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ORIGINAL RESEARCH

Treatment of Slow-Flow After Primary Percutaneous Coronary Intervention With Flow-Mediated Hyperemia: The Randomized RAIN-FLOW Study

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BACKGROUND: ST-segment–elevation myocardial infarction complicated with no reflow after primary percutaneous coronary intervention is associated with adverse outcomes. Although several hyperemic drugs have been shown to improve the Thrombolysis in Myocardial Infarction flow, optimal treatment of no reflow remains unsettled. Saline infusion at 20 mL/min via a dedicated microcatheter causes (flow-mediated) hyperemia. The objective is to compare the efficacy of pharmacologic versus flow-mediated hyperemia in patients with ST-segment–elevation myocardial infarction complicated with no reflow.

METHODS AND RESULTS: In the RAIN-FLOW (Treatment of Slow-Flow After Primary Percutaneous Coronary Intervention With Flow-Mediated Hyperemia) study, 67 patients with ST-segment–elevation myocardial infarction and no reflow were randomized to receive either pharmacologic-mediated hyperemia with intracoronary adenosine or nitroprusside (n=30) versus flow-mediated hyperemia (n=37). The angiographic corrected Thrombolysis in Myocardial Infarction frame count and the minimal microcirculatory resistance, as assessed with intracoronary pressure-thermistor wire, dedicated microcatheter, and thermodilution techniques, were compared after study interventions. Both Thrombolysis in Myocardial Infarction frame count(40.2±23.1 versus 39.2±20.7; *P*=0.858) and minimal microcirculatory resistance (753.6±661.5 versus 993.3±740.8 Wood units; *P*=0.174) were similar between groups. Thrombolysis in Myocardial Infarction 3 flow was observed in 26.7% versus 27.0% (*P*=0.899). Flow-mediated hyperemia showed 2 different thermodilution patterns during saline infusion indicative of the severity of the no reflow phenomenon. In-hospital death and nonfatal heart failure were observed in 10.4% and 26.9%, respectively.

CONCLUSIONS: Both treatments showed similar (and limited) efficacy restoring coronary flow. Flow-mediated hyperemia with thermodilution pattern assessment allowed the simultaneous characterization of the no reflow degree and response to hyperemia. No reflow was associated with a high rate of adverse outcomes. Further research is warranted to prevent and to treat no reflow in patients with ST-segment–elevation myocardial infarction.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04685941.

Key Words: absolute coronary blood flow ■ hyperemia ■ no reflow phenomenon ■ primary percutaneous coronary intervention ■ ST-segment-elevation myocardial infarction

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study investigating the efficacy of flow-mediated hyperemia for therapeutic uses in patients with ST-segment–elevation myocardial infarction with no reflow after primary percutaneous coronary intervention.

What Are the Clinical Implications?

- In this study, flow-mediated hyperemia showed similar efficacy as pharmacologic-mediated hyperemia to treat no reflow after primary percutaneous coronary intervention.
- In addition, flow-mediated hyperemia with the combination of a pressure wire allowed a continuous monitoring of the treatment response.
- Flow-mediated hyperemia can be considered in patients with no reflow to improve the final Thrombolysis in Myocardial Infarction flow.

Nonstandard Abbreviations and Acronyms

cTFC	corrected TIMI frame count
MMR	minimal microcirculatory resistance
TIMI	Thrombolysis in Myocardial Infarction

Current treatment of ST-segment–elevation myocardial infarction (STEMI), including emergent primary percutaneous coronary intervention (PPCI), has drastically improved the survival of patients admitted for STEMI.[1,2] However, despite best care interventions, in-hospital mortality remains around 5%.[1,2] Cardiogenic shock is the main cause of death in patients with STEMI (>50%).[3,4] Predictors of cardiogenic shock are patient's age, diabetes, heart failure, culprit lesions located in large vessels, and the presence of no reflow (or slow flow) after stent implantation.[3]

The no reflow phenomenon is defined as the absence of normal flow (compared with the other coronary arteries) after appropriate culprit (epicardial) vessel revascularization.[5] It is indicative of an unsuccessful microcirculatory reperfusion.[5] Usually, no reflow is classified according to the Thrombolysis in Myocardial Infarction (TIMI) flow between 0 and 2 and is observed in around 10% to 30% of patients with STEMI undergoing PPCI.[6] Although multiple pharmacological and mechanical interventions have been investigated to prevent and treat the no reflow phenomenon, none of those interventions have been shown to be effective at reducing the infarcted area.[5,7] Intracoronary infusion of microcirculatory vasodilators (such as nitroprusside and adenosine) is often used to treat no reflow in the clinical practice.[5] However, according to the current practice guidelines, bailout administration of IIb/IIIa glycoprotein inhibitors is the only recommended strategy when no reflow is observed after PPCI.[8,9]

In patients with chronic coronary syndromes, intracoronary infusion of saline at 15 to 30 mL/min via a dedicated microcatheter has been demonstrated to cause (flow-mediated) steady hyperemia in a similar or superior degree than intracoronary or intravenous adenosine.[10] Flow-mediated hyperemia is caused by vasodilation of the microcirculation and is often achieved at 15 seconds of saline infusion.[10] Prolonged, steady, and sustained flow-mediated hyperemia may be more effective to reopen occluded microvessels of the infarcted territory and to restore coronary flow than intracoronary boluses of hyperemic drugs.

The safety and efficacy of flow-mediated hyperemia to treat the no reflow phenomenon in patients with STEMI is unknown. The objective of the present study is to investigate the immediate safety and efficacy of flow-mediated hyperemia, as compared with standard-of-care pharmacologic-mediated hyperemia, in patients with STEMI presenting with slow flow after PPCI.

METHODS

End Points

The present study has 2 co-primary end points: to compare the corrected TIMI frame count (cTFC) and the thermodilution-based minimal microcirculatory resistance (MMR) between the 2 study groups. Both co-primary end points were immediately assessed after no reflow treatment with 1 of the 2 study interventions. Other secondary end points, such as the ST-segment resolution or clinical outcomes, were assessed at the end of the PPCI. A detailed description of the co-primary end points and secondary end points is shown in the Data S1.[11] All study end points have been assessed by a central core-laboratory (Barcelona Cardiac Imaging core-laboratory; BARCICORE-lab, Spain) blinded to the study allocation.

Study Design and Population

The RAIN-FLOW (Treatment of Slow-Flow After Primary Percutaneous Coronary Intervention With Flow-Mediated Hyperemia) study (NCT 04685941) is an investigator-initiated, proof-of-concept, 2-arm, randomized, and multicenter study. The study was performed according to the provisions of the Declaration of Helsinki, and the ethics committee of each participating center approved the study protocol. The ethics committee of the University Hospital of Bellvitge acted as referring ethics committee. Oral consent

was mandated (as per protocol), and all participants signed written informed consent after the procedure. All authors had access to the study data, and the corresponding author takes responsibility for its integrity and the data analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients with STEMI undergoing PPCI within 12 hours of symptom onset and presenting with sustained slow coronary flow after stent implantation (or stent post dilatation) were eligible for the study. Patients with cardiogenic shock, high bleeding risk (including previous stroke, creatinine clearance <30 mL/min, and active bleeding), visualization of distal thrombus embolization with several occluded branches of the study vessel, stent thrombosis, or culprit lesion located in coronary bypass were not eligible. Patients accepting to participate were 1:1 randomized to 1 of the study interventions for slow flow treatment: (1) standard of care pharmacologic-mediated hyperemia with intracoronary adenosine or nitroprusside or (2) treatment with flow-mediated hyperemia with saline infusion via a dedicated microcatheter located in the proximal segment of the culprit vessel. Randomization was performed electronically using computer-generated random algorithms.

The sample size was estimated to demonstrate superiority of the experimental arm for both co-primary end points. According to the sample size calculation, a total of 100 patients were needed (50 per group). The Data S2 reports the assumptions of the sample size calculation.[12,13] However, after nearly 2 years of inclusion, the study showed a slow recruitment rate, and only two-thirds of the prespecified population had been recruited. For this reason, the steering committee decided to perform an unplanned interim analysis of the study results. According to the interim analysis, the study hypotheses of both co-primary end points were unlikely to be achieved with the estimated sample size. Moreover, a recalculation of the sample size using a noninferiority study design (using the data of the present study) showed that >100 patients per group were needed. Considering the slow recruitment rate and the results of the interim analysis, it was decided to terminate the study prematurely.

Study Interventions

Study interventions are detailed in the Data S3 and are summarized in Figure 1. As per protocol, all patients were randomized to 1 of the 2 study interventions: pharmacologic-mediated hyperemia or flow-mediated hyperemia. Flow-mediated hyperemia was performed with intracoronary saline infusion via a dedicated microcatheter (Ray Flow, Hexacath, France) at 20 mL/minute for 135 seconds. Continuous recording of the absolute coronary blood flow and MMR was assessed using dedicated pressure-thermistor coronary wire (Pressurewire X, Abbott) and software (Coroflow, Abbott) as appropriate.[14–16]

Statistical Analysis

Categorical variables were presented as counts and percentages, and quantitative variables as mean±SD. Continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test. Comparisons of categorical variables were estimated with Fisher exact test, and comparisons of quantitative values between groups were estimated with Student *t* test for paired and nonpaired samples as appropriate. A 2-sided *P* value <0.05 was considered statistically significant. Statistical analysis was performed with the SPSS software, version 20.0 (SPSS Inc., IL).

RESULTS

Patients

From January 23, 2021, to November 9, 2022, a total of 1257 patients underwent PPCI in 3 participating institutions. A total of 132 patients with slow flow fulfilled the inclusion criteria, and 67 were included in the study (30 patients were allocated to pharmacologic and 37 to flow-mediated hyperemia treatment). Most of the eligible patients not included in the study were admitted during nonworking hours, especially at nighttime. The flow chart of the study is shown in Figure 2.

Clinical, Angiographic, and Procedural Characteristics

Both groups presented with similar baseline characteristics. Table 1 shows the clinical baseline characteristics of the study groups. The mean age was 67.7±12.3 years, and 76.1% were men. Clinical, angiographic, and procedural characteristics of the STEMI treatment are shown in Table 2. Both groups presented with similar reperfusion time (median of 250 minutes from symptom onset to PCI; interquartile range, 150–525 minutes), and STEMI location (53.7% of patients had anterior ST-segment elevation). At hospital admission, heart failure was present in 28.4% of patients, with a trend toward a lower percentage of patients with Killip class >1 in the pharmacologic than in the flow-mediated hyperemia group (16.6% versus 37.8%; *P*=0.155).

TIMI flow at randomization (observed after stent implantation or post dilatation and before no reflow treatment) was similarly observed in both groups (Table 3). TIMI flow 0 was observed in 4.5% of patients (3.3% pharmacologic versus 5.4% flow-mediated group), TIMI flow 1 in 40.3% (43.3% versus 37.8%), and TIMI

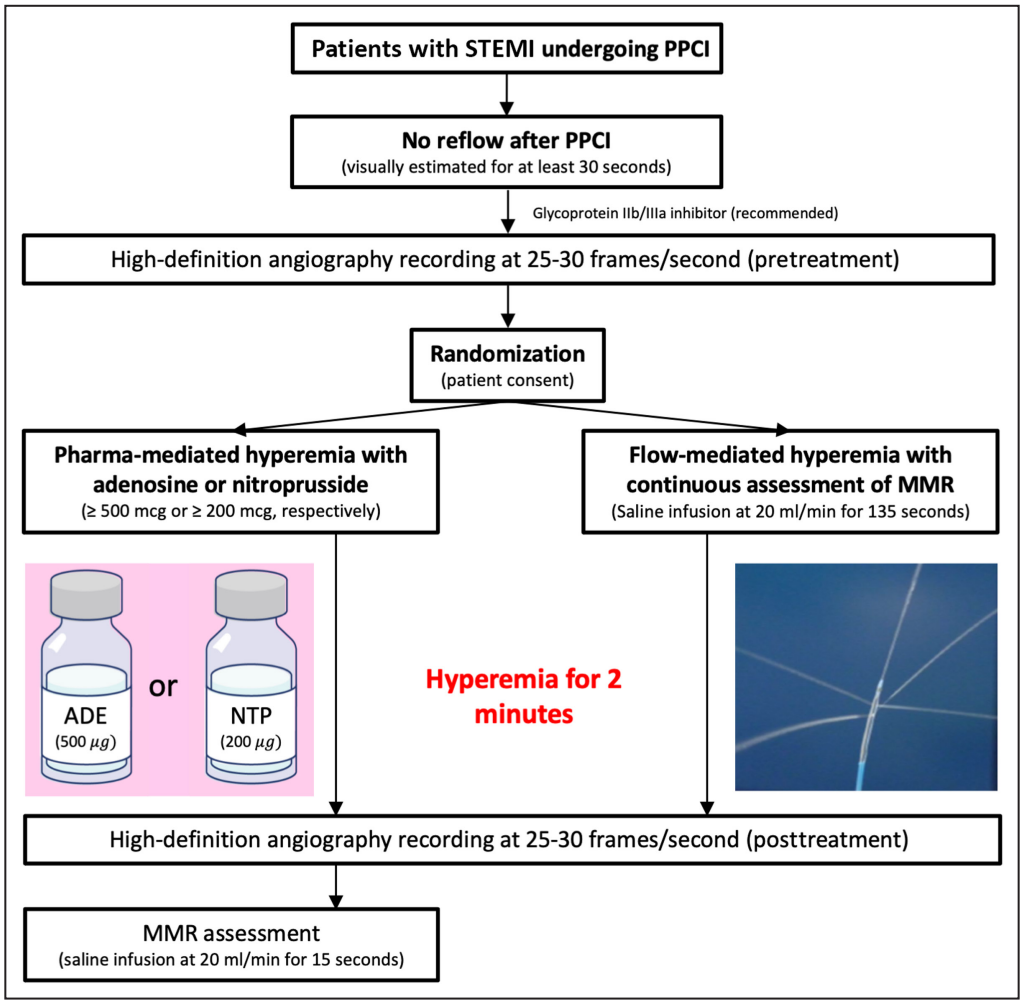

Figure 1. Study interventions (as per protocol).
ADE indicates adenosine; MMR, minimal microcirculatory resistance; NTP, nitroprusside; PPCI, primary percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

flow 2 in 55.2% (53.3% versus 56.8%, respectively); *P*=0.853. The preintervention angiographic cTFC was also similar between groups (59.3±26.7 versus 55.1±28.3; *P*=0.552).

Slow-Flow Treatment

All patients included in the study successfully underwent to the allocated intervention. A total of 30 patients underwent pharmacologic-mediated hyperemia with intracoronary adenosine (n=11; mean dose of 591±170 μg), nitroprusside (n=11; mean dose of 464±103 μg), or a combination of both agents (n=8, doses of 405±238 and 356±140 μg, respectively); and 37 patients underwent flow-mediated hyperemia with saline infusion. One patient in this group presented with proximal dissection of the left circumflex artery caused by the pressure wire. This patient was treated according to the study protocol (with flow-mediated hyperemia) after treatment of the coronary dissection with stent implantation without further complications. No other complications (such as clinically relevant bradycardia or hypotension, arrythmia or heart failure) were observed during study interventions.

The mean time required to start the study interventions was statistically significantly shorter in the pharmacologic than in the flow-mediated hyperemia group (3.7±3.3 versus 5.9±4.3 minutes; *P*=0.025). A total of 40% of patients undergoing flow-mediated hyperemia were also treated with hyperemic drugs but only after all study interventions were finalized, as bailout, due to persistent slow flow.

End Points

The study end points observed after slow flow treatment are shown in Tables 3 and 4 and are summarized in Figure 3. Both co-primary end points were successfully assessed in all patients without treatment cross-over.

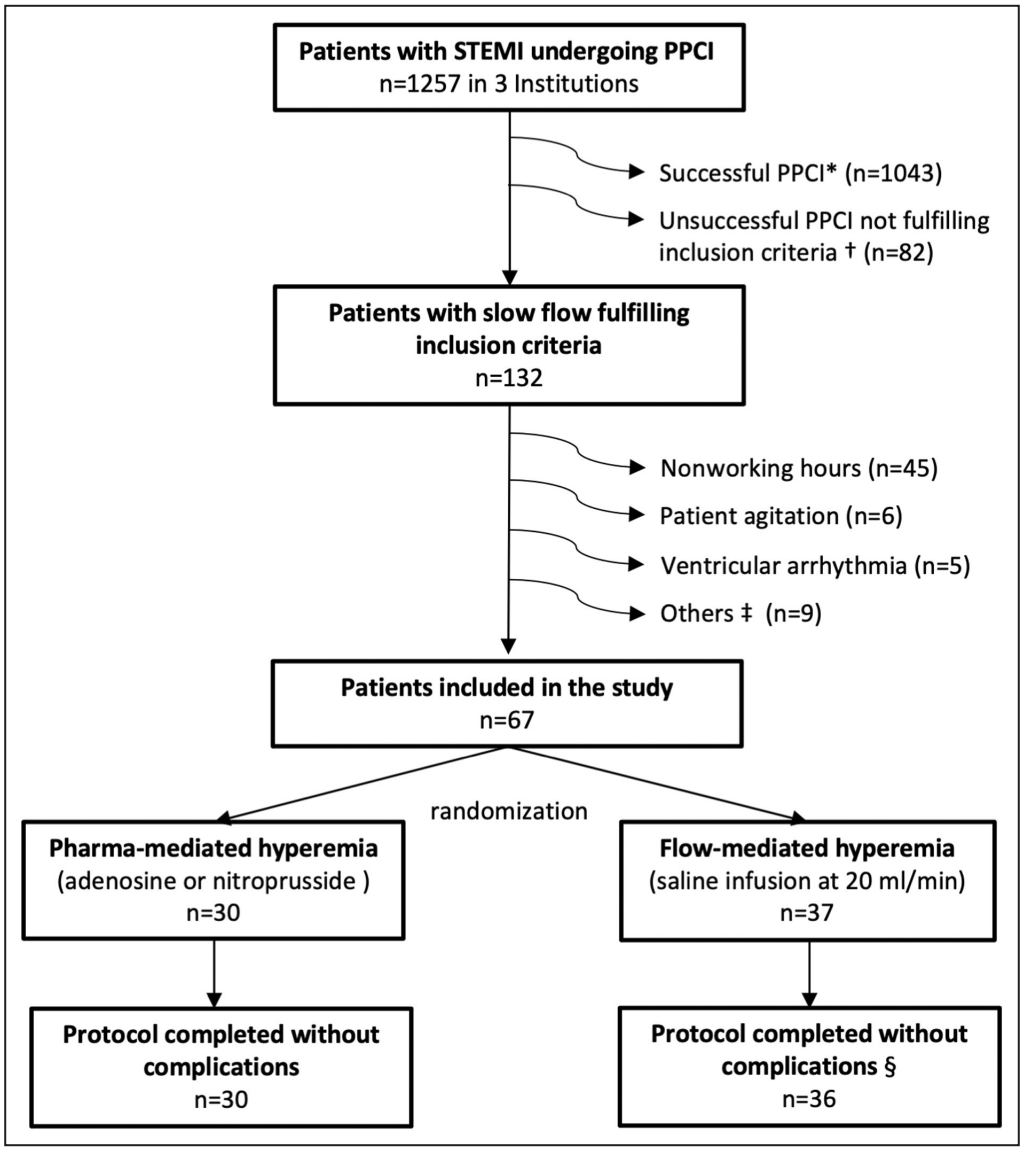

Figure 2. Study flow chart.

*Successful PPCI was defined as final TIMI 3 flow. †Patients with unsuccessful PPCI not suitable for the study were mostly subacute myocardial infarction, end-stage renal dysfunction, distal thrombus embolization during PPCI, patients resuscitated from out-of-hospital cardiac arrest, and cardiogenic shock. Those patients were not registered in the screening failure list. ‡Other causes of screening failure included urgency to end the procedure for laboratory demand (n=4), technical issues with the infusion pump (n=2), patient refused to participate (n=2), and included in other clinical trial (n=1). §One patient of the flow-mediated hyperemia group presented with coronary dissection during the advance of pressure wire and required a stent implantation. This patient completed the study protocol after treatment of the coronary dissection. PPCI indicates primary percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

The cTFC was improved in both arms between pre- and poststudy interventions. In the pharmacologic-mediated hyperemia group, cTFC was reduced from 59.3±26.7 to 40.2±23.1 frames (P<0.001); and in the flow-mediated hyperemia group from 55.1±28.3 to 39.2±20.7 frames (P<0.001). There were no statistically significant differences regarding the posttreatment cTFC (P=0.858) and the delta change cTFC (P=0.248) between groups.

MMR after study interventions (obtained at 15 seconds in the pharmacologic and at 135 seconds in the flow-mediated hyperemia group) was numerically lower in the pharmacologic (753.6±661.5 Wood units) than in the flow-mediated hyperemia group (993.3±740.8); P=0.174.

In patients treated with flow-mediated hyperemia, MMR worsened from the beginning (849.9±702.0 Wood units measured at 15 seconds) to the end of

Table 1. Baseline Clinical Characteristics

	Pharma-mediated hyperemia (n=30)	Flow-mediated hyperemia (n=37)	*P* value
Age, y	65.7±10.5	69.4±13.5	0.222
Male sex	25 (83.3%)	26 (70.3%)	0.258
Body mass index	28.0±4.4	27.5±4.0	0.604
Smoking status			0.067
Never	9 (30.0%)	20 (54.1%)	
Former	14 (46.7%)	8 (21.6%)	
Current	7 (23.3%)	9 (24.3%)	
Hypertension	16 (53.3%)	22 (59.5%)	0.630
Hypercholesterolemia	19 (63.3%)	21 (56.8%)	0.625
Diabetes	11 (36.7%)	14 (38.9%)	1.000
Insulin treated	3 (10.0%)	6 (16.2%)	0.721
Comorbidities			
Chronic kidney disease	4 (13.3%)	11 (29.7%)	0.145
Chronic obstructive pulmonary disease	1 (3.3%)	2 (5.4%)	1.000
Peripheral artery disease	0	2 (5.4%)	0.498
Previous percutaneous coronary intervention	4 (13.3%)	1 (2.7%)	0.165
Chronic treatment			
Antiplatelet therapy	2 (6.7%)	5 (13.5%)	0.447
Beta blocker	4 (13.3%)	6 (16.2%)	1.000
Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers	16 (53.3%)	18 (48.6%)	0.807
Statin	11 (36.7%)	9 (24.3%)	0.296
Oral anticoagulation	2 (6.7%)	3 (8.1%)	1.000

saline infusion (993.3±740.8 Wood units measured at 135 seconds); *P*<0.001. MMR changes were explained by different distal temperature values, indicative of the temperature of the mixed blood and the infused saline at room temperature, observed at the beginning (–0.53°) and at the end (–0.65°) of the saline infusion. However, 2 different thermodilution patterns were observed during saline infusion in this group. Figure 4 shows the 2 different thermodilution patterns observed during saline infusion in the flow-mediated hyperemia group (appropriate versus insufficient saline clearance patterns). Appropriate saline clearance pattern was considered when the distal temperature was steadily maintained during the saline infusion. In contrast, insufficient saline clearance pattern was defined by a progressive distal temperature decrease (>2 SDs of the delta value between the distal temperature at beginning and at the end of the saline infusion: –0.44°). In this pattern, the progressive drop of the distal temperature was explained by a deficient clearance of the infused saline (at 20 mL/min) that accumulates in the distal segment of the treated vessel.

The insufficient saline clearance pattern was observed in 7 patients (18.9%) of the flow-mediated hyperemia group. Those patients presented with more severe angiographic no reflow and with lower absolute coronary blood flow and higher MMR before no reflow treatment than patients with appropriate saline clearance. Moreover, insufficient clearance pattern was associated with a poor response to flow-mediated hyperemia. Table S1 shows the main clinical and angiographic characteristics of patients treated with flow-mediated hyperemia presenting with different thermodilution patterns.

In-Hospital Clinical Outcomes

No reflow was associated with a remarkable rate of in-hospital major adverse cardiac events. A total of 7 patients (10.4%) died due to cardiogenic shock (n=3), cardiac rupture (n=2), acute ventricular septal defect (n=1), and stent thrombosis (n=1). Moreover, nonfatal heart failure was observed in 18 patients (26.9%). In-hospital left ventricle ejection fraction was 44.1±9.7% (45.2±9.3% versus 43.7±10.1%; *P*=0.529). Elective revascularization of nonculprit lesions was performed in 20 patients (30.0%): 19 with PCI and 1 patient with coronary artery bypass graft. Table 5 shows the in-hospital outcomes observed in the present study.

Follow-Up Physiology Assessment

A total of 14 patients undergoing percutaneous revascularization for nonculprit lesions (73.7%) were

Table 2. Clinical, Angiographic, and Procedural Characteristics of the Myocardial Infarction Treatment

	Pharma-mediated hyperemia (n=30)	Flow-mediated hyperemia (n=37)	*P* value
Location of myocardial infarction			0.296
Anterior	13 (43.3%)	23 (62.2%)	
Lateral	2 (6.7%)	3 (8.1%)	
Inferior	14 (46.7%)	11 (29.7%)	
Unknown	1 (3.3%)*	0	
Time of myocardial infarction, min			
Chest pain onset to PCI	248 (140–525)	285 (165–520)	0.634
ECG to PCI	58 (50–85)	60 (50–75)	0.437
Initial Killip-Kimball class			0.136
I	25 (83.3%)	23 (62.2%)	
II	4 (13.3%)	12 (32.4%)	
III	1 (3.3%)	2 (5.4%)	
Culprit vessel			0.133
Left anterior descending artery	13 (43.3%)	24 (64.9%)	
Left circumflex artery	5 (16.7%)	2 (5.4%)	
Right coronary artery	12 (40.0%)	11 (29.7%)	
Preprocedural Thrombolysis in Myocardial Infarction flow			0.200
0	17 (56.7%)	28 (75.7%)	
1	3 (10.0%)	4 (10.8%)	
2	8 (26.7%)	5 (13.5%)	
3	2 (6.7%)	0	
Number vessel disease			0.127
1	17 (56.7%)	17 (45.9%)	
2	7 (23.3%)	17 (45.9%)	
3	6 (20.0%)	3 (8.1%)	
Chronic total occlusion in nonculprit vessel	4 (13.3%)	2 (5.4%)	0.396
Periprocedural anticoagulation			0.396
Unfractionated heparin	26 (86.7%)	35 (94.6%)	
Low-molecular-weight heparin	4 (13.3%)	2 (5.4%)	
Periprocedural antiplatelet therapy			
Aspirin	30 (100.0%)	37 (100.0%)	NA
Clopidogrel	15 (50.0%)	18 (48.6%)	1.000
Prasugrel/ticagrelor	15 (50.0%)	19 (51.4%)	1.000
Cangrelor	1 (3.3%)	1 (2.7%)	1.000
Glycoprotein IIb/IIIa inhibitor	14 (48.3%)	15 (40.5%)	0.620
Reperfusion technique			
Thrombus aspiration	14 (46.7%)	23 (62.2%)	0.227
Predilatation	17 (56.7%)	22 (59.5%)	1.000
Postdilatation	4 (13.3%)	1 (2.7%)	0.165
Number of stents			0.437
1	25 (83.3%)	34 (91.9%)	
2	4 (13.3%)	3 (8.1%)	
3	1 (3.3%)	0	

NA indicates not applicable; and PCI, percutaneous coronary intervention.
*One patient had pacemaker rhythm.

reinvestigated with intracoronary physiology of the culprit lesion (at mean of 3.4 days after PPCI). Absolute coronary blood flow increased from 102.8±43.7 to 142.4±57.0 mL/min (*P*=0.071), and MMR decreased from 926.4±420.1 to 609.1±282.2 Wood units (*P*=0.009). Figure 5 shows the changes in absolute

Table 3. Angiographic and ECG Results Before and After Slow Flow Treatment

	Pharma-mediated hyperemia (n=30)	Flow-mediated hyperemia (n=37)	*P* value
TIMI flow before slow-flow treatment			0.917
0	1 (3.3%)	2 (5.4%)	
1	13 (43.3%)	14 (37.8%)	
2	16 (53.3%)	21 (56.8%)	
3	0	0	
TIMI flow after slow-flow treatment			0.938
0	0	0	
1	3 (10.0%)	5 (13.5%)	
2	19 (63.3%)	22 (59.5%)	
3	8 (26.7%)	10 (27.0%)	
Angiographic corrected TIMI frame count, n			
Before slow flow treatment*	59.3±26.7	55.1±28.3	0.552
After slow flow treatment	40.2±23.1	39.2±20.7	0.858
Delta	22.4±29.5	15.2±18.2	0.248
Comparison before–after (*P* value)	<0.001	<0.001	NA
Angiographic myocardial blush (post), n			0.870
0	11 (36.7%)	10 (27.0%)	
1	14 (46.7%)	20 (54.1%)	
2	4 (13.3%)	6 (16.2%)	
3	1 (3.3%)	1 (2.7%)	
ECG maximal ST-elevation, mm†			
Before PCI	3.9±2.4	3.5±2.4	0.474
After PCI	1.4±0.83	1.8±1.1	0.117
ECG maximal ST resolution, %†			
≥50%	18 (69.2%)	18 (51.4%)	0.195
≥70%	9 (34.6%)	7 (20.0%)	0.246

PCI indicates percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

*TIMI frame count was not estimated in 6 patients (2 in the pharmacologic and 4 in the saline-induced hyperemia group) because contrast did not reach the distal landmark for TIMI frame count analysis.

†ECG was not analyzable in 6 patients (1 pacemaker rhythm and 5 no ECG control post PCI).

coronary blood flow and MMR between baseline posttreatment and follow-up.

DISCUSSION

The main findings of this study are (1) flow-mediated hyperemia with saline infusion via dedicated microcatheter showed similar efficacy as conventional hyperemic agents to improve the coronary flow in patients with STEMI presenting with no reflow after PPCI; (2) few patients achieved normal coronary TIMI 3 flow after treatment with either pharmacologic or flow-mediated hyperemia; (3) no reflow after PPCI was associated with a high rate of in-hospital major adverse cardiac events, irrespective of the given treatment; (4) although the angiographic cTFC improved between pre- and postsaline infusion in patients treated with flow-mediated hyperemia, the observed MMR values worsened during saline infusion in this group. This disagreement between angiographic and physiologic results (at the end of flow-mediated hyperemia) was probably explained by unreliable thermodilution-based physiologic values as result of insufficient saline clearance; and (5) the thermodilution pattern observed during saline infusion was able to characterize patients with no response to flow-mediated hyperemia.

No reflow phenomenon is caused by several simultaneous mechanisms. First, coronary reperfusion of the culprit lesion is associated with microembolisms of thrombi and plaque detritus migrating to the microcirculatory system. Second, the microcirculation of the culprit vessel is externally compressed by inflammation of the infarcted myocardium and by microhemorrhages of the surrounding perivascular tissue. Finally, arteriolar spasm of the culprit vessel is often observed after reperfusion due to severe endothelial dysfunction.[8]

Several pharmacological and mechanical interventions have been investigated to prevent and treat the slow flow phenomenon in patients with STEMI (ie, adenosine, nitroprusside, epinephrine, hypothermia, coronary postconditioning, remote ischemic conditioning, or tools to reduce the embolization of thrombotic material).[5] However, none of those therapies have been shown to be effective at reducing the infarcted area in large clinical trials.[7]

The present study adds a new strategy to treat the slow flow phenomenon after PPCI. According to previous studies, saline infusion at 20 mL/min via dedicated microcatheter causes local hemolysis in the selected artery.[17] The local release of vasodilatory agents by the disruption of red blood cells (such as adenosine and nitric oxide) is the most plausible cause of flow-mediated hyperemia.[17] Flow-mediated hyperemia may be of interest in patients with certain hemodynamic conditions (such as severe hypotension or cardiac rhythm disorders) hampering the use of hyperemic drugs. Moreover, flow-mediated hyperemia, with continuous assessment of thermodilution-based physiologic parameters, allows characterization of the treatment response simultaneously. Patients with appropriate saline clearance pattern had better pre- and posttreatment cTFC and thermodilution-based physiologic parameters than patients with insufficient clearance pattern. Moreover, those patients also presented with better response to hyperemia than

Table 4. Physiologic Results After Slow Flow Treatment

	Pharma-mediated hyperemia at 15 s (n=30)	Flow-mediated hyperemia group (n=37)		P*	P value†	P value‡
		At 15 s	At 135 s			
Pressure at hyperemia, mm Hg						
Aortic	84.0±18.9	82.5±19.6	82.4±18.1	0.901	0.747	0.715
Distal	81.4±19.5	77.0±20.1	77.0±18.7	1.000	0.372	0.353
Fractional flow reserve, value	0.97±0.05	0.93±0.07	0.93±0.08	0.254	0.021	0.048
Absolute coronary blood flow, mL/min	161.8±101.1	149.6±122.5	117.4±84.0	<0.001	0.665	0.056
Normalized value	166.2±105.8	159.8±130.4	121.6±82.0	0.001	0.828	0.058
Minimal microcirculatory resistance, Wood units	753.6±661.5	849.9±702.0	993.3±740.8	<0.001	0.571	0.174

*P value indicates the paired differences of physiologic parameters at 15 and at 135 seconds in the flow-mediated hyperemia group.
†P value indicates the difference between the study groups at 15 seconds of the saline infusion.
‡P value indicates the difference between the physiologic results obtained at 15 seconds in the pharmacologic and at 135 seconds in the flow-mediated hyperemia group.

patients with insufficient saline clearance pattern (ie, 60% of patients with appropriate clearance improved by at least 1 degree the TIMI flow between pre- and posttreatment compared with only 29% of patients with insufficient clearance) (Table S1). Other physiologic indices, such as the Index of Microcirculatory Resistance (IMR), have been demonstrated to identify patients with worse prognosis after PPCI.[18] However, assessment of this index requires intravenous perfusion of adenosine (or analogues) and, therefore, does not allow comparison of different hyperemic strategies for no reflow treatment. Finally, in patients undergoing new coronary angiography (ie, in cases with scheduled treatment of nonculprit lesions) and reinvestigated with thermodilution-based techniques, the use of physiology was useful to investigate the coronary flow restoration few days after the index procedure. Therefore, this technique may be of interest to future research on slow flow dedicated therapies.

The present study has several limitations. First, the study failed to achieve the prespecified sample size due to slow recruitment. Considering the results of the coprimary end points and the achieved sample size, the study presents with a statistical power to assess differences between treatments <50%. Therefore, all comparisons between the study groups should be interpreted with caution and are merely hypothesis generating. Second, the present study was designed to assess the immediate efficacy of flow-mediated hyperemia to treat the no reflow phenomenon after

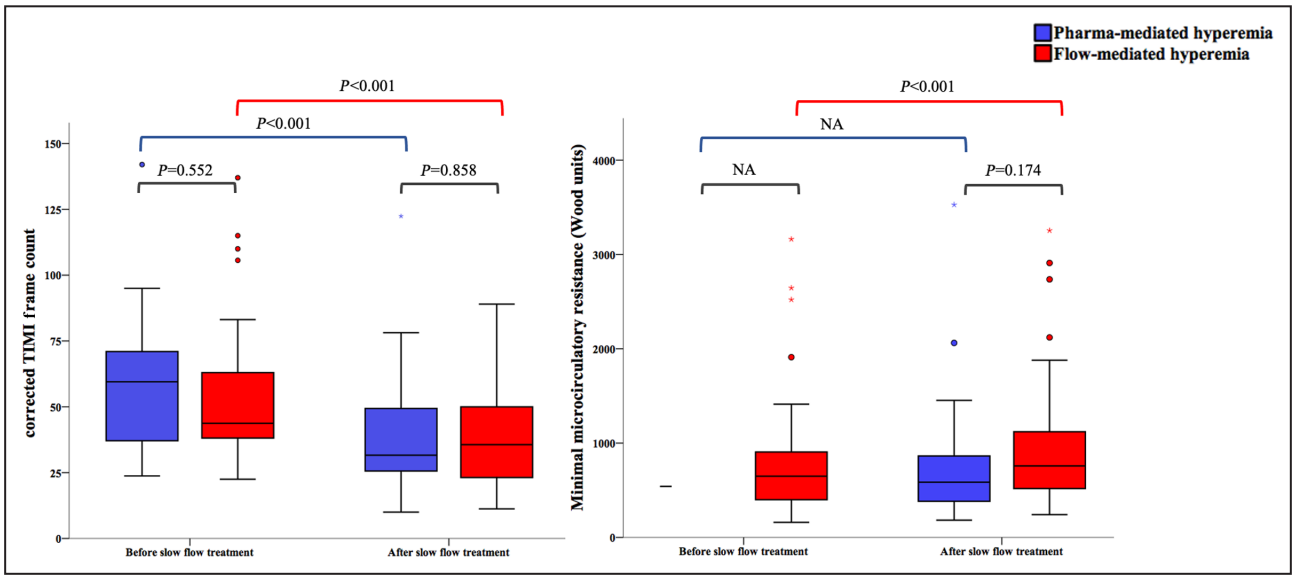

Figure 3. Primary end points.
Boxplot of the study end points before and after treatment. Of note, MMR was not assessed before treatment in the pharmacologic group. In this group, MMR was assessed after administration of hyperemic drugs. In the flow-mediated hyperemia group, MMR values were assessed during saline infusion at 15 (before treatment) and at 135 seconds (after treatment). MMR indicates minimal microcirculatory resistance; and TIMI, Thrombolysis in Myocardial Infarction.

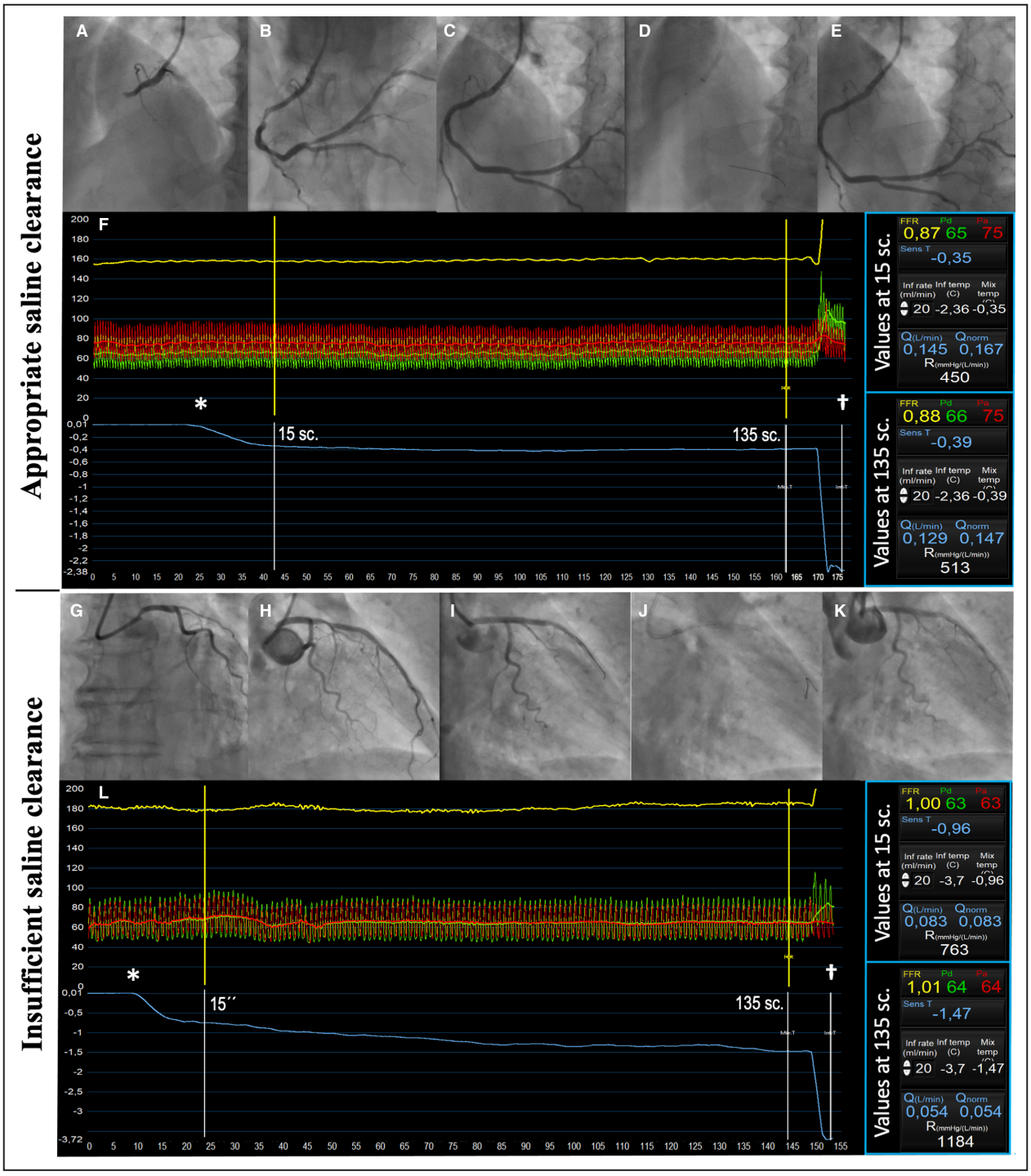

Figure 4. Saline-induced thermodilution patterns in patients with slow-flow.
*Start of saline infusion; †Saline temperature. Appropriate saline clearance is shown in images (**A** through **F**). Acute RCA occlusion (**A**). Restoration of TIMI 2 flow after thrombus aspiration (**B**) with no improvement after stent implantation (**C**). Flow-mediated hyperemia (**D**). The thermodilution-based ACBF and MMR (**F**) showed similar values at 15 seconds (145 mL/min and 450 Wood units) and at 135 seconds (129 mL/min and 513 Wood units) without variation of the distal temperature (from −0.35 to −0.39°). However, normal TIMI 3 flow restoration was observed after flow-mediated hyperemia (**E**). Deficient saline clearance is shown in images (**G** through **L**). Acute LAD artery occlusion (**G**). Restoration of TIMI 3 flow after thrombus aspiration (**H**) followed by no reflow (TIMI flow 1) after stent implantation (**I**). Flow-mediated hyperemia (**J**). The thermodilution-based ACBF and MMR (**L**) showed significant changes from 15 seconds (83 mL/min and 763 Wood units) to 135 seconds (54 mL/min and 1184 Wood units) due to progressive decrease of distal temperature (from −0.96 to −1.47°) during saline infusion (**J**). TIMI 2 flow was observed posttreatment (**K**). ACBF indicates absolute coronary blood flow; LAD, left anterior descending; MMR, minimal microcirculatory resistance; RCA, right coronary artery; and TIMI, Thrombolysis in Myocardial Infarction.

Table 5. In-Hospital Outcomes

	All patients (n=67)	Pharma-mediated hyperemia group (n=30)	Saline-mediated hyperemia group (n=37)	*P* value
All-cause death	7 (10.4%)	2 (6.7%)	5 (13.5%)	0.447
Cardiac rupture	2 (3.0%)	0	2 (5.4%)	
Acute ventricular septal defect	1 (1.5%)	0	1 (2.7%)	
Cardiogenic shock	3 (4.5%)	1 (3.3%)	2 (5.4%)	
Stent thrombosis	1 (1.5%)	1 (3.3%)*	0	
Nonfatal heart failure	18 (26.9%)	5 (16.7%)	13 (35.1%)	0.105
Hemodynamic support				
Inotropic drugs	9 (13.4%)	2 (6.9%)	7 (18.9%)	0.279
Inotropic drugs+left ventricle assist device	4 (6.0%)	0	4 (11.1%)	0.120
Stent thrombosis	2 (3.0%)	1 (3.3%)*	1 (2.7%)	1.000
Revascularization of nonculprit vessels	20 (30.0%)	7 (23.3%)	13 (35.1%)	0.140
Other nonfatal complications				
Atrial fibrillation (unknown)	2 (3.0%)	2 (6.7%)	5 (13.5%)	0.498
Need permanent pacemaker	1 (1.5%)	0	1 (2.7%)	1.000
Major bleeding	3 (4.5%)	2 (6.7%)	1 (2.7%)	1.000
Intraventricular thrombus	3 (4.5%)	1 (3.3%)	2 (5.4%)	1.000

*One patient with stent thrombosis presented with in-hospital cardiogenic shock and death.

PPCI. A total of 40% of patients in the flow-mediated hyperemia group were treated with hyperemic drugs (as bailout) after the study intervention because of persistent slow flow. Although the treatment crossover did not affect the results of the co-primary end points (that were assessed before the crossover), all comparisons performed after the baseline procedure (ie, ECG ST-segment resolution or clinical outcomes) may have been influenced. Finally, as per protocol, both groups underwent to saline infusion (the pharmacologic for 15 seconds and the flow-mediated hyperemia group for 135 seconds) to assess the MMR. At 15 seconds, saline infusion has been shown to cause hyperemia in patients with chronic coronary syndrome. Therefore, the pharmacologic-mediated hyperemia group has been exposed to 2 different (pharmacologic and

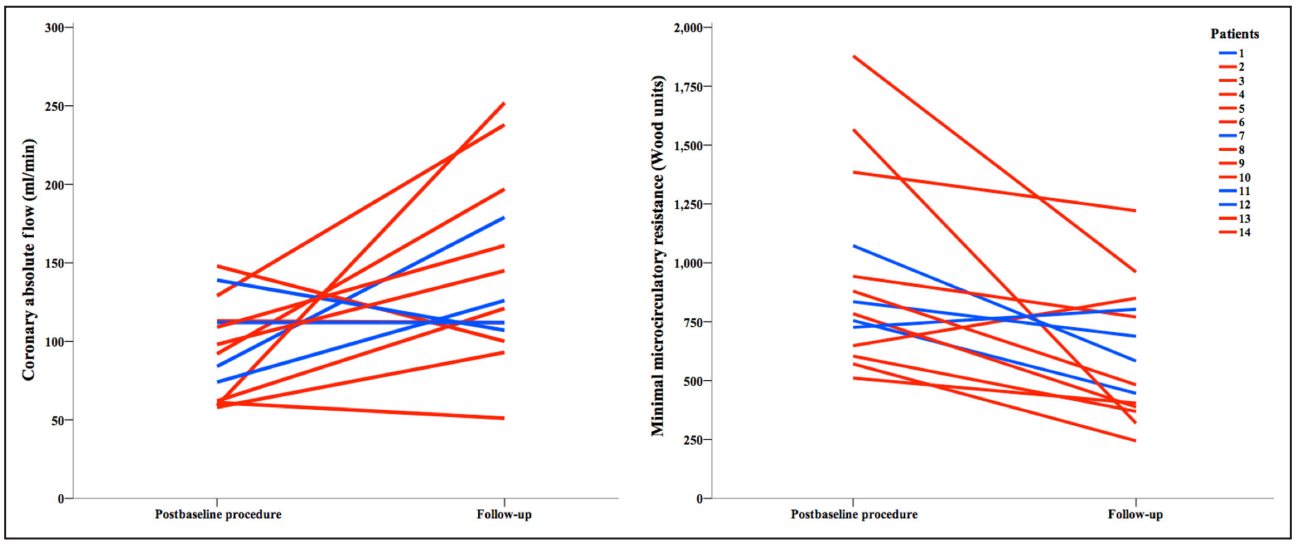

Figure 5. Absolute coronary blood flow and minimal microcirculatory resistance changes between baseline and follow-up procedures.
Fourteen patients underwent thermodilution-based physiologic assessment at baseline (post intervention) and at follow-up. Baseline values were estimated at 15 seconds in the pharmacologic (blue) and at 135 seconds in the flow-mediated hyperemia group (red).

flow-mediated) hyperemic stimuli when the MMR was assessed post intervention, and this may influence the MMR results of this group.

CONCLUSIONS

In conclusion, the results of the present study should be carefully interpreted due to the lack of statistical power to assess differences between groups. According to the data obtained with 67% of the prespecified sample size, patients with slow flow after PPCI treated with flow-mediated hyperemia seemed to have similar immediate angiographic and intracoronary physiologic results as patients treated with standard of care hyperemic drugs for slow flow treatment (such as adenosine and nitroprusside). Few patients achieved restoration of normal coronary flow, and a remarkable number of patients presented with in-hospital major adverse cardiac events, irrespective of the given treatment. It is noteworthy that flow-mediated hyperemia with thermodilution pattern assessment allowed the simultaneous characterization of the no reflow degree and response to hyperemia. However, the physiologic mechanisms, prevention, and treatment of coronary slow flow warrants further investigations.

ARTICLE INFORMATION

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Supplemental Material

Data S1–S3
Table S1

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1. Study endpoints

Corrected Thrombolysis In Myocardial Infarction (TIMI) frame count (cTFC) calculation

High-definition cine-fluoroscopic recordings of the infarct-related artery (IRA) at 25 or 30 frames/second were off-line analyzed by the study core-laboratory (Barcelona Cardiac Imaging core-laboratory; BARCICORE-lab, Spain) with a dedicated software (QAngio 7.3, Medis, The Netherlands). The analysts were blinded to the study allocation. The TIMI frame count was defined as the number of cine-frames needed for dye to reach standardized distal landmarks [11]. The first frame is counted when dye fully enters to the artery. For the left anterior descending (LAD) artery, the standardized distal landmark was the distal bifurcation (moustache), for the left circumflex artery was the distal bifurcation with the longest distance to the culprit lesion, and for the right coronary artery the first branch of the posterolateral artery [11].

CTFC was calculated according to the cine frame rate (TIMI frame rate acquisitions at 25 frames/second were corrected with *1.2 factor to homogenize with acquisitions at 30 frames/second) and to the vessel length (TIMI frame count of culprit lesions located in the LAD were corrected with /1.6) as appropriate [11].

Minimal microcirculatory resistance (MMR) calculation

MMR was assessed by intracoronary thermodilution techniques with a dedicated pressure wire (Pressurewire X, Abbott, United States), software (Coroflow, Abbott, United States) and microcatheter (RayFlow, Hexacath, France) during saline infusion at 20 ml/min. MMR was measured offline by the core-laboratory at 15 seconds of the saline infusion in the standard medical treatment group and at 135 seconds in the experimental group.

Secondary endpoints

Secondary objectives of the study include: to compare the absolute coronary blood flow, fractional flow reserve, the angiographic TIMI flow between the two study groups after slow-flow treatment. The study also aims to compare the ST segment resolution between the two groups at 90 minutes of the primary percutaneous coronary intervention (PPCI).

Electrocardiogram ST elevation assessment

All patients were requested to record the pre-PPCI electrocardiogram (ECG) and to perform a 90-minutes ECG post-PPCI. ST elevation was assessed by blinded analysts of the study core-laboratory. Maximal ST elevation of the 12-lead ECG, measured in mm, was estimated in the pre-PPCI ECG. ST elevation was assessed in the same lead in the 90-minutes ECG post-PCI.

Data S2. Sample size calculation

The RAIN-FLOW study was powered to test superiority for two co-primary endpoints. The first co-primary endpoint was the final cTFC, expressed in number of frames. According to previous studies in STEMI patients presenting with post-PCI slow flow, the mean cTFC obtained after > 120 mcg of intracoronary nitroprusside (NTP) was 30 ± 12 frames [12]. Considering a 25% superiority margin with the experimental treatment (7 frames) after 2-minute of saline infusion, a total of 47 patients per group were needed with 80% of statistical power and 5% of alfa error.

The second co-primary endpoint was the MMR value, expressed in Wood units, after study slow flow treatment. Both groups were investigated to assess this value after 2 minutes of pharmacologic or flow-mediated hyperemia. According to previous studies in STEMI patients presenting with slow flow, the observed MMR value was 537± 289 Wood units [13] (this value was obtained after the conversion of the reported MMR in this study (42,948 ± 23,084 dynes.sec.cm^{-5}) using the conversion factor of 1 Wood unit = 80 dynes.sec.cm^{-5}). This co-primary endpoint was estimated to be 30% lower in the experimental group (160 UW). In this case, a total of 50 patients per group are needed to show differences between the study treatments with 80% of statistical power and 5% of alfa error.

Data S3. Study interventions

As per protocol, all eligible patients with no reflow after PPCI (TIMI flow 0-2) were recommended to be treated with IIb/IIIa glycoprotein inhibitor and intracoronary nitroglycerin. In case of sustained (>30 seconds) slow flow, oral informed consent was obtained. Then, all patients were imaged with a high-definition (25-30 frames/second) cine-fluoroscopic recording and were randomized to one of the two study interventions:

1. Pharmacologic-mediated hyperemia was induced using intracoronary bolus of either adenosine or nitroprusside by the guiding catheter for 2 minutes. Both treatments were given by repeated boluses of 250 mcg of adenosine or 100 mcg of nitroprusside with > 30 seconds clearance. The objective was to achieve at least 500 mcg of adenosine or 200 mcg of nitroprusside. As per protocol, the hyperemic agent was chosen according to the operator's preference, culprit vessel and patient's hemodynamics.
2. Flow-mediated hyperemia was performed with intracoronary saline infusion via a dedicated micro-catheter (Ray Flow, Hexacath, France) at 20 ml/min for 135 seconds. According to previous studies in patients with chronic coronary syndromes, steady hyperemia is achieved in most of the patients at 15 seconds. Therefore, flow-mediated hyperemia was given for 2 minutes in this group too. Continuous recording of the absolute coronary blood flow (ACBF) and MMR was assessed using a dedicated pressure wire (Pressurewire X, Abbott, United States) and software (Coroflow, Abbott, United States) as appropriate.

After two minutes of either pharmacologic or flow-mediated hyperemia, all patients were imaged with a new high-definition (25-30 frames/second) cine-fluoroscopic recording.

Of note, patients included in the pharmacologic-mediated hyperemia group also underwent ACBF and MMR assessment once the post-intervention cine-fluoroscopic

acquisition was recorded. ACBF and MMR were obtained using the same technique as the flow-mediated hyperemia group but for only 15 seconds. In the flow-mediated hyperemia group, ACBF and MMR were continuously recorded during saline infusion. ACBF and MMR were offline assessed at 15 seconds (pre-intervention) and at 135 seconds (post-intervention) by the core laboratory. In this group, post-intervention cine-fluoroscopic recording was obtained after saline infusion. All study interventions are summarized in **Figure 1**.

As per protocol, patients with persistent slow flow after all study interventions were allowed to be treated with any additional dose of hyperemic drugs, even in patients of the flow-mediated hyperemia group.

Table S1. Main characteristics of patients with different thermodilution patterns undergoing 2-minute flow-mediated hyperemia.

	Insufficient saline clearance pattern (n=7)	Appropriate saline clearance pattern (n=30)	p
Baseline clinical characteristics:			
Age	72.7 ± 9.6	69.4 ± 13.8	0.552
Males	3 (42.9%)	22 (75.9%)	0.167
Hypertension	6 (85.7%)	15 (51.7%)	0.200
Hypercholesterolemia	3 (42.9%)	18 (62.1%)	0.418
Diabetes mellitus	3 (42.9%)	11 (39.3%)	1.000
STEMI characteristics:			
Chest pain onset to PPCI, min	555.0 ± 246.6	295.0 ± 189.8	0.004
Killip class > 1	3 (42.9%)	11 (36.7%)	1.000
Number vessel disease > 1	3 (42.9%)	16 (53.3%)	0.684
Initial TIMI flow 0	7 (100.0%)	21 (72.4%)	0.309
LAD as culprit vessel	4 (57.1%)	19 (65.5%)	0.686
TIMI flow before slow flow treatment			0.161
0	0	2 (6.9%)	
1	5 (71.4%)	9 (31.0%)	
2	2 (28.6%)	18 (62.1%)	
3	0	0	
TIMI flow after slow flow treatment			0.023
0	0	0	
1	3 (42.9%)	2 (6.9%)	
2	4 (57.1%)	18 (62.1%)	
3	0	9 (31.0%)	
Angiographic cTFC, n:			
Before slow-flow treatment*	76.3 ± 41.9	50.6 ± 23.2	0.045
After slow-flow treatment	60.3 ± 23.2	34.9 ± 17.0	0.002
Delta	15.7 ± 18.2	14.6 ± 18.7	0.891
Physiologic values at 15 seconds			
Absolute coronary blood flow, ml/min	68.9 ± 28.0	169.1 ± 128.7	0.050
Minimal microcirculatory resistance	1384.0 ± 872.3	721.0 ± 603.6	0.023
Fractional flow reserve	0.95 ± 0.09	0.93 ± 0.07	0.408
Physiologic values at 135 seconds			
Absolute coronary blood flow, ml/min	51.9 ± 22.9	133.2 ± 85.9	0.019
Minimal microcirculatory resistance	1711.0 ± 967.7	820.1 ± 570.4	0.003
Fractional flow reserve	0.94 ± 0.11	0.93 ± 0.07	0.723
In-hospital outcomes:			
Death	2 (28.6%)	3 (10.3%)	0.244
Non-fatal Heart Failure	3 (42.9%)	10 (34.5%)	0.686

cTFC= corrected Thrombolysis In Myocardial Infarction (TIMI) frame count; STEMI= ST-segment elevation myocardial infarction.