conducted using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria), Prism 8 (GraphPad Software, San Diego, USA), and Stata software, version 16.0 (StataCorp).

Results

Patient characteristics

In total, 101 STEMI patients at the Peking University First Hospital and Miyun Hospital and three STEMI patients at the Peking University First Hospital received fibrinolysis from January 2015 to December 2020. Patients who underwent rescue PCI (one patient), received medical therapy alone (nine patients), required CABG after coronary angiography (five patients), and had a caIMR that could not be measured (eight patients) were excluded from the study. The FPCI group comprised 81 patients who underwent successful FPCI (Figure S2). During the same period, 472 patients with STEMI underwent PPCI at the Peking University First Hospital. Of these patients, 5 who received CABG after angiography and 52 who had a caIMR that could not be measured were excluded from the study. Thus, the PPCI group comprised 415 patients.

The characteristics of the patients are presented in *Table 1*. The patients were significantly more likely to be younger and have fewer risk factors in the FPCI group than the PPCI group. The hypertension and hyperlipidemia percentages were higher in the PPCI group than the FPCI group, but their blood pressure was lower and their lipid profiles were similar to the FPCI group at admission. The two groups had a similar Killip class, CK-MB peak values, and culprit artery distributions. The number of stents and intra-aortic balloon pumps used did not differ between the two groups. However, the time from symptom onset to FMC (2.5 *vs.* 3.0 hours; P=0.002) and the time from symptom onset to initiation of reperfusion (3.0 *vs.* 4.5 hours; P<0.001) were both shorter in the FPCI group than the PPCI group. The time from fibrinolysis to PCI was 7.3±4.0 days.

We were able to match 76 patients receiving FPCI to 173 patients receiving PPCI. Patient characteristics, including age, history of diabetes mellitus, hypertension, hypercholesterolemia, chronic kidney disease, and symptom onset to reperfusion time, were included in the propensity model. The propensity score matched cohorts were well balanced.

Assessment of microvascular dysfunction

In the entire cohort, the caIMR was significantly lower in the FPCI group than that in the PPCI group (median 20.34 *vs.* 40.33; P<0.001) (*Figure 1* and Table S1). Similarly, in the propensity score matched cohort, the caIMR was lower in the FPCI group than that in the PPCI group (median 20.19 *vs.* 39.38; P<0.001). The median caFFR was 0.93 in both groups. Table S2 shows the multivariable model for the prediction of the caIMR. The reperfusion strategy, symptom onset to reperfusion time, and CK-MB peak values were related to the caIMR (all P<0.001). Compared to the PPCI strategy, the association of the FPCI strategy with the caIMR remained significant (β, −18.758; 95% confidence interval, −26.361 to −11.155; P<0.001) after adjustment for other clinical parameters.

Clinical outcomes

In terms of the in-hospital adverse events and major bleeding, no differences in these outcomes were observed (*Table 2*). In total, 463 (93.35%) patients were followed up, and 36 (6.65%) patients dropped out of the study. The median follow-up period was 4.1 (2.6–5.3) years. In the entire cohort, the FPCI group had lower rates of MACE during the follow-up period than the PPCI group (*Figures 2,3*). The rate of cardiac death was significantly lower in the FPCI group than the PPCI group (0 *vs.* 7.6%).

Table 1 Baseline clinical characteristics of the FPCI and PPCI patients

Characteristics	FPCI (n=81)	PPCI (n=415)	P
Male, n (%)	68 (84.0)	335 (80.7)	0.496
Age, years	55.0±11.3	63.8±13.2	<0.001
Hypertension, n (%)	37 (45.7)	253 (61.0)	0.011
Diabetes mellitus, n (%)	12 (14.8)	127 (30.6)	0.004
Hyperlipidemia, n (%)	7 (8.6)	141 (34.0)	<0.001
History of smoking, n (%)	60 (74.1)	276 (66.5)	0.183
History of chronic heart failure, n (%)	0	1 (0.2)	>0.99
Chronic kidney disease, n (%)	0	16 (3.9)	0.087
Family history, n (%)	0	79 (19.0)	<0.001
Peripheral artery disease, n (%)	4 (4.9)	16 (3.9)	0.551
Chronic obstructive pulmonary disease, n (%)	0	1 (0.2)	>0.99
Previous stroke/TIA, n (%)	6 (7.4)	56 (13.5)	0.130
Previous MI, n (%)	1 (1.2)	28 (6.7)	0.066
Previous PCI, n (%)	1 (1.2)	32 (7.7)	0.032
Previous CABG, n (%)	0	1 (0.2)	>0.99
Medications before admission, n (%)			
Antiplatelet agents	0	66 (15.9)	<0.001
Statins	1 (1.2)	52 (12.5)	0.003
Systolic blood pressure, mmHg	128.4±19.4	119.9±20.7	0.001
Diastolic blood pressure, mmHg	79.4±12.4	70.7±13.2	<0.001
Heart rate, beats/min	72.0 (63.0–84.0)	77.0 (67.0–88.0)	0.052
Killip class, n (%)			0.552
I	70 (86.4)	328 (79.0)	
II–IV	11 (13.6)	87 (21.0)	
Laboratory tests			
Leukocyte, 10^9/L	10.0±3.0	10.2±3.4	0.716
Hemoglobin, g/L	140.0 (129.5–151.5)	141.0 (131.0–151.0)	0.827
Platelet, 10^9/L	208.0 (180.0–247.5)	205.0 (168.8–254.0)	0.960
Scr, mmol/L	66.0 (60.0–74.0)	85.7 (74.9–99.0)	<0.001
Blood glucose, mmol/L	6.2 (5.2–7.5)	7.7 (6.2–9.8)	<0.001
Triglyceride, mmol/L	1.6 (1.0–2.5)	1.4 (1.0–2.1)	0.241
Total cholesterol, mmol/L	4.3 (3.8–4.9)	4.3 (3.7–5.1)	0.582
LDL-C, mmol/L	2.7±0.8	2.7±0.9	0.839
HDL-C, mmol/L	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.173

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	FPCI (n=81)	PPCI (n=415)	P
Procedural characteristics			
CK-MB peak value, ng/mL	233.0 (143.0–320.0)	222.5 (106.9–390.3)	0.860
Infarct-related vessel, n (%)			0.203
Left anterior descending	37 (45.7)	190 (45.8)	
Left circumflex artery	6 (7.4)	59 (14.2)	
Right coronary artery	38 (46.9)	166 (40.0)	
Radial artery access, n (%)	80 (98.8)	365 (88.0)	0.003
Symptom onset to first medical contact, hours	2.5 (2.0–4.0)	3.0 (2.0–7.0)	0.002
Symptom onset to reperfusion time, hours	3.0 (2.0–4.0)	4.5 (3.0–8.1)	<0.001
Fibrinolysis to arterial sheath insertion, days	7.3±4.0	–	–
Stent implantation numbers	1.0 (1.0–2.0)	1.0 (1.0–1.0)	0.001
Intra-aortic balloon pump, n (%)	2 (2.5)	21 (5.1)	0.400
Fibrinolytic agent, n (%)			
Alteplase	5 (6.2)	–	
Reteplase	73 (90.1)	–	
Recombinant human urokinase	1 (1.2)	–	
Recombinant staphylokinase	2 (2.5)	–	
Medication at hospital discharge, n (%)			
Aspirin	81 (100.0)	403 (97.1)	>0.99
Ticagrelor	16 (19.8)	131 (31.6)	0.026
Clopidogrel	67 (82.7)	275 (66.3)	0.008
Statins	80 (98.8)	403 (97.1)	>0.99
Beta-blocker	64 (79.0)	348 (83.9)	0.141
ACEI/ARB	41 (50.6)	322 (77.6)	<0.001
Diuretic	10 (12.3)	59 (14.2)	0.612

Data are presented as the median (interquartile range), n (%), or mean ± standard deviation. FPCI, fibrinolysis followed by elective percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; TIA, transient ischemic attacks; MI, myocardial infarction; CABG, coronary artery bypass grafting; Scr, serum creatinine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CK-MB, creatine kinase-MB; ACEI/ARB, angiotensin converting enzyme inhibitors/Angiotensin receptor blocker.

In the propensity score matched cohort and adjusted model, there were no significant difference in the MACE rates (Table S3). The all-cause death rate was also similar between the two groups (1.22% *vs.* 5.06%; P=0.211).

Discussion

In this study, the STEMI patients who underwent FPCI showed less severe microvascular dysfunction than those who underwent PPCI. The clinical outcomes were similar after propensity score matching between groups. Despite being the preferred reperfusion strategy for STEMI patients, achieving timely PPCI remains a challenge in practice, and it was especially challenging during the Coronavirus Disease 2019 pandemic, during which time the percentage of patients receiving PPCI decreased by one-

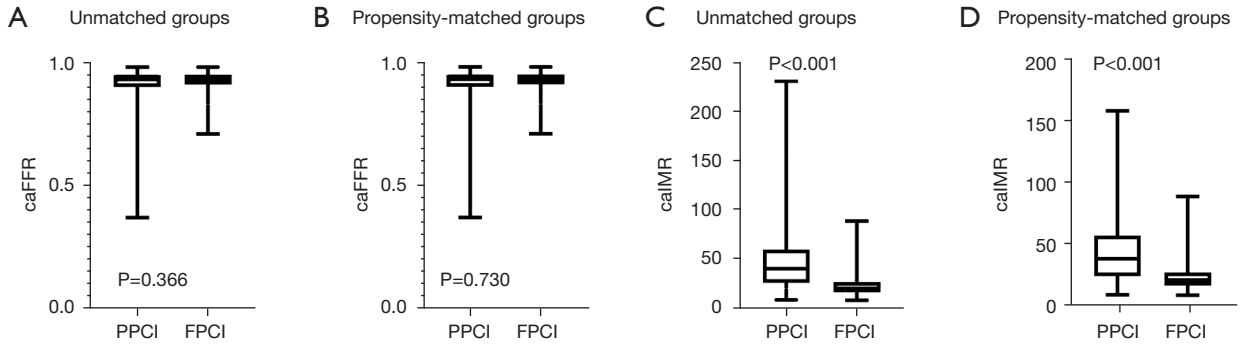

Figure 1 The caIMR results of the FPCI and PPCI groups before and after propensity score matching. (A) The caFFR results of the FPCI and PPCI groups among all patients. (B) The caFFR results of the FPCI and PPCI groups among patients after propensity score matching. (C) The caIMR results of the FPCI and PPCI groups among all patients. (D) The caIMR results of the FPCI and PPCI groups among patients after propensity score matching. PPCI, primary percutaneous coronary intervention; FPCI, fibrinolysis followed by elective percutaneous coronary intervention; caIMR, coronary angiography-derived index of microvascular resistance; caFFR, coronary angiography-derived fractional flow reserve.

Table 2 In-hospital clinical and safety outcomes

Outcomes	FPCI (n=81), n (%)	PPCI (n=415), n (%)	P
In-hospital complications	1 (1.23)	15 (3.61)	0.489
Stroke	0	1 (0.24)	>0.99
Stent thrombosis	1 (1.23)	2 (0.48)	0.415
In-hospital death	0	12 (2.89)	0.230
In-hospital safety outcomes	1 (1.23)	2 (0.48)	0.415
BARC ≤2 bleeding events	1 (1.23)	2 (0.48)	0.415
BARC 3 or 5 bleeding events	0	0	–

FPCI, fibrinolysis followed by elective percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; BARC, Bleeding Academic Research Consortium.

half and the percentage of patients receiving thrombolysis increased dramatically (18).

Previous studies proposed that FPCI was comparable to PPCI in terms of clinical outcomes, and was even superior to delayed PPCI (4,5,19). In the EARLY-MYO study, for STEMI patients presenting ≤6 hours after symptom onset and with an expected PCI-associated delay, the use of a pharmocol-invasive strategy was superior to PPCI in terms of the occurrence of complete epicardial and myocardial reperfusion (19). In addition, the STREAM (20), GRACIA-2 (21), and Transfer-AMI (22) trials all reported similar favorable results.

Consistent with previous studies (4,5,19), our study showed that early FPCI was equivalent to PPCI in terms of the clinical outcomes. More importantly, early FPCI appeared to achieve better microvascular perfusion than PPCI. This might be due to several factors. First, it has been reported that the IMR value is correlated with symptom onset-to-balloon time, and that there is no relationship between cardiovascular risk factors and procedural factors (23). The time from symptom onset to the initiation of reperfusion was significantly shorter in the FPCI group than the PPCI group, which may lead to better microvascular reperfusion. Second, microvascular obstruction is related to the embolization of plaque or thrombosis downstream in the infarct-related artery. During PCI, mechanical fragmentation is a key reason for embolization. Previous studies have shown that aspiration before stenting during PPCI results in improved myocardial reperfusion (24,25). Thus, we speculated that FPCI may

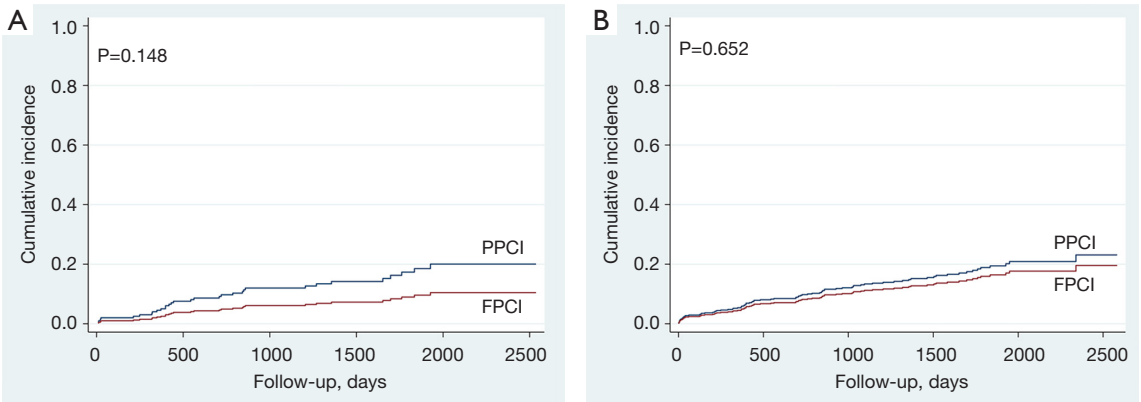

Figure 2 Adjusted cumulative major adverse cardiac events during follow-up between the FPCI and PPCI groups. (A) Propensity score matching model; (B) adjusted model. Model was adjusted for age, sex, diabetes, hypertension, dyslipidemia, chronic kidney disease, CK-MB peak value, symptom onset to reperfusion time, and stent number. PPCI, primary percutaneous coronary intervention; FPCI, fibrinolysis followed by elective percutaneous coronary intervention; CK-MB, creatine kinase-MB.

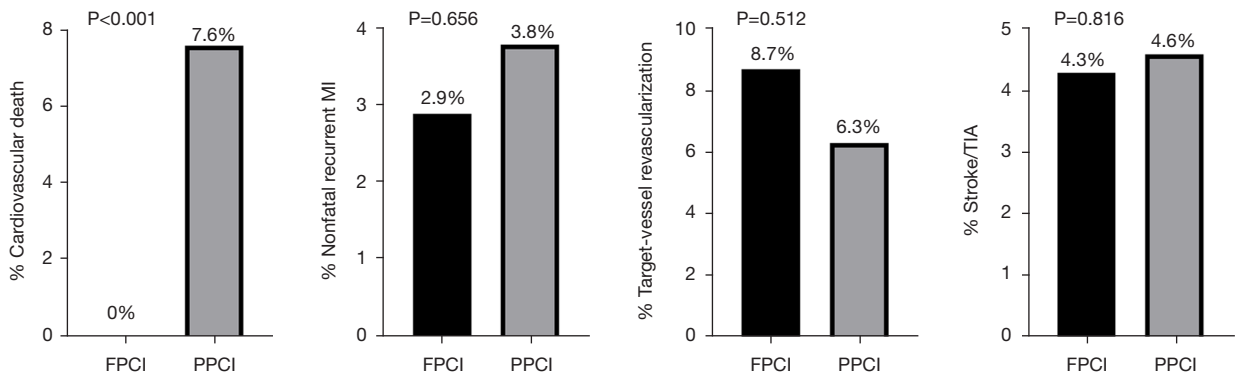

Figure 3 Major adverse cardiovascular events during follow-up period among all patients. PPCI, primary percutaneous coronary intervention; FPCI, fibrinolysis followed by elective percutaneous coronary intervention; MI, myocardial infarction; TIA, transient ischemic attacks.

reduce the thrombus burden and improve microvascular function. Third, in the first 6 hours of myocardial reperfusion, chemo-attractants released from injured endothelial cells and cardiomyocytes draw neutrophils into the infarct zone, which then migrate into the myocardial tissue over the next 24 hours. This process causes vascular plugging and the release of degradative and proteolytic enzymes and reactive oxygen species (26,27). This acute inflammatory response may have caused a higher caIMR in the PPCI group.

In this retrospective real-world study, the duration from successful fibrinolysis to PCI was almost 1 week, which is far beyond the 2–24 hours recommended in the guidelines (28). Based on a pooled patient-level analysis of six randomized trials, very early angiography (<2 hours) after fibrinolysis is not related to improved outcomes, and patients benefit from early angiography (<4 hours) (29). Our study showed that the clinical outcomes were similar between the PPCI and FPCI groups. This favorable prognosis might be due to timely reperfusion, intense surveillance and, individualized therapy during hospitalizations. As far as we know, no previous trial has compared such a prolonged delay from fibrinolysis to PCI. Our study indicated that rapid reperfusion is more important for prognosis. The FPCI and PPCI groups exhibited similar clinical outcomes in this study; however, the patients in the FPCI group required close monitoring in the intensive care unit before the subsequent PCI. This requirement not only caused patient discomfort but also extended the duration of hospitalization. Caution

is recommended when extrapolating our findings to all STEMI patients, as these findings need to be tested further.

In STEMI patients with anticipated delays in PCI, a combined approach of administering half-dose fibrinolysis alongside PCI demonstrated comparable efficacy outcomes to PPCI alone, without an increased risk of bleeding (19,30,31). Further, the pharmaco-invasive strategy led to more complete epicardial and myocardial reperfusion. In the EARLY-MYO study, the incidence of microvascular obstruction was similar between the pharmaco-invasive and PPCI groups (70.7% *vs.* 73.3%, P=0.652). Our study used the caIMR to quantify the level of microvascular obstruction, and found that the FPCI was associated with better microvascular function than the PPCI. Apart from the successful patency of epicardial coronary flow, sufficient myocardial reperfusion is no less important. Microvascular dysfunction is involved in patient prognosis after STEMI. Elevated IMR values at the time of PPCI are correlated with larger infarct sizes, adverse left ventricular function, and even increased mortality (8,10).

Currently, cardiac magnetic resonance imaging is generally used to assess microvascular dysfunction; however, it is rarely performed at the acute phase of STEMI, and its costs limit its wide use in practice (32). Other angiographic indexes evaluating microcirculatory function, such as the TIMI frame count, the TIMI flow grade, and myocardial blush grade, are semiquantitative and lack prognostic ability (32,33). The IMR is a reliable invasive measure for assessing coronary microvascular dysfunction; however, the use of IMR in STEMI patients remains limited, and its application during PPCI is hindered by the inconvenience associated with additional non-culprit vessel wire manipulation and adenosine administration. The caIMR overcomes these obstacles. It is also easily available, reproducible, and prognostic. An angio-IMR value >40 U was shown to be an independent predictor of cardiac death or readmission for heart failure, which is consistent with the IMR (8,34). In our study, the FPCI strategy was correlated with lower caIMR values, which suggests that early reperfusion is crucial for microvascular function. The symptom onset to reperfusion time was positively correlated with the caIMR, which provides further support for these findings. Thus, our study provides further evidence that FPCI may be an alternative treatment when early PCI is not available.

Limitations

Our study had the limitations inherent to retrospective studies. A propensity score analysis was used, but selection bias may still exist. The patients who underwent PPCI had more comorbidities than those who underwent FPCI, which suggests that the physicians might have selected higher-risk patients for PPCI, even when faced with longer FMC-to-balloon times. Moreover, the time from fibrinolysis to routine early PCI in our study might not be applicable to all populations and further studies need to be conducted to explore optimal timing. Additionally, the average time from onset to the caIMR measurement was significantly longer in the PPCI group than the FPCI group. In the PPCI group, the caIMR was measured after revascularization in the acute phase of MI, while in the FPCI group, the caIMR was measured after the lesion had stabilized following an average of 7 days of pharmacological therapy. Thus, the risk of distal embolization might be lower during PCI after stabilization of the culprit lesion has been achieved. In the future, prospective randomized controlled trials need to be conducted that implement the pharmaco-invasive strategy to verify the results.

Conclusions

In STEMI patients, successful early FPCI may be associated with better microvascular function and comparable long-term clinical outcomes as compared with PPCI.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-666/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Peking University First Hospital, and the requirement of individual consent for this retrospective analysis was waived.

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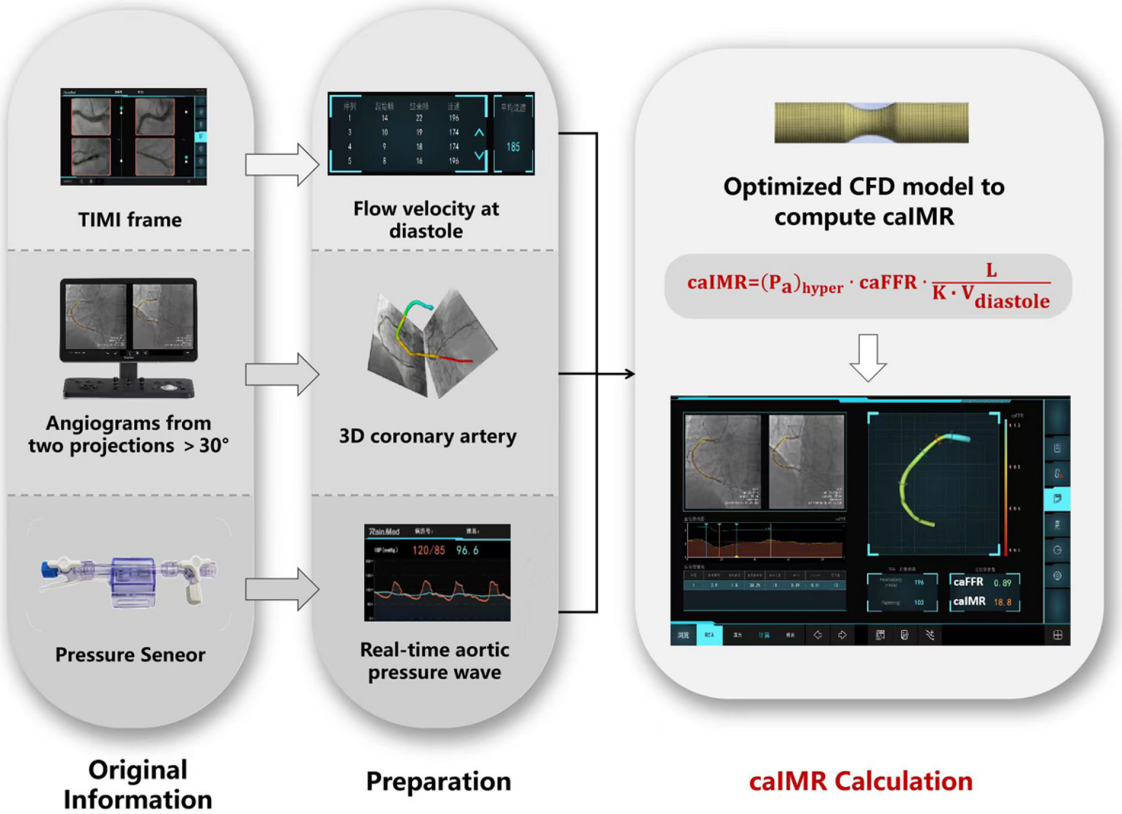

Figure S1 The schematic of the caIMR and caFFR systems. TIMI, thrombolysis in myocardial infarction; CFD, computational fluid dynamics; caIMR, coronary angiography-derived index of microvascular resistance; caFFR, coronary angiography-derived fractional flow reserve.

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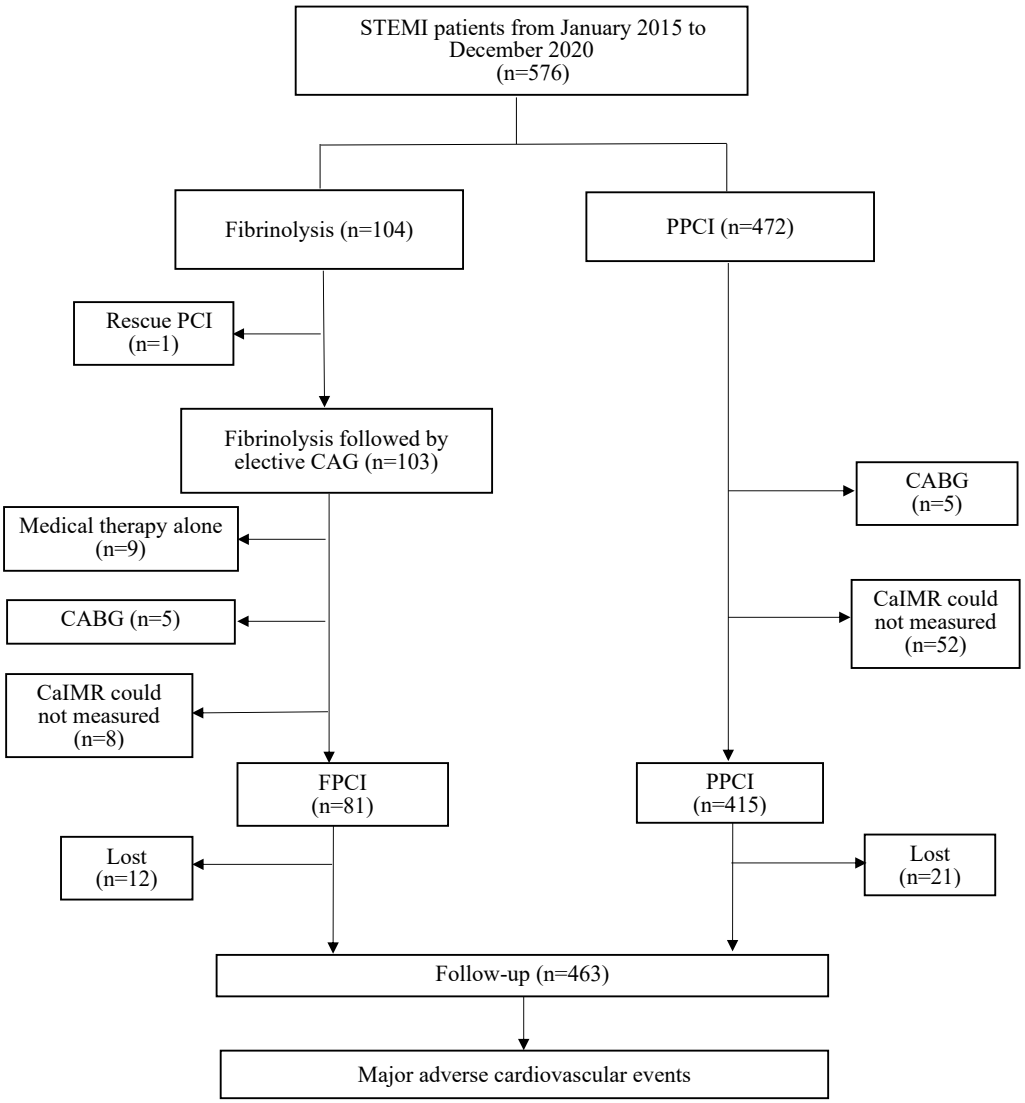

Figure S2 Flowchart for the study. STEMI, ST-segment-elevation myocardial infarction; PPCI, primary percutaneous coronary intervention; CAG, coronary angiogram; CABG, coronary artery bypass grafting; caIMR, coronary angiography-derived index of microvascular resistance; FPCI, fibrinolysis followed by elective percutaneous coronary intervention.

Table S1 The caIMR results in the FPCI and PPCI groups before and after propensity score matching

	Unmatched groups			Propensity score matched groups		
	FPCI (n=81)	PPCI (n=415)	P	FPCI (n=76)	PPCI (n=173)	P
caIMR	20.34 (16.42–26.87)	40.33 (25.70–59.73)	<0.001	20.19 (16.37–26.24)	39.38 (25.05–56.75)	<0.001
caFFR	0.93 (0.91–0.95)	0.93 (0.90–0.95)	0.366	0.93 (0.91–0.95)	0.93 (0.90–0.95)	0.730

caIMR, coronary angiography-derived index of microvascular resistance; FPCI, fibrinolysis followed by elective percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; caFFR, coronary angiography-derived fractional flow reserve.

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Table S2 Linear regression analysis for the prediction of microvascular dysfunction

	Univariable analysis		Multivariable analysis	
	β (95% CI)	P value	β (95% CI)	P value
Reperfusion strategy		<0.001		<0.001
PPCI	Control		Control	
FPCI	−23.191 (−29.943 to −16.440)		−18.758 (−26.361 to −11.155)	
Symptom onset to reperfusion time	1.055 (0.627 to 1.484)	<0.001	1.354 (0.843 to 1.865)	< 0.001
Peak CK-MB	0.019 (0.010 to 0.027)	<0.001	0.019 (0.010 to 0.028)	< 0.001
Age	0.220 (0.025 to 0.415)	0.027	0.026 (−0.191 to 0.244)	0.813
Sex		0.980		0.628
Male	Control		Control	
Female	−0.086 (−6.769 to 6.596)		−1.711 (−8.648 to 5.227)	
Stent numbers	−2.214 (−6.741 to 2.313)	0.337	1.444 (−3.020 to 5.908)	0.525
Hypertension		0.098		0.231
No	Control		Control	
Yes	4.449 (−0.829 to 9.727)		3.280 (−2.095 to 8.654)	
Diabetes mellitus		0.958		0.991
No	Control		Control	
Yes	−0.155 (−5.962 to 5.653)		0.032 (−5.923 to 5.988)	
Hyperlipidemia		0.628		0.699
No	Control		Control	
Yes	1.407 (−4.292 to 7.106)		−1.129 (−6.864 to 4.605)	
Previous stroke/TIA		0.470		0.194
No	Control		Control	
Yes	−2.902 (−10.784 to 4.980)		−5.256 (−13.197 to 2.685)	
Previous MI		0.138		0.076
No	Control		Control	
Yes	−8.397 (−19.489 to 2.694)		−10.172 (−21.429 to 1.085)	
Chronic kidney disease		0.907		0.257
No	Control		Control	
Yes	−0.877 (−15.639 to 13.885)		−8.346 (−22.803 to 5.111)	
Killip class		0.721		0.767
I	Control		Control	
II–IV	0.662 (−2.980 to 4.305)		0.561 (−3.159 to 4.281)	
LDL-C	−0.733 (−3.887 to 2.422)	0.315	−1.537 (−4.540 to 1.467)	0.291

PPCI, primary percutaneous coronary intervention; FPCI, fibrinolysis followed by elective percutaneous coronary intervention; CK-MB, creatine kinase-MB; TIA, transient ischemic attacks; MI, myocardial infarction; LDL-C, low-density lipoprotein cholesterol.

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Table S3 Major adverse cardiovascular events during the follow-up period

Major adverse cardiovascular events	All Patients				Adjusted model		Propensity score matched patients			
	FPCI (n=69)	PPCI (n=394)	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	FPCI (n=61)	PPCI (n=170)	Adjusted HR (95% CI)	P value
Cardiovascular death	0 (0)	30 (7.6)	1.78e–19	–	4.08e–07	<0.001	0 (0)	10 (5.9)	5.06e–20	<0.001
Non-fatal recurrent MI	2 (2.9)	15 (3.8)	0.71 (0.16–3.16)	0.656	1.30 (0.29–5.81)	0.735	1 (1.6)	4 (2.4)	0.65 (0.07–5.83)	0.697
Target-vessel revascularization	6 (8.7)	25 (6.3)	1.33 (0.56–3.15)	0.512	1.47 (0.59–3.67)	0.404	5 (6.4)	9 (5.3)	0.94 (0.26–3.41)	0.929
Stroke/TIA	3 (4.3)	18 (4.6)	0.90 (0.27–3.02)	0.861	1.51 (0.33–7.00)	0.596	3 (4.9)	8 (4.7)	0.99 (0.26–3.66)	0.982
Total	7 (10.1)	82 (20.8)	0.46 (0.21–0.99)	0.048	0.83 (0.37–1.87)	0.652	5 (8.2)	29 (17.1)	0.49 (0.19–1.28)	0.148

Model was adjusted for age, sex, diabetes, hypertension, dyslipidemia, chronic kidney disease, creatine kinase-MB peak value, symptom onset to reperfusion time, stent numbers. FPCI, fibrinolysis followed by elective percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attacks.

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