A Randomized Controlled Clinical Trial of Prolonged Stent Deployment Strategy in Primary Percutaneous Coronary Intervention for ST-segment Elevation Myocardial Infarction: A Pilot study

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Abstract

Background

Primary percutaneous coronary intervention (PPCI) is the most standard reperfusion strategy for ST-segment elevation myocardial infarction (STEMI), but the no-reflow phenomenon is still common and is associated with adverse outcomes. Little is known about the consequences of different strategies of deploying stents on outcomes in STEMI patients. The aim of this study was to evaluate whether prolonged inflation would decrease the no-reflow phenomenon in PPCI compared with the conventional rapid inflation/deflation strategy.

Methods

This was a prospective, single-center, blinded, randomized controlled trial. Patients were randomized 1:1 to a prolonged deployment strategy group or a conventional deployment strategy group. A subset of patients was included in a cardiac magnetic resonance (CMR) examination assessment. The primary outcomes were the number of patients with Thrombolysis in Myocardial Infarction (TIMI) flow grade 3, the incidence of intraoperative no-reflow/slow flow, the corrected TIMI frame count, the myocardial blush grade, and the number of patients with ST-segment resolution>50%. The secondary outcome was major cardiovascular adverse events at one month and one year following the index PPCI.

Results

TIMI flow grade 3 was found in 96.7% of the prolonged deployment strategy group and 63.3% of the conventional deployment group (P=0.005). The prolonged inflation strategy and inflation/deflation strategy group respectively showed the following rates: 0% vs 30% no-reflow or slow flow (P=0.002); 90% vs 66.7% ST-segment resolution ≥50% (P=0.028); 35.6±14.5 frames vs 49.18±25.2 frames on corrected TIMI frame count (P=0.014); and 60% vs 20% myocardial blush grade 3 (P=0.001). The major cardiovascular adverse event rate was 3.3% in both groups at one month and 3.3% for the prolonged inflation strategy group vs 6.7% for the rapid inflation/deflation strategy group at one year (P=1.0). In the CMR subset of cases, the presence of microvascular obstruction (MVO) was detected in 6.7% of patients in the prolonged inflation strategy group and in 50% of patients in the rapid inflation/deflation strategy group (P=0.023).

Conclusions

In the patients with STEMI who underwent PPCI, the effect of the prolonged inflation strategy could decease the no-reflow phenomenon and improve myocardial microcirculation perfusion, but there were no benefits for the 30-day or one-year clinical outcomes. (ClinicalTrials.gov number: NCT03199014.Registered June 23, 2017,http://https://clinicaltrials.gov/ct2/show/NCT03199014?term=NCT03199014&cntry=CN&draw=2&rank=1)

Background

Although there has been an increase in the use of primary percutaneous coronary intervention (PPCI) for ST-segment elevation myocardial infarction (STEMI) in recent decades in China, the in-hospital mortality and long-term prognosis has not significantly changed[1]. Coronary no-reflow is defined as a phenomenon in which, despite revascularization therapy with PPCI, the cardiac tissue fails to perfuse normally and has a negative effect on outcomes, negating the potential benefits of PPCI[2–5].

The pathophysiology of the no-reflow phenomenon is multifactorial, and it is now referred to as microvascular obstruction (MVO), which includes injury related to ischemia, reperfusion, endothelial cell edema, thrombus embolization, and embolization of atherosclerotic plaque fragments[6].Therefore, these injuries are of concern during PPCI[7].In theory, the manipulation of factors during PPCI may contribute to no-reflow; however, the balloon pressure, inflation time, repeated balloon dilations, and number of stents did not affect the incidence of no-reflow in a retrospective analysis[8]. In small vessels, it is possible that the stent itself affixes the thrombus to the vessel wall, especially if the thrombus is more fibrous [9].

The duration of stent inflation has a significant impact on stent expansion, and rapid inflation/deflation may not be enough to fully expand the stent [10, 11]. Therefore, a fully expanded stent may entrap the atherothrombus under the struts that are more fixed and reduce distal embolization in PPCI. However, this hypothesis has not been well investigated in randomized controlled studies. The present study was undertaken to evaluate whether prolonged inflation would decrease the no-reflow phenomenon in PPCI compared with the conventional rapid inflation/deflation strategy. (ClinicalTrials.gov number: NCT03199014)

Materials And Methods

Trial Design And Study Participants

We conduct this single-center randomized, single-blinded parallel pilot trial to compare a prolonged stent deployment strategy with a rapid inflation/deflation deployment strategy. The randomization was performed using a simple random sampling method that was generated by a computer program. The random allocation list was enclosed in sequentially numbered, opaque, sealed envelopes. The eligible patients were assigned in a 1:1 ratio to the prolonged inflation group or the rapid inflation/deflation group. The trial design was approved by the Regional Ethics Review Board of West China Hospital. The research paper is written in accordance with the international CONSORT 2010 statement[12].

Patients were eligible for enrollment if they met the following criteria: 1) age ≥ 18 years; 2) patients with STEMI who were referred to PPCI within 12 hours after the onset of symptoms and with ST-segment elevation ≥ 1 mm in ≥ 2 contiguous leads or a presumed new left bundle branch block or a true posterior myocardial infarction; 3) admission within 12 hours of symptom onset or admission between 12 and 24 hours if there was evidence of continuing ischemia. The exclusion criteria were: the left main coronary artery was a target vessel; an artery reference diameter 2 mm; vessel calcification or tortuosity, a true

bifurcation lesion; cardiogenic shock; prior coronary artery surgery; previous percutaneous coronary intervention(PCI) of the target segment; a contraindication to CMR imaging (e.g., pacemaker, claustrophobia),and inability to give informed consent.

Procedures

Patients who fulfilled the inclusion criteria were randomly assigned after coronary angiography to the prolonged stent deployment group or to the conventional rapid inflation/deflation deployment group during PCI. An experienced cardiologists preformed the procedures. All patients received 300 mg of oral aspirin and 600 mg clopidogrel (or 180 mg ticagrelor) as soon as the diagnosis was confirmed. Heparin (60U/kg) was given to all patients in the emergency department and was administered throughout the procedure to maintain an ACT≥300 seconds. Patients were immediately taken to the cardiac catheterization lab, and coronary angiography was performed by using the standard Judkins technique with a transradial approach. If the patient had a high thrombus burden, thrombus aspiration was performed when the floppy, steerable guidewire passed through the target lesion, according to the operator's judgment. If the operator predicted that direct stenting was possible, predilation was not performed. if direct stenting was impossible, predilation with a single low-pressure inflation was performed. In all patients, only the infarct-related artery was treated.

All placed stents were drug-eluting stents, and patients were given the option between two commercially available drug-eluting stents: the PROMUS Element stent (Boston Scientific, Boston, Massachusetts) or a GuReater stent (Lepu, China). The diameters of the stent and balloon were selected by visual estimation to achieve a balloon-to-vessel ratio of 1:1. In the experimental group, the stent was deployed with a single balloon inflation, and low-pressure inflation was sustained for > 30 seconds after the target balloon inflation pressure had been achieved. If the patient could not tolerate the procedure, showed signs of ischemia, or had chest pain, arrhythmia, or a decrease in blood pressure, the stent balloon was immediately deflated. A rapid inflation/deflation strategy was adopted in the control group, in which the stent balloon inflation time was less than 10 seconds. Additional dilation, expansion pressure, and postdilation were left to the discretion of operators. For both study groups, a GP Ⅱb/Ⅲa inhibitor (tirofiban) was used as a preventive or bailout therapy at the operator's discretion. After stent implantation, if the no-reflow phenomenon was present, pharmacological intervention including common vasodilators (nitroprusside, diltiazem) was used.

Endpoints, Assessment Of Outcomes And Definitions

The primary outcome of this study was the incidence of the no-reflow phenomenon according to TIMI flow. The no-reflow phenomenon was defined as a TIMI flow grade ≤ 2 that was transient or sustained after the occluded epicardial artery was opened; incomplete lesion dilation, epicardial vascular spasm, dissection or in situ thrombosis were carefully excluded[13]. Two experienced cardiologists independently assessed the occurrence of no-reflow after stent implantation, the TIMI flow grade, the TIMI frame count,

and the myocardial blush grade on the most recent angiogram. Thrombolysis in the myocardial infarction (TIMI) risk score flow grading system was used to evaluate blood flow. TIMI 0 flow is defined as no antegrade flow beyond the point of occlusion. TIMI 1 flow is defined as faint antegrade flow beyond the occlusion with incomplete filling of the distal vascular bed. TIMI 2 flow is defined as delayed antegrade flow with complete filling of the distal vascular bed. TIMI 3 flow is defined as normal flow with complete filling of the distal vascular bed. The number of angiogram frames required for the dye to reach a specified distal segment in the coronary artery was referred to as the corrected TIMI frame count[14]. All angiograms were recorded on 21 mm cine film at 15 frames/second (UNIQ FD 10, Philips, USA). The myocardial blush grade (MBG) was used to assess the filling and clearance of contracts in the myocardium. MBG 0 was defined as no apparent tissue-level perfusion in the distribution of the culprit artery. MBG 1 was defined as no clearance from the microvasculature. MBG 2 was defined as the blush clearing slowly. MBG 2 was defined as blush beginning to clear during washout[15]. The thrombus burden was evaluated by the TIMI thrombus scale, which was classified as a grade between 0 and 5[16]. A heavy thrombus burden was considered to be present with a TIMI grade ≥ 4. Electrocardiographic resolution of ST-segment elevation was defined as an ST-segment reduction of > 50% in the same lead within 60 min after the index procedure[17].

The secondary outcomes were major adverse cardiovascular events (MACEs), which were defined as any events of target vessel revascularization, recurrent MI or cardiovascular mortality. These outcomes were examined 30 days and one year after the primary PCI. The procedure time, total fluoroscopy time, and radiation dose were also assessed. The safety outcome of major bleeding is defined using a definition of major bleeding from the International Society on Thrombosis & Hemostasis (ISTH)[18]; the bleeding events that are not defined as major will be counted as minor bleeding.

A subset of patients was included in the cardiac magnetic resonance (CMR) examination approximately 3 to 5 days after the index procedure. To assess infarct size, myocardial salvage index, presence and extent of MVO, myocardium hemorrhage, myocardial edema, and left ventricular ejection fraction(LVEF) and left ventricular(LV) volume. Examinations were performed on a 3.0-T whole-body scanner with an18-element body phased arraycoil (Skyra; Siemens Medical Solutions, Erlangen, Germany). Standard two-, three, and four-chamber cine images were acquired using a TrueFISP sequence. The area at risk was assessed on the initial examination using a T2-weighted short-tau inversion-recovery sequence. Infarct size, LVEF, and LV volume were assessed on both examinations using delayed, contrast-enhanced, electrocardiogram-triggered inversion-recovery images and steady-state free precession(SSFP) cine images. The myocardial salvage index was calculated as [area at risk (mass) – infarct size (mass)]/area at risk (mass). Delayed contrast-enhanced images were obtained 10 min after an intravenous injection of 0.1 mmol/kg body weight gadolinium-based contrast (Gadovist, Bayer Schering, Berlin, Germany). All images were obtained in the short-axis plane, with 8-mm slices without gaps covering the entire LV[19–21].

A subgroup analysis was prespecified to examine factors associated with an increased risk of the no-reflow phenomenon: age (≥ 65 and < 65 years), thrombus burden, thrombosis aspiration, direct stenting,

infarct location (anterior and nonanterior), multiple complex lesions, and door-to-balloon time.

Statistical analysis

The trial was powered for the outcome of ST-segment reduction of > 50% in the same lead within 60 min after the index procedure. The results of previous studies showed that the incidence of electrocardiographic resolution was 60–70% under conventional rapid inflation/deflation strategy in PPCI. We therefore hypothesized that in our trial more patients in the prolonged inflation group achieved ST-segment reduction of > 50%, and the anticipated relative risk reduction (RRR) was 30%. We calculated that 53 patients would need to be enrolled in this study. The sample size was increased by about 10% to total 60 patients to account for loss to follow up. The data are expressed as percentages and means (standard deviations). Categorical variables were compared using the chi-square test at a two-sided significance level of 5%. Continuous variables were compared using t test or analysis of variance (ANOVA). A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 17.0 software (SPSS, Inc., Chicago, Illinois).

Result

Patients characteristics

Between November 2016 and May 2017, 97 patients with STEMI were considered for inclusion, of whom 60 patients were enrolled according to the eligibility criteria (Fig. 1). After angiography, patients were randomly assigned to undergo either a prolonged inflation group during PCI (30 patients) or a rapid inflation/deflation group during PCI (30 patients). The baseline clinical characteristics were similar in the two groups (Table 1). The procedural and angiographic characteristics of the study patients are shown (Table 2). After undergoing randomization, 10% of the patients in the prolonged inflation group could not tolerate the ischemic deflation of the stenting balloon in advance. The mean time of inflation was 35.87 seconds in the prolonged inflation group and 10.07 seconds in the rapid inflation/deflation group. None of the patients who underwent randomization were lost to follow-up.

Table 1

Baseline characteristics of the patients according to the randomization allocation

Characteristic	Prolonged inflation group (n = 30)	Rapid inflation/deflation group (n = 30)	P value
Age-years	64.2 ± 10.9	61.9 ± 12.5	0.445
Male sex-no. (%)	25	22	0.347
Body mass index	25.0 ± 2.8	24.5 ± 3.7	0.602
History			
Hypertension-no. (%)	14 (46.7)	17 (56.7)	0.438
Current smoking-no. (%)	22 (73.3)	17 (56.7)	0.176
Previous myocardial infarction	0 (0)	0 (0)	NA
Diabetes mellitus-no. (%)	6 (20)	4 (13.3)	0.488
Previous stroke-no. (%)	4 (13.3)	2 (6.7)	0.389
Previous atrial fibrillation-no. (%)	1 (3.3)	1 (3.3)	1.0
Medication used			
ACEI-no. (%)	0 (0)	1 (3.3)	0.313
ARB-no. (%)	2 (6.7)	1 (3.3)	0.554
CCB-no. (%)	4 (13.3)	5 (16.7)	0.718
Metformin-no. (%)	1(3.3)	2 (6.7)	0.554
β-blocker-no. (%)	0	2 (6.7)	0.492
Clopidogrel-no. (%)	22 (73.3)	20 (66.7)	0.779
Ticagrelor-no. (%)	8 (26.7)	10 (33.3)	0.779
Fibrinolysis before randomization -no. (%)	0 (0)	2 (6.7)	0.492
Door-to-balloon time-min	67 ± 17	67 ± 25	0.972
Target coronary artery			0.663
Left coronary artery-no. (%)	14 (46.7)	12 (40)	
Left circumflex-no. (%)	2 (6.7)	4 (13.3)	

ACEI:angiotensin-converting enzyme inhibitor;ARB:angiotensin receptor blocker;CCB: calcium channel block ;TIMI:thrombolysis in myocardial infarction;LDL:low density lipoprotein .

Characteristic	Prolonged inflation group (n = 30)	Rapid inflation/deflation group (n = 30)	P value
Right coronary artery-no. (%)	14 (46.7)	14 (46.7)	
Multivessel coronary disease-no. (%)	15 (50)	15 (50)	1.00
Killip class-no. (%)			0.431
1	27	26	
2	2	4	
3	1	0	
4	0	0	
Systolic blood pressure in lab-mmHg	125.4 ± 21.0	120.2 ± 21.2	0.359
Diastolic blood pressure in lab-mmHg	79.8 ± 16.6	75.7 ± 13.7	0.301
Heart rate in lab-bpm	76.9 ± 11.6	84.1 ± 20.9	0.095
TIMI flow-no. (%)			0.193
0 or 1	25 (83.3)	19 (63.3)	
2	2 (6.7)	3 (10)	
3	3 (10)	8 (26.7)	
Thrombus burden-no. (%)			0.643
0	1 (3.3)	3 (10)	
1	3 (10)	5 (16.7)	
2	2 (6.7)	3 (10)	
3	2 (6.7)	3 (10)	
4	3 (10)	1 (3.3)	
5	19 (63.3)	15 (50)	
Laboratory tests			
Total cholesterol-mmol/L	3.8 ± 2	3.9 ± 1.8	0.893
LDL-mmol/L	3.2 ± 0.94	2.9 ± 0.98	0.335

ACEI:angiotensin-converting enzyme inhibitor;ARB:angiotensin receptor blocker;CCB: calcium channel block ;TIMI:thrombolysis in myocardial infarction;LDL:low density lipoprotein .

Characteristic	Prolonged inflation group (n = 30)	Rapid inflation/deflation group (n = 30)	P value
C-reactive protein-mg/L	6.8 ± 19	4.5 ± 6.5	0.56
Creatinine-mmol/L	80.2 ± 20.1	77.6 ± 20.2	0.627
Troponin (CTn)-ng/L	6319.7 ± 3559	6275.4 ± 3451.8	0.961
Ejection fraction (EF)-%	51.8 ± 8.6	53.7 ± 10.1	0.427
ACEI:angiotensin-converting enzyme inhibitor;ARB:angiotensin receptor blocker;CCB: calcium channel block ;TIMI:thrombolysis in myocardial infarction;LDL:low density lipoprotein .			

Table 2

Characteristics of the procedural data

Characteristic	Prolonged inflation group (n = 30)	Rapid inflation/deflation group (n = 30)	P value
Direct stenting-no. (%)	15 (50)	9 (37.5)	0.114
Thrombectomy-no. (%)	10 (33.3)	5 (16.7)	0.136
Predilation balloon diameter-mm	2.4 ± 0.21	2.4 ± 0.21	0.945
No. of stents-no. (%)	1.13 ± 0.35	1.17 ± 0.38	0.723
Type of drug-eluting stent-no. (%)			0.554
PROMUS Element	28 (93.3)	29 (96.7)	
GuReater	2 (6.7)	1 (3.3)	
Total stent length-mm	33.1 ± 14.5	31.3 ± 14.6	0.640
Stent diameter-mm	3.17 ± 0.29	3.09 ± 0.41	0.418
Inflation time-seconds	35.87 ± 10.38	10.07 ± 7.19	0.0001
Inflation pressure-atm	13.47 ± 1.28	13.40 ± 2.23	0.89
Postdilation-no. (%)	5 (16.7)	9 (30)	0.222
Medication use-no. (%)			
Glycoprotein IIb/IIIa inhibitor	16 (53.3)	15 (50)	0.796
Nitroprusside	0	2 (6.7)	0.492
Diltiazem	1 (3.3)	2 (6.7)	0.554

Procedural Outcomes

Primary outcome

The proportion of patients with an immediate TIMI grade 3 flow was higher in the prolonged inflation group than in the rapid inflation/deflation group after the stent was deployed (90% vs 63.3%, respectively, P = 0.005) (Table 3). The final no-reflow proportion was lower in the prolonged inflation group than in the rapid inflation/deflation group (0% vs 30%, respectively, P = 0.002). In addition, 78% (7/9) of patients exhibiting the no-reflow phenomenon in the rapid inflation/deflation group recovered after pharmacological intervention. The corrected TIMI frame count (cTFC) was lower in the prolonged inflation group than in the rapid inflation/deflation group (35.6 ± 14.5 vs 49.18 ± 25.2, respectively, P = 0.014), and more patients in the prolonged inflation group had a ST-segment resolution ≥ 50% than in the rapid inflation/deflation group (90% vs 66.7%, respectively, P = 0.028). The percentage of patients achieve a myocardial blush grade (MBG) of 3 was higher in the prolonged group than in the rapid inflation/deflation group (60% vs 20%, P = 0.01).

Table 3
Primary and secondary outcomes

outcome	Prolonged inflation group (n = 30)	Rapid inflation/deflation group (n = 30)	P value
Immediate TIMI flow-no. (%)			0.005
TIMI 0–1	0 (0)	1 (3.3)	
TIMI 2	1 (3.3)	10 (33.3)	
TIMI 3	29 (96.7)	19 (63.3)	
The incidence of no-reflow-no. (%)	0 (0)	9 (30)	0.002
ST-segment resolution ≥ 50%-no. (%)	27 (90)	20 (66.7)	0.028
Corrected TIMI frame count-no. (%)	35.6 ± 14.5	49.18 ± 25.2	0.014
Distal embolization of culprit vessels-no. (%)	0	1 (3.3)	0.313
Myocardial blush grade-no. (%)			0.001
1	0 (0)	6 (20)	
2	12 (40)	18 (60)	
3	18 (60)	6 (20)	
Procedure time-min	37 ± 11.8	39 ± 18	0.572
Radiation exposure time-min	1208.6 ± 757.7	932.69 ± 452.9	0.130
Bleeding events-no. (%)	0	1 (3.3)	0.313
30-day clinical outcomes-no. (%)	4 (13.3)	7 (23.3)	0.506
Target vessel revascularization	2 (6.7)	3 (10)	1.000
Recurrent myocardial infarction	1 (3.3)	3 (10)	0.612
Cardiovascular mortality	1 (3.3)	1 (3.3)	1.00
One-year clinical outcomes-no. (%)	7 (23.3)	11 (36.7)	0.399
Target vessel revascularization	3 (10)	5 (16.7)	0.706
Recurrent myocardial infarction	3 (10)	4 (13.3)	1.00
Cardiovascular mortality	1 (3.3)	2 (6.7)	1.00

Secondary outcome

There was no significant difference in the procedure time, radiation exposure time, or contrast volume. The number of bleeding events and clinical end point were also not significantly different between the two groups (Table 3). The subset analysis was show in Fig. 2. According to the CMR subset, the prolonged inflation strategy can reduce the incidence of MVO and improve cardiac function (Table 4, Fig. 3).

Table 4

Cardiac magnetic resonance data

Endpoint	Prolonged inflation group (n = 15)	Rapid inflation/deflation group (n = 10)	P value
Infarct size (%LVM)	12.1 (4.5)	13.4 (3.9)	0.512
Presence of MVO-no. (%)	1/15 (6.7)	5/10 (50)	0.023
Presence of IMH-no. (%)	3/15 (20)	4/10 (25)	0.378
Myocardial salvage index	60.5 (22.1)	56.4 (20.1)	0.081
LVEF (%)	50.2 (7.5)	42.1 (6.3)	0.026

%LVM = percentage of LV mass, MVO = microvascular vessel obstruction, IMH = intramyocardial hemorrhage, LVEF = left ventricular ejection fraction

Discussion

To the best of our knowledge, this study is the first to investigate the effect of prolonged inflation time in PPCI. We designed this small proof-of concept pilot study to determine whether prolonged or rapid strategies could provide more short- and long-term benefits for STEMI patients. The major findings of the present study were as follows: 1) the prolonged inflation strategy reduced the no-reflow phenomenon and improved myocardial microcirculation perfusion, but there were no benefits in the 30-day and one-year clinical outcomes; 2) there were no significant differences between the study groups in terms of the procedure time, radiation exposure time and the number of bleeding events (for safety surveillance); 3) according to the subset analysis, it seems that the prolonged inflation strategy was more effective in patients who were male, had a thrombectomy, had a heavy thrombosis burden, and nonanterior wall infraction; and 4) as evaluated by theCMR subset, the prolonged inflation strategy can reduce the incidence of MVO and improve cardiac function.

In the early days of coronary angioplasty, an autoperfusion balloon angioplasty catheter was used for long balloon inflation, which was based on the hypothesis that the loose flap of dissection may be definitively “tacked back” and might deliver a better result[22–24]. A human study found that in

approximately half of patients whose initial angioplasty was a failure, could be reverted to a success by prolonged dilation[25]. With the wide application of stents, this technique was not used. Subsequently, an in vitro human study investigated the duration of balloon inflation for optimal stent deployment[10, 11]. Prolonged balloon inflation could have a significant impact on stent expansion and strut apposition, as evaluated by intravascular ultrasound (IVUS) or optical coherence tomography (OCT)[26–28]. However, these studies were not limited to patients with STEMI.

Despite the use of PPCI and the development of emergency transports resulting in shorter ischemic times, STEMI-related mortality remains considerable[29]. The no-reflow phenomenon can offset, at least in part, the benefits of PPCI[30]. Coronary microvascular dysfunction plays a key role in the development of no-reflow phenomenon[31]. This phenomenon occurs in approximately 50% of STEMI patients after PPCI[21]. Thrombotic material and thromboembolisms will travel distally either spontaneously or at the time of PPCI when an angioplasty balloon is expanded or a stent is deployed[3]. The debris released from a PPCI can also include soluble substances such as vasoactive agents or inflammatory mediators that may stimulate microvascular arteriolar spasms[32, 33]. Thus, the removal of an intravascular thrombus with an extraction catheter during the procedure for reducing atherothrombotic embolization is an active strategy that has been evaluated in RCT trials and meta-analyses [34]. Although there were negative results from the TASTE and TOTAL trials and recent guidelines no longer recommend routine aspiration for STEMI[35, 36], neither study allows us to rule out the possibility that thrombus aspiration might be beneficial in high-risk patients[37, 38]. Even so, with more than 30% of patients showing minimal particles after thrombectomy and persistent residual thrombus in vitro models, distal embolization may not fully prevent thrombectomy[39, 40]. Direct stenting is another strategy to reduce the risk of distal embolization of thrombus fragments[41, 42]. A meta-analysis found that direct stenting significantly reduced short-term and one-year mortality and the after-procedural no-reflow phenomenon[43]. However, few studies have been limited to STEMI patients. Recently, the Thrombectomy Trialists Collaboration conducted a patient-level meta-analysis that found that direct stenting was not significantly associated with improved clinical outcomes compared with conventional stenting among patients with STEMI undergoing PCI[44]. Approximately 37% of patients in that study underwent direct stenting[45]. In our study, direct stenting and thrombectomy were performed more often in the prolonged inflation group (50% and 33.3%, respectively) than in the rapid inflation/deflation group, but the differences were not significant. Even though the data from the Thrombectomy Trialists Collaboration affirm the facilitation of direct stenting by aspiration thrombectomy, there was no significant interaction between thrombus aspiration and any of the clinical outcome variables investigated[45]. According to our subset analysis, patients with thrombectomy and heavy thrombosis burden may have better angiographic myocardial reperfusion outcomes, but there was not enough statistical power, and the interaction was not excluded. Three randomized studies investigated filter devices for distal protection, but these studies failed to show a benefit in terms of reperfusion measures or clinical outcomes[46–48]. A recent randomized study evaluated the utility of distal protection in patients with acute coronary syndrome with native coronary artery lesions and attenuated plaque ≥ 5 mm in length on pre-PCI intravascular ultrasound. The incidence of the no-reflow phenomenon was decreased in these high-risk distal embolization patients[49]. However,

no study found that distal protection could affect the infarct size[50]. Because of the potential disadvantages of thrombectomy, distal protection devices and direct stenting, and the neutral effect for distal embolization, another novel strategy to prevent the no-reflow phenomenon is a clinical imperative.

In the present study, the prolonged inflation strategy during stent deployment may work through the following mechanisms: First, a long inflation time and a low-pressure inflation could reduce iatrogenic rupture of thin-cap fibroatheroma through stent expansion, which induced distal embolization, particularly in lesions with low-echoic structures and large amounts of atherosclerotic plaque with vulnerable components[51]. Second, although thrombectomy may reduce thrombus burden, persistent residual thrombus may also cause distal embolization[39]. When added to direct stenting, the loosened atherothrombus material was affixed to the vessel wall under the stent struts[52]. However, incomplete stent deployment and inadequate apposition may weaken the “confinement effect” for atherothrombus material. Therefore, the conventional rapid inflation/deflation strategy was not enough[10], especially in the PPCI setting in which postdilation should be avoided. Third, prolonged inflation may be analogous to the postcondition that was performed within 1 minute of reflow by brief episodes of reversible ischemia-reperfusion during angioplasty. A meta-analysis found that postconditioning following PCI induced by transient coronary ischemia in STEMI patients may reduce myocardial injury biomarkers and improve cardiac function[53]. However, the POST and DANAMI-3–iPOST trials found that ischemic postconditioning did not improve myocardial reperfusion and clinical outcomes[54, 55]. The primary endpoint results contribute to the theory that postconditioning algorithm, in which postconditioning is instituted after a very short reperfusion time, might be a more effective method[54]. In the present study, if the occlusion persisted for more than 30 seconds after the stent was deployed, the conditioning therapy was completed before reperfusion injury could occur. Therefore, this postconditioning algorithm may be effective.

The indexes of angiography for evaluating coronary microvascular circulation in the cardiac catheterization laboratory are semiquantitative and can be subjective[56]. CMR is the gold standard method to assess the MVO, MI size, LV volume and LVEF, but it is expensive and not yet widely available[56]. Areas of no-reflow have been associated with MVO as seen on magnetic resonance images and correlate with a higher degree of myocardial damage[57]. Therefore, in the present study, we designed a subset of CMR to assess the no-reflow phenomenon after PPCI. Approximately 50% of the patients included in this study underwent CMR. The incidence of MVO was 50% in the conventional rapid inflation/deflation group and was consistent with previous studies[58]. The prolonged inflation strategy could reduce the incidence of MVO and improve cardiac function, but not infarction size, as evaluated by CMR. Kloner[3] found that no-reflow did not directly contribute to myocyte cell death, and several studies showed that it was independent of the size of the infarction[59, 60]. The no-reflow phenomenon is associated with poor healing of the infarct scar[61], including thinner scars and more infarct expansion; therefore, it appears that some therapies that can reduce no-reflow without reducing infarct size[62].

Limitations

This study included the following limitations of note.Firstly,this was a single-center study with a relatively small sample.Second,the study was underpowered for detecting significant differences in 30-day and one-year clinical outcomes.Because high-risk patients with more complex lesions and unstable hemodynamics were excluded, the results cannot be applied to all STEMI patients. However, this study implemented rigorous inclusion criteria to reduce the risk of confounding bias. Furthermore, few studies have reported data in this area, thus contributing to the value of our study. We aim to fullfillment this study in our future research endeavors.

Conclusions

we evaluated the effect of a prolonged inflation strategy that could reduce the no-reflow phenomenon of MVOs and improve the myocardial microcirculation perfusion, but there were no benefits in the 30-day and one-year clinical outcomes. However, large-sample, randomized controlled clinical trials with a long-term follow-up period are needed to confirm this preliminary result.

Abbreviations

PPCI:Primary percutaneous coronary intervention;STEMI:ST-segment elevation myocardial infarction;CMR:cardiac magnetic resonance; TIMI:Thrombolysis in Myocardial Infarction;MVO: microvascular obstruction;MBG:myocardial blush grade; MACEs: major adverse cardiovascular events; MI:myocardial infarction;LVEF:left ventricular ejection fraction;LV:left ventricular; RRR:relative risk reduction; cTFC: corrected TIMI frame count;OCT: optical coherence tomography;IVUS: intravascular ultrasound.

Declarations

Author's Contribution:Y.H conceived of the study, and participated in its design. M.M and L.W coordination, drafted the manuscript, collect data and algorithms. KY.D take responsibility of the imaging data analysis. Y.ZG and H.Y are both the study guarantors, had full access to the data in the study and take responsibility of the study design and the accuracy of the data analysis, and had the final responsibility to submit for publication. All authors read and approved the final manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request

Consent for publication
Not applicable

Ethics approval and consent to participate
The study complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of West China Hospital, Sichuan University, Chengdu, Sichuan, China. Written informed consents were obtained from all the study participants.

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Figures

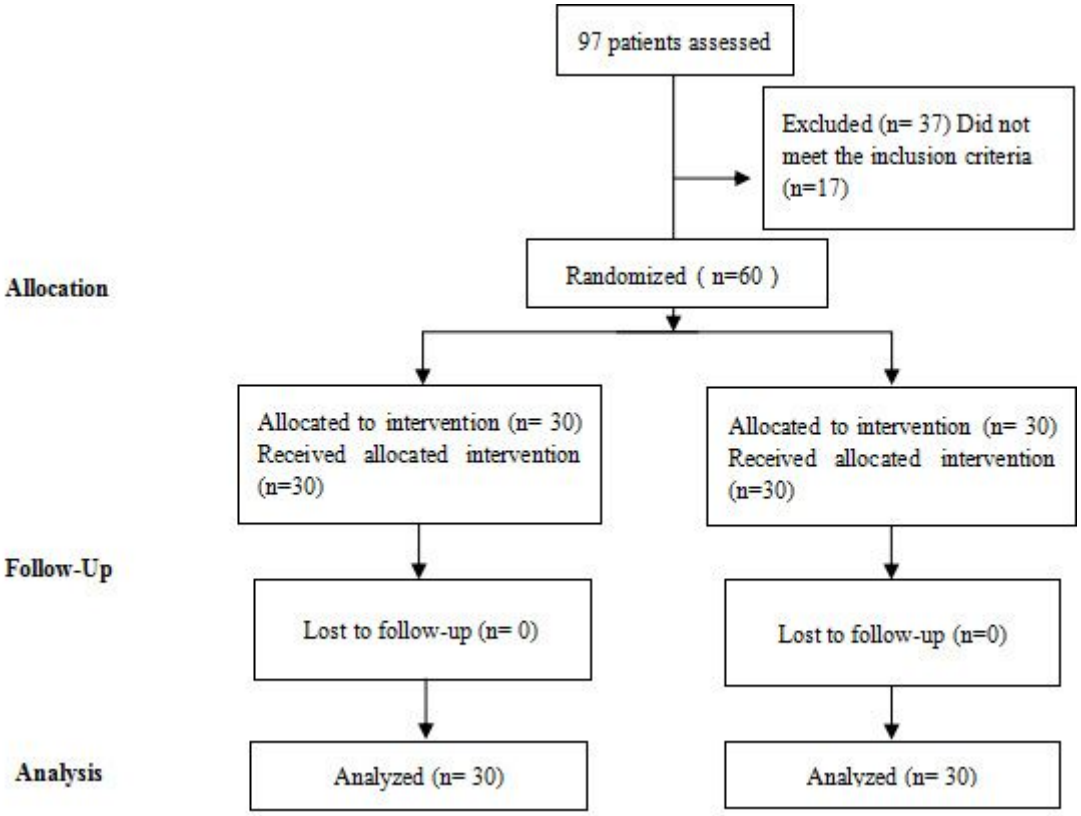

Figure 2

Study flow chart

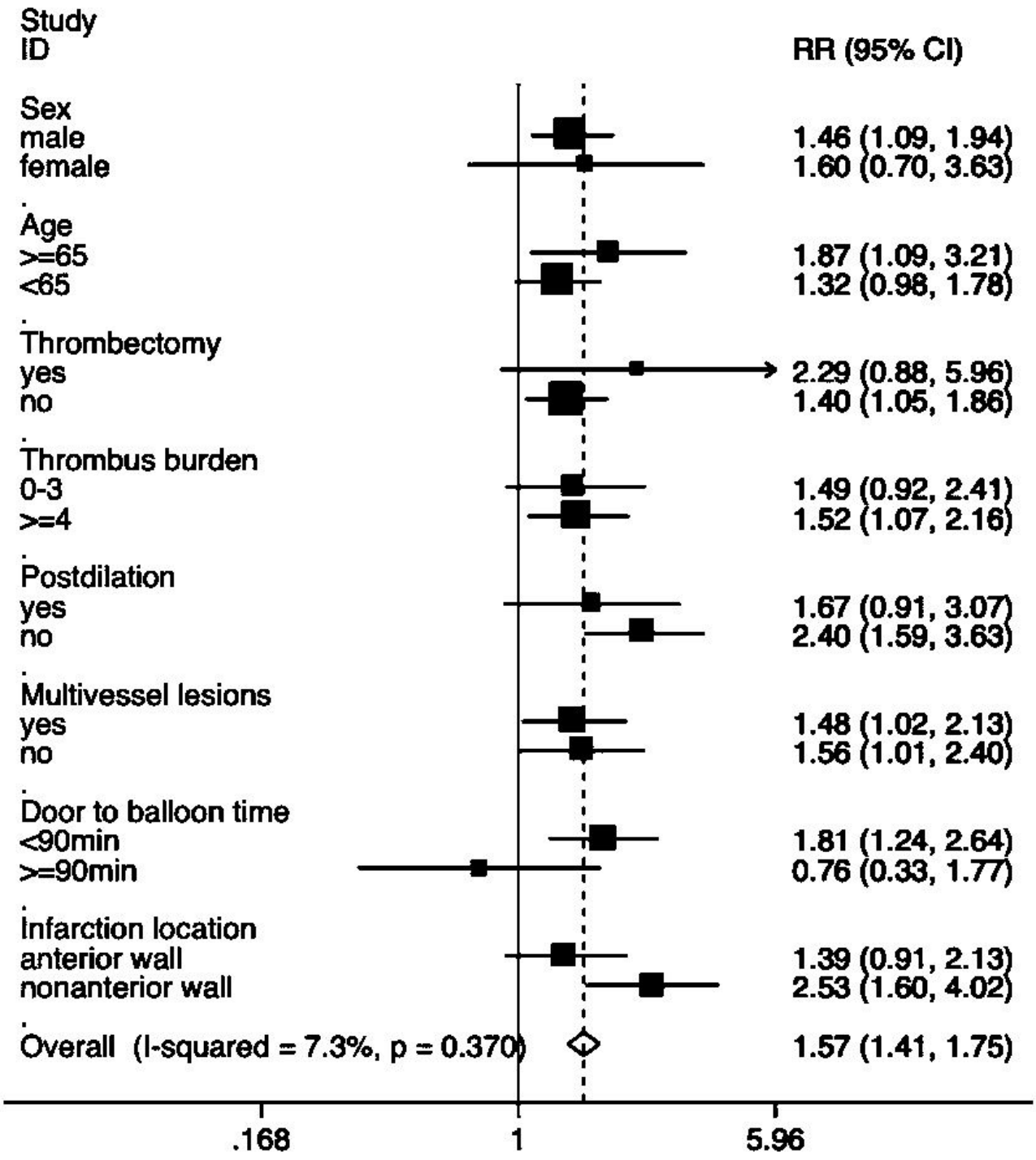

Figure 3

Forest plot of Subset analysis

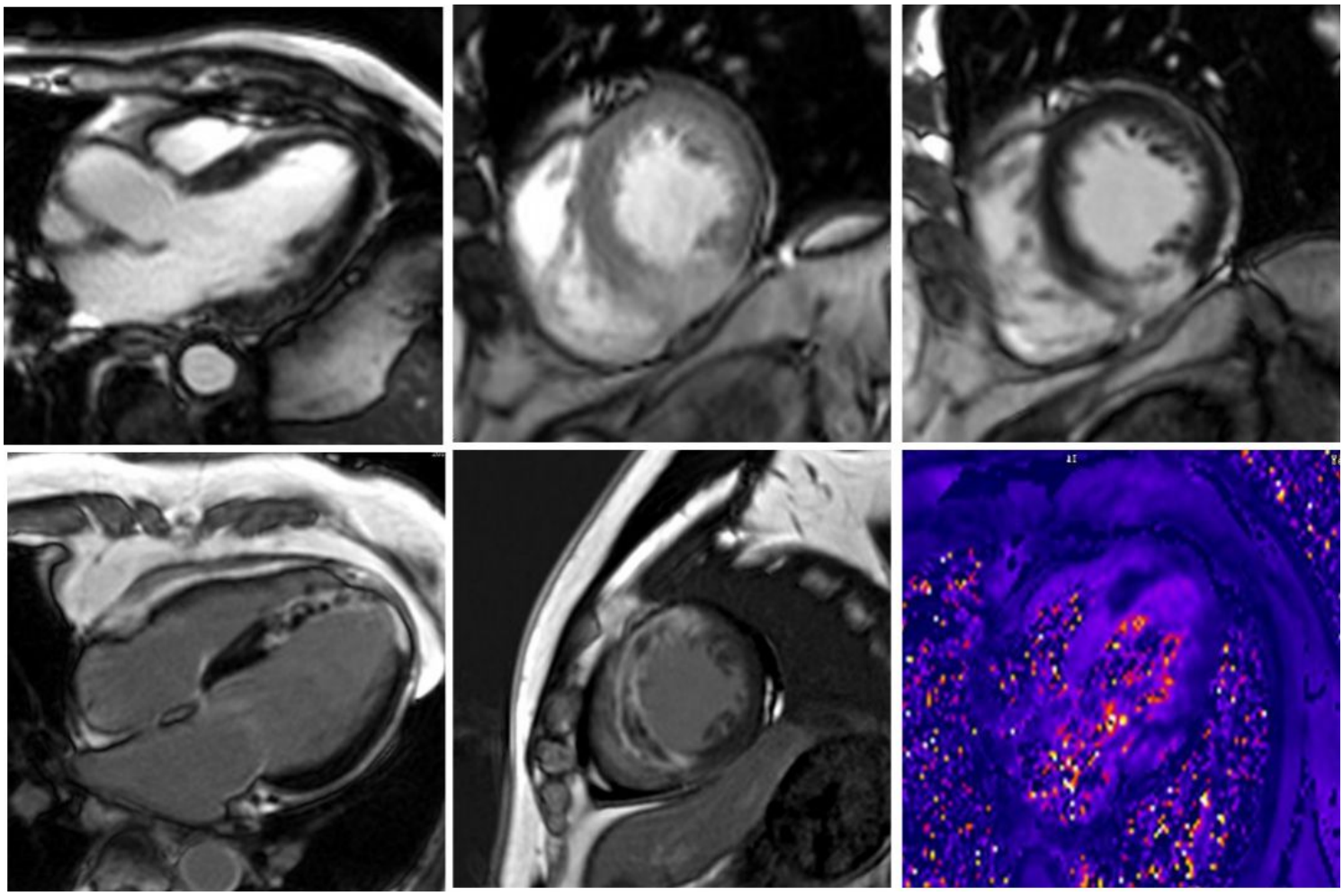

Figure 5

Cardiac magnetic resonance image. The top row was from a patient who under prolonged inflation group, there is no imaging features of microvascular obstruction. Bottom row was from a patient with anteroseptal infarct who under rapid inflation/deflation strategy, there is imaging features of microvascular obstruction.