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ORIGINAL RESEARCH

Gradual Versus Abrupt Reperfusion During Primary Percutaneous Coronary Interventions in ST-Segment–Elevation Myocardial Infarction (GUARD)

Murat Sezer, MD; Javier Escaned, MD, PhD; Christopher J. Broyd, MBBS, PhD; Berrin Umman, MD; Zehra Bugra, MD; Ilke Ozcan, MD; Mehmet Rasih Sonsoz, MD; Alp Ozcan, BSc; Adem Atici, MD; Emre Aslanger, MD; Z. Irem Sezer, MD; Justin E. Davies, MBBS, PhD; Niels van Royen, MD, PhD; Sabahattin Umman, MD

BACKGROUND: Intramyocardial edema and hemorrhage are key pathological mechanisms in the development of reperfusion-related microvascular damage in ST-segment–elevation myocardial infarction. These processes may be facilitated by abrupt restoration of intracoronary pressure and flow triggered by primary percutaneous coronary intervention. We investigated whether pressure-controlled reperfusion via gradual reopening of the infarct-related artery may limit microvascular injury in patients undergoing primary percutaneous coronary intervention.

METHODS AND RESULTS: A total of 83 patients with ST-segment–elevation myocardial infarction were assessed for eligibility and 53 who did not meet inclusion criteria were excluded. The remaining 30 patients with totally occluded infarct-related artery were randomized to the pressure-controlled reperfusion with delayed stenting (PCRDS) group (n=15) or standard primary percutaneous coronary intervention with immediate stenting (IS) group (n=15) (intention-to-treat population). Data from 5 patients in each arm were unsuitable to be included in the final analysis. Finally, 20 patients undergoing primary percutaneous coronary intervention who were randomly assigned to either IS (n=10) or PCRDS (n=10) were included. In the PCRDS arm, a 1.5-mm balloon was used to achieve initial reperfusion with thrombolysis in myocardial infarction grade 3 flow and, subsequently, to control distal intracoronary pressure over a 30-minute monitoring period (MP) until stenting was performed. In both study groups, continuous assessment of coronary hemodynamics with intracoronary pressure and Doppler flow velocity was performed, with a final measurement of zero flow pressure (primary end point of the study) at the end of a 60-minute MP. There were no complications associated with IS or PCRDS. PCRDS effectively led to lower distal intracoronary pressures than IS over 30 minutes after reperfusion (71.2±9.37 mm Hg versus 90.13±12.09 mm Hg, P=0.001). Significant differences were noted between study arms in the microcirculatory response over MP. Microvascular perfusion progressively deteriorated in the IS group and at the end of MP, and hyperemic microvascular resistance was significantly higher in the IS arm as compared with the PCDRS arm (2.83±0.56 mm Hg.s.cm^{-1} versus 1.83±0.53 mm Hg.s.cm^{-1}, P=0.001). The primary end point (zero flow pressure) was significantly lower in the PCRDS group than in the IS group (41.46±17.85 mm Hg versus 76.87±21.34 mm Hg, P=0.001). In the whole study group (n=20), reperfusion pressures measured at predefined stages in the early reperfusion period showed robust associations with zero flow pressure values measured at the end of the 1-hour MP (immediately after reperfusion: r=0.782, P<0.001; at the 10th minute: r=0.796, P<0.001; and at the 20th minute: r=0.702, P=0.001) and peak creatine kinase MB level (immediately after reperfusion: r=0.653, P=0.002; at the 10th minute: r=0.597, P=0.007; and at the 20th minute: r=0.538, P=0.017). Enzymatic myocardial infarction size was lower in the PCRDS group than in the IS group with peak troponin T (5395±2991 ng/mL versus 8874±1927 ng/mL, P=0.006) and creatine kinase MB (163.6±93.4 IU/L versus 542.2±227.4 IU/L, P<0.001).

CONCLUSIONS: In patients with ST-segment–elevation myocardial infarction, pressure-controlled reperfusion of the culprit vessel by means of gradual reopening of the occluded infarct-related artery (PCRDS) led to better-preserved coronary microvascular integrity and smaller myocardial infarction size, without an increase in procedural complications, compared with IS.

Correspondence to: Murat Sezer, MD, Department of Cardiology, Istanbul Faculty of Medicine, Istanbul University, Capa, Istanbul, Turkey. E-mail: sezermr@gmail.com

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Key Words: coronary microvascular resistance ■ intramyocardial hemorrhage ■ microvascular injury ■ myocardial edema ■ primary PCI ■ reperfusion injury ■ ST-segment–elevation myocardial infarction

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CLINICAL PERSPECTIVE

What Is New?

- This study shows for the first time that pressure-controlled reperfusion by stepwise reopening of the occluded infarct-related artery with delayed stenting performed at 30 minutes after successful reperfusion in patients with thrombosis in myocardial infarction grade 3 flow was associated with significantly better preserved coronary microvascular integrity and lower peak enzyme estimates of infarct size compared with standard immediate stenting in patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention.
- In addition, for the first time, the time course of the evolution of coronary microvascular injury over 1 hour after successful reperfusion established by primary percutaneous coronary intervention has been elucidated in humans.
- Our findings demonstrate that abrupt reopening of the occluded infarct-related artery and immediate and full reconstitution of distal intracoronary pressure by successful primary percutaneous coronary intervention as per standard practice may paradoxically aggravate microvascular injury and is associated with a progressive deterioration of the microvascular perfusion.

What Are the Clinical Implications?

- In patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention, pressure-controlled, gradual reperfusion modulating initial reperfusion pressure might be a new and promising reperfusion strategy aiming to limit vascular reperfusion injury in the subtended coronary microcirculation.
- Moreover, pressure-controlled reperfusion with gradual reopening of any given acutely occluded artery supplying different organ parts (eg, lung, leg, brain, and small intestine) may also be a new promising player in the protection of architectural integrity of microcirculation in the jeopardized perfusion territory.

Nonstandard Abbreviations and Acronyms

APV	average peak velocity
APV_h	hyperemic average peak velocity
ARI	arteriolar resistance index
hMR	hyperemic microvascular resistance
IS	immediate stenting
MP	monitoring period
PCRDS	pressure-controlled reperfusion with delayed stenting
P_d,	mean distal pressure
Pzf	zero flow pressure

The primary goal in the treatment of ST-segment–elevation myocardial infarction (STEMI) is to terminate ongoing ischemic damage as soon as possible. Although the most effective method to achieve this goal is reperfusion with primary percutaneous coronary intervention (pPCI), microvascular damage worsens in about half of patients with STEMI following this procedure, indicating further tissue loss and a poor prognosis.[1,2] Major randomized trials addressing potential causes of microcirculatory damage during pPCI, including aspiration thrombectomy,[3] distal protection devices, mesh-covered stents,[4] and deferred stenting,[5] have failed to show any benefit in limiting final infarct size and improving patient outcome. Adjunctive pharmacological therapies in this setting have also proven controversial and inconsistent.[6,7] Moreover, important attempts to reduce myocardial reperfusion injury by mechanical (ischemic) and pharmacologic postconditioning with different agents have failed to show any benefit in terms of coronary microvascular protection or improvement in clinical outcomes, although it was initially perceived as a promising concept and rapidly supported by several positive clinical studies.[8–10]

In the interim, intraluminal microvascular obstruction and extravascular compression of microcirculation have been identified as key mechanisms involved in the development of post-pPCI microvascular injury.[11] There is evidence suggesting that prompt and full restoration of distal coronary flow and pressure in the infarct-related

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artery (IRA) is a major contributor to the generation of microvascular damage. This may be related to the joint effect of increased capillary permeability downstream of the occlusion caused by ischemia-induced endothelial disruption[12,13] and overpressurization following abrupt reperfusion. To date, there is no reported therapeutic modality exclusively aimed to prevent or limit extravascular compression of the microcirculation by alleviating the surrounding myocardial edema and intramyocardial hemorrhage (IMH), both of which are inevitable results of reperfusion after prolonged ischemia. At this point, avoiding a sudden and full-pressure reperfusion may play a key role in the solution. Interventions geared at modulating initial reperfusion pressure may, therefore, attenuate the initial reperfusion-driven wave of edema and consequently IMH.

In this study, we propose that pressure-controlled (low pressure), gradual reopening of the acutely occluded coronary artery allowing adequate time for temporarily malfunctioned (stunned) arterioles to regain adaptive vasoconstrictor response may prevent an abrupt pressure rise in downstream microvascular bed during the early reperfusion phase and may, therefore, limit the formation of edema and hemorrhage compressing microvascular bed externally in the surrounding myocardium. To test this hypothesis, we evaluated the effect of mechanically modulated, pressure-controlled (low pressure) reperfusion on coronary microcirculation in patients undergoing pPCI in a randomized proof-of-concept pilot trial. The secondary objective of the study was to elucidate the time course of the evolution of microvascular injury over 1 hour after reperfusion established by pPCI.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

We performed a single-center, prospective, randomized, open-label, parallel-arm study. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by Istanbul University's Istanbul Faculty of Medicine ethics committee. The clinical trial registration number is NCT02732080 (https://www.clinicaltrials.gov).

Patients

Patients presenting with their first STEMI undergoing pPCI within 6 hours of symptom onset were considered for trial enrollment. Inclusion criteria were ongoing chest pain, ST-segment elevation on ECG, and total occlusion (thrombolysis in myocardial infarction [TIMI] flow grade of 0) of a major coronary artery at the proximal or mid region on angiography. The main exclusion criteria were spontaneously recanalized IRA with a TIMI flow grade of 1 to 3 and hemodynamic instability.

Study Protocol

Immediately after diagnostic angiography showing proximal or mid occlusion of a major coronary artery, patients were asked for oral informed consent at the catheterization laboratory, which was witnessed by an independent person. Written informed consent was obtained in the coronary care unit within 24 hours of the procedure. After oral informed consent was obtained, patients were randomized to either immediate stenting (IS; standard balloon angioplasty followed by immediate stent implantation) or the delayed stenting (gradual, pressure-controlled reperfusion with delayed stenting [PCRDS]) groups according to a computer-generated random sequence.

In both groups, in the first attempt, a 0.014-inch guidewire equipped with a dual sensor (pressure and Doppler sensors) on the tip (ComboWire XT, Philips, Volcano) was used to cross the fresh thrombotic occlusion. When the attempt was successful, balloon angioplasty and stenting were performed over the dual-sensor coronary guidewire. When the attempt was not successful (2 patients in each group), a standard floppy wire was used to cross the occluded segment, and it was immediately replaced with the dual-sensor guidewire after balloon angioplasty. The stenting procedure was performed over the dual-sensor guidewire.

In the IS group, standard balloon angioplasty (the balloon size was left to the operators' discretion) was followed by IS over the dual-sensor guidewire. In the reopened IRA, intracoronary pressure and flow velocity signals were continuously followed during a 1-hour monitoring period (MP) by means of the same dual-sensor guidewire, which was kept in place distal to the stented coronary segment.

In the PCRDS group, after establishing TIMI grade 3 flow in the IRA by means of balloon angioplasty performed using a 1.5-mm balloon inflated at nominal pressure and after ensuring TIMI grade 3 flow with complete resolution of chest pain, stent implantation was delayed for 30 minutes until autoregulatory vasoconstrictor tonus of the arterioles was expected to be recovered. To avoid capillary overpressurization and reocclusion, patients with a residual stenosis were carefully followed with continuous distal pressure and flow monitorization in these 30 minutes. IRA was then stented after these 30 minutes of low-pressure reperfusion with TIMI grade 3 flow. Intracoronary pressure and flow were monitored for a further 30 minutes via the dual-sensor guidewire, which was kept in the same position distal to the reopened coronary artery.

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Activated coagulation time was kept between 260 seconds and 300 seconds during the procedure in all patients.

Real-time monitorization by continuous pressure and flow signals obtained from the intracoronary dual-sensor wire for a 1-hour period were performed in each patient. Resting pressure and flow data were recorded immediately after establishing initial reperfusion by angioplasty with a 1.5-mm balloon in the PCRDS group and after stent implantation in the IS group. Measurements were repeated at every 10th minute thereafter (7 recordings). In the same way, hyperemic pressure and flow data were recorded immediately after establishing initial reperfusion by angioplasty with a 1.5-mm balloon in the PCRDS group and by stent implantation in the IS group. Recordings were repeated at every 20th minute thereafter (4 recordings) until the end of the 1-hour monitorization period (Figure S1). At each of these specified timepoints, resting and hyperemic pressure and flow recordings were repeated three times and averaged.

Venous blood samples were collected from all patients at 6-hour intervals within the first 24 hours after pPCI to determine peak troponin T and creatine kinase MB (CK-MB) levels. All patients received optimal medical therapy in accordance with the most recent guidelines[14] (Table 1).

Intracoronary Hemodynamic Measurements

Intracoronary pressure and flow velocity data were obtained simultaneously and continuously with a dual-sensor–equipped guidewire (ComboWire XT, Philips Volcano). The tip of the dual-sensor guidewire was positioned just distal to the reopened segment in the IRA and manipulated until clear Doppler velocity envelopes were obtained. Doppler average peak velocity (APV), mean aortic pressure, and mean distal pressure (P_d) were simultaneously and continuously monitored with the ComboMap console (ComboMap console, Philips, Volcano). All hemodynamic signals were recorded during resting and maximum hyperemia induced by a bolus of intracoronary papaverine (15 mg for the right coronary artery and 20 mg for the left system). Three consecutive recordings were obtained at each prespecified timepoint for the calculations. All intracoronary hemodynamic data acquired during the procedure were analyzed offline by one of the authors blinded to the randomization group (C.J.B.). Baseline stenosis resistance was calculated as the ratio of the stenosis pressure gradient to resting flow velocity. Hyperemic stenosis resistance was calculated as the ratio of the stenosis pressure gradient to hyperemic flow velocity. Baseline microvascular resistance was calculated as resting P_d divided by resting APV.

Table 1. Baseline Demographic, Clinical, and Angiographic Characteristics in the PCRDS and IS Arms

	PCRDS (n=10)	IS (n=10)	*P* value
Main characteristics			
Age, y	55.30±11.73	50.40±12.44	0.377
Men, n	9	10	0.90
Smoking, n	7	8	1
Diabetes, n	3	1	0.354
Hypertension, n	4	5	0.211
Dyslipidemia, n	7	7	1
History of preinfarct angina, n	2	3	0.255
Anterior infarct location, n	6	7	0.921
Initial ST-segment elevation, mm	15.85±9.55	17.50±10.93	0.456
Concomitant medication used during pPCI and in the coronary care unit			
Aspirin, n	10	10	1
β-Blocker, n	9	10	0.920
P2Y12 antagonists, n	10	10	1
Statins, n	10	10	1
ACEIs, n	8	9	0.915
Angiographic characteristics			
Infarct-related coronary artery, n			
Left anterior descending artery	6	7	0.921
Right coronary artery	3	2	0.554
Circumflex artery	1	1	1
No. of diseased vessels, n			
1	7	8	1
2	3	2	0.554
3	0	0	
Periprocedural findings			
Pain-to-balloon time, min	167±61	159±75	0.809
Needle-to-TIMI grade 3 flow time, min	5.25±0.72	5.45±0.64	0.672
Peak myocardial enzyme levels			
Peak troponin T, ng/mL	5395±2991	8874±1927	0.006
Peak CK-MB, U/l	163.6±93.4	542.2±227.4	<0.001
Procedural findings			
Reference vessel size, mm	2.9±0.4	3.0±0.4	0.910
Lesion length, mm	13. 5±3.8	12.3±3.1	0.851
TIMI grade			
0/1	3	4	0.83
2	5	4	0.83

(*Continued*)

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Table 1. Continued

	PCRDS (n=10)	IS (n=10)	*P* value
3	2	2	1
4	0	0	1
Residual stenosis after PTCA, %	60±9	…	…
Stent diameter, mm	3±0.6	3.1±0.5	0.911
Inflation pressure, atm	17±3	16±3	0.859

ACEI indicates angiotensin-converting enzyme inhibitor; CK-MB, creatine kinase MB; IS, immediate stenting; PCRDS, pressure-controlled reperfusion with delayed stenting; pPCI, primary percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; and TIMI, thrombosis in myocardial infarction.

Hyperemic microvascular resistance (hMR) was calculated under maximal hyperemia as P_d/APV_h. Arteriolar resistance index (ARI) was expressed as baseline microvascular resistance – hMR. Zero-flow pressure (Pzf) was calculated from the pressure-flow relationship in mid-late diastole using bespoke MATLAB software (version R2015a, the MathWorks). Individual cardiac cycles were delineated according to the R-R interval and ensemble averaging was performed. Each cardiac cycle was manually inspected to ensure accuracy, in particular of the automated flow tracking system of the ComboMap console; subjectively poor-quality cycles were excluded. Mid-to-late diastole was identified manually with reference to the flow and pressure signals. Pzf was taken to be the linear intercept of the x-axis from this section (Figure S2).

Study End Points

The primary end point of this study was the Pzf at the end of a 1-hour MP. The secondary end point was the hMR at the same time end.

Statistical Analysis

The estimated mean value for the Pzf was obtained from the published literature.[15,16] Using GraphPad Instat software, we then calculated the number of patients necessary to detect a difference of 50% between the immediate and delayed stenting group for Pzf with an α of 0.05 and a β of 0.20 and a statistical power of 0.80. The necessary number of patients per group was 10. All statistical analyses were performed with SPSS software (version 21; IBM). Group percentages were compared with the use of Fisher exact test. Group means for variables with normal and non-normal distributions were compared using Student *t* test and Mann-Whitney *U* test, respectively. Correlations between continuous parameters were analyzed using Pearson correlation analysis. The effects of potential confounding factors (pain-to-balloon time and culprit coronary artery [left anterior descending artery and nonleft anterior descending artery]) on primary and secondary end points were analyzed using univariate ANOVA. Two-tailed *P* values of <0.05 were considered to indicate statistical significance.

RESULTS

Study Patients

A total of 83 patients were screened for enrollment in the study (Figure 1). Thirty patients were enrolled and randomly assigned to the PCRDS (n=15) or IS group (n=15). In the PCRDS group, Doppler recordings were uninterpretable for the Pzf calculation in 3 patients and initial angioplasty with 1.5-mm balloon involuntarily caused an uncontrolled high distal pressure reperfusion in 2 patients. Therefore, the remaining 10 patients were included in the analysis. In the IS group, Doppler recordings were found ineligible for Pzf calculation in 4 patients and a significant distal lesion detected after establishing flow in IRA by angioplasty in 1 patient. Therefore, the remaining 10 patients constituted the IS group. Patients' demographic, clinical, and angiographic characteristics are listed in Table 1.

IRA was successfully reopened in all patients, each of whom received 1 stent. There were no differences between groups in terms of lesion length and thrombus burden (Table 1) No major complication occurred in any patients. In 1 patient assigned to the PCRDS group, a subtotal reocclusion occurred at the site of primary intervention at the first 15 minutes of the MP after angioplasty but before stenting. A decline in distal pressure was immediately detected by means of a dual-sensor guidewire kept distal to the reopened segment, and TIMI grade 3 flow was immediately reestablished by angioplasty with a 1.5-mm balloon inflated at nominal pressure before the patient developed chest pain. The MP was completed in all patients in accordance with the protocol without any problems.

Peak troponin T (5395±2991 ng/mL versus 8874±1927 ng/mL, *P*=0.006) and CK-MB (163.6±93.4 IU/L versus 542.2±227.4 IU/L, *P*<0.001) values were significantly lower in the PCRDS group than in the IS group (Table 1).

Assessment of Microcirculation

Distal Intracoronary Pressure Values Throughout a 1-Hour MP

Mean resting pressures distal to the intervention site immediately after reperfusion initiated with angioplasty by a 1.5-mm balloon in the PCRDS group and with angioplasty and prompt stenting in the IS group were 69.50±9.62 mm Hg and 89.50±8.94 mm Hg, respectively, (*P*<0.001). During

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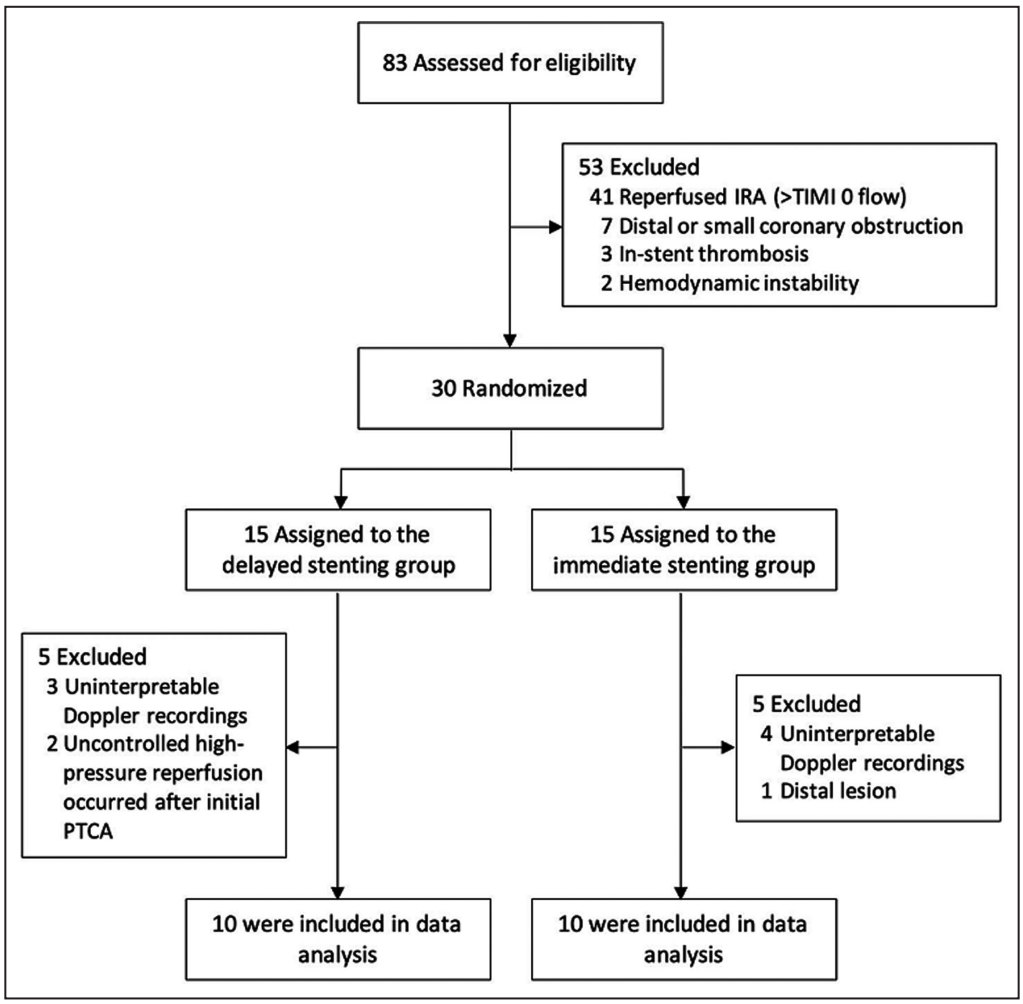


Figure 1. Assessment of eligibility, enrollment, randomization, and final groups.
IRA indicates infarct-related artery; PTCA, percutaneous transluminal coronary angioplasty; and TIMI, thrombosis in my-ocardial infarction.

the first 30 minutes of the MP, resting P_d remained significantly lower in the PCRDS group than in the IS group at all prespecified timepoints. Resting distal pressures became comparable between the 2 groups after stenting performed at the 30th minute in the PCRDS group (Figure 2A and Table 2). Reperfusion began with a mean hyperemic distal pressure of 61.70±13.80 mm Hg in the PCRDS group and with 82.00±7.28 mm Hg in the IS group (P=0.001). In the PCRDS group, hyperemic P_d remained significantly lower at all prespecified timepoints when measurements were performed during the first 30 minutes of the MP than in the IS group. After stenting performed at the 30th minute in the PCRDS group, distal hyperemic pressures became comparable between the 2 groups (Figure 2B and Table 2). Aortic pressures remained stable and comparable in the 2 groups throughout the procedure.

Time Course of Arteriolar and Epicardial Resistance After Reperfusion

In the IS group, ARI measured immediately after full-pressure reperfusion was 0.10±0.51 mm Hg.cm^{-1}.s, indicating exhausted coronary autoregulation when stenting was performed (Figure 3A). In the PCRDS group, coronary autoregulation was observed to be already recovered, as evidenced by a significantly increased ARI, when full-pressure reperfusion was initiated by stenting at 30 minutes after establishing initial reperfusion (Figure 3A, Table 2). Although ARI increased immediately after reperfusion in both groups, it was significantly higher in the PCRDS arm throughout the period beginning from establishment of full-pressure reperfusion (1.11±0.37 versus 0.62±0.75, P=0.048) until the end of the 60-minute MP (1.16±0.46 versus 0.58±0.49, P=0.015), which indicated markedly better arteriolar protection of microcirculation in this group of patients (Table 2). In the first 30 minutes

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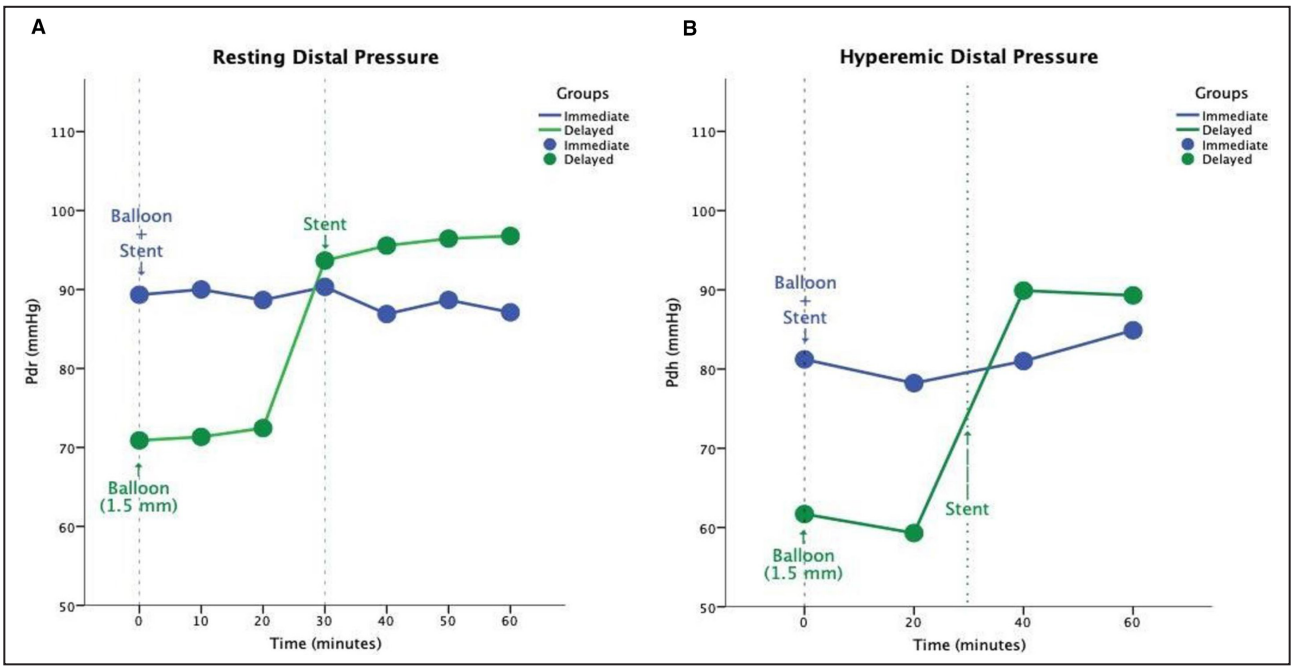


Figure 2. Time course of the mean resting (Pd_r) (A) and hyperemic (B) distal pressure (Pd_h) values (mm Hg) recorded distal to the intervention site in the delayed (pressure-controlled reperfusion with delayed stenting [PCRDS]) and immediate stenting (IS) groups.
In each group, initial measurements were performed immediately after establishing reperfusion. Thereafter, resting pressures were recorded at every 10th minute and hyperemic pressures were recorded at every 20th minute throughout a 1-hour monitoring period. Mean initial reperfusion pressure was ≈90 mm Hg in the IS and 70 mm Hg in the PCRDS groups (**A**).

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of MP, before recovery of autoregulation, baseline stenosis resistance remained significantly higher (high enough to protect microcirculation from overpressurization and low enough not to produce ischemia) in the PCRDS than in the IS group. After stent implantation in the PCRDS group at the 30th minute, the difference in baseline stenosis resistance between the groups disappeared (Figure 3B, Table 2).

Time Course of Microvascular Resistance and Coronary Flow After Reperfusion

In both groups, following the initial postocclusive reactive increase, a progressive decrease was observed in resting APV values during first 30 minutes of the MP. Notably, resting APV values were comparable between the 2 groups during the first 30 minutes of the MP despite remaining residual stenosis in the PCRDS group (Table 2, Figure S3A). In accordance with these findings, a steep increase was observed in baseline microvascular resistance during the first 30 minutes of reperfusion in both groups and, thereafter, a steady state stabilization occurred (Figure 4A).
In the IS group, a progressive increase in hMR (Figure 4B) and a corresponding progressive decrease in APV_h (Figure S3B) were observed throughout the 1-hour MP. In the PCRDS group, APV_h remained relatively stable until stenting was performed at 30 minutes (Table 2, Figure S3B). A transient but significant increase in hMR and a corresponding decrease in APV_h were observed after stenting in the PCRDS group (Figure 4B, Table 2). However, at the end of the 1-hour MP, hMR was significantly lower and APV_h was significantly higher in the PCRDS group than in the IS group (2.83±0.56 mm Hg.s.cm^{-1} versus 1.83±0.53 mm Hg.s.cm^{-1}, P=0.001) (Table 2, Figure S4). Effects of potential confounders (pain-to-balloon time [P=0.743] and culprit artery [P=0.774]) on hMR measured at 1 hour were not significant in univariate ANOVA.

Time Course of Pzf Values After Reperfusion

In the IS group, a progressive and significant increase was observed in Pzf over the 1-hour MP. In the PCRDS group, although an insignificant increase was observed in Pzf following stenting performed at 30 minutes, it then decreased significantly between 40 and 60 minutes. At the end of the 1-hour MP, Pzf was significantly lower in the PCRDS group than in the IS group (41.46±17.85 mm Hg versus 76.87±21.34 mm Hg, P=0.001) (Figure 5A and 5B, Table 2). In univariate ANOVA, the effects of potential confounders (pain-to-balloon time [P=0.873] and culprit artery [P=0.791]) on Pzf measured at 1 hour were not significant.

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Table 2. Intracoronary Hemodynamic Measurement Performed in the Pressure-Controlled Reperfusion With IS and PCRDS Arms During the First Hour of Reperfusion

		Initial	10th min	20th min	30th min	40th min	50th min	60th min
Resting P_d, mm Hg	IS	89.50±8.94	90.90±14.30	90.00±13.10	90.90±11.92	88.19±8.63	88.50±11.83	88.20±14.21
	PCRDS	69.50±9.62	70.10±9.07	74.00±9.42	94.80±10.50	95.55±10.23	96.44±14.21	97.50±12.14
	P	<0.001	0.001	0.006	0.45	0.31	0.23	0.133
Hyperemic P_d, mm Hg	IS	82.00±7.28		80.00±11.61		82.70±12.73		84.89±11.01
	PCRDS	61.70±13.80		59.30±8.15		89.90±15.07		89.30±12.63
	P	0.001		<0.001		0.26		0.431
APV_r, cm/s	IS	43.60±12.50	35.90±10.48	30.40±11.76	28.50±9.25	29.20±9.75	29.33±5.80	28.8±4.18
	PCRDS	41.10±10.97	37.30±10.16	34.70±6.44	30.20±5.78	32.11±8.49	32.60±5.33	33.60±5.81
	P	0.64	0.765	0.32	0.63	0.46	0.089	0.049
APV_h, cm/s	IS	44.40±12.42		35.20±9.93		32.70±7.49		30.30±5.27
	PCRDS	43.20±18.42		44.50±14.34		40.50±9.87		49.70±16.26
	P	0.87		0.109		0.06		0.004
BSR, mm Hg.s.cm^{-1}	IS	0.06±0.05	0.20±0.23	0.11±0.13	0.13±0.13	0.16±0.14	0.127±0.11	0.11±0.10
	PCRDS	0.61±0.10	0.61±0.16	0.56±0.11	0.15±0.15	0.15±0.10	0.010±0.11	- 0.01±0.18
	P	<0.001	0.002	<0.001	0.67	0.79	0.029	0.217
HSR, mm Hg.s.cm^{-1}	IS	0.27±0.24		0.46±0.35		0.34±0.29		0.29±0.22
	PCRDS	1.13±0.63		1.12±0.41		0.15±0.29		0.21±0.23
	P	0.002		0.001		0.16		0.455
BMR, mm Hg.s.cm^{-1}	IS	2.25±0.83	2.79±1.12	3.51±1.91	3.57±1.26	3.44±0.73	3.43±0.75	3.45±0.67
	PCRDS	1.79±0.49	2.19±0.84	2.31±0.51	3.17±0.72	3.27±0.77	3.08±0.63	3.00±0.67
	P	0.150	0.192	0.074	0.39	0.62	0.278	0.155
ARI, mm Hg.s.cm^{-1}	IS	0.10±0.51		0.54±0.76		0.62±0.75		0.58±0.49
	PCRDS	−0.03±0.54		0.77±0.42		1.11±0.37		1.16±0.46
	P	0.57		0.428		0.048		0.015
hMR, mm Hg.s.cm^{-1}	IS	2.15±0.79		2.56±0.87		2.82±0.94		2.83±0.56
	PCRDS	1.82±0.56		1.62±0.36		2.36±0.71		1.83±0.53
	P	0.31		0.008		0.23		0.001
Pzf, mm Hg	IS	53.43±17.07		58.46±16.04		66.76±14.07		76.87±21.34
	PCRDS	52.59±8.39		49.70±14.71		57.03±18.59		41.46±17.85
	P	0.89		0.219		0.21		0.001

APV_h indicates hyperemic average peak velocity; APV_r, resting average peak velocity; ARI, arteriolar resistance index; BMR, baseline microvascular resistance; BSR, baseline stenosis resistance; hMR, hyperemic microvascular resistance; HSR, hyperemic stenosis resistance; IS, immediate stenting; PCRDS, pressure-controlled reperfusion with delayed stenting; P_d, distal pressure; and Pzf, zero flow pressure.

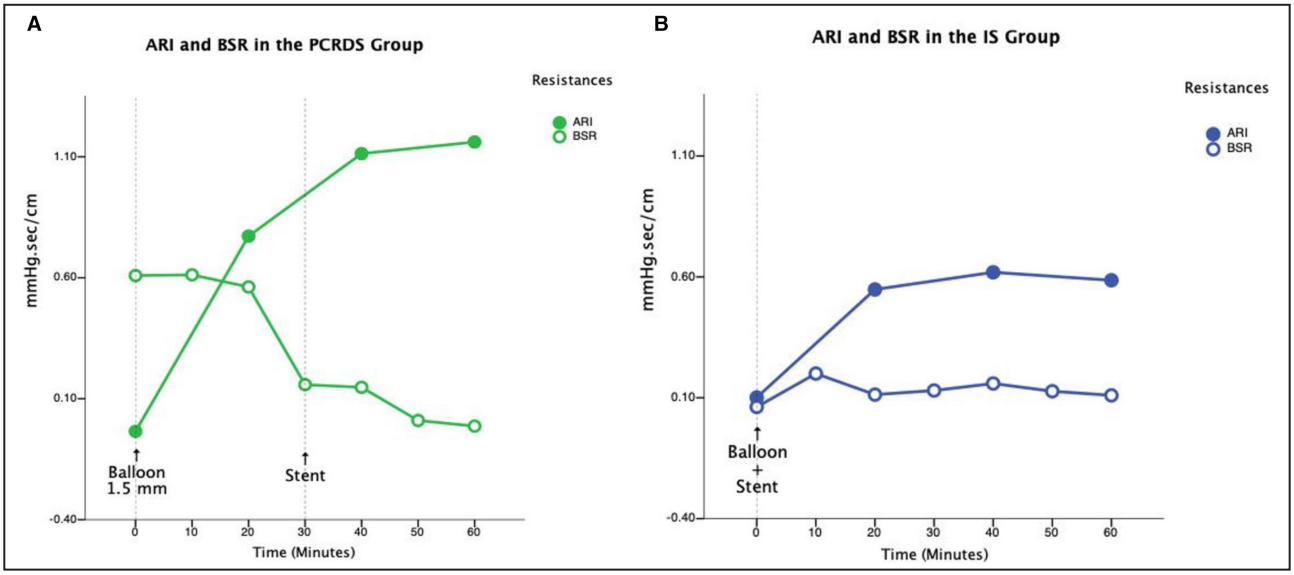


Figure 3. Time course of the arteriolar resistance in relation to changes in stenosis resistance in PCRDS and IS groups.
A, In the delayed stenting group (pressure-controlled reperfusion with delayed stenting [PCRDS], green lines), complete distal repressurization was established at 30 minutes after reperfusion by the time the arteriolar resistance index (ARI) was close to its highest value, which indicates almost totally recovered autoregulation. In the PCRDS group, mean baseline stenosis resistance (BSR) values were high enough to protect distal microcirculation from the overpressurization after initial balloon angioplasty until the ARI was recovered but low enough not to produce ischemia. **B**, In the immediate stenting (IS) group (blue lines), reperfusion pressure was completely and abruptly reestablished by stenting at the beginning of the reperfusion by the time ARI value was ≈0, which indicated totally exhausted autoregulation. BSR values became comparable between the 2 arms after stenting was performed in the delayed arm at 30 minutes.

Relationship Between Reperfusion Pressure Values in the Early Reperfusion Period and Pzf Measured at the End of the 1-Hour MP

Overall data combining both groups (n=20) showed robust associations between reperfusion pressures measured at the predefined stages in the early reperfusion period and Pzf values measured at the end of the 1-hour MP (immediately after reperfusion: r=0.782, P<0.001; at the 10th minute: r=0.796, P<0.001; and at the 20th minute: r=0.702, P=0.001) (Figure 6A).

Relationship Between Reperfusion Pressure Values in the Early Reperfusion Period and Postmyocardial Infarction Peak CK-MB Levels

Likewise, in the whole data set combining both groups (n=20), there were significant correlations between resting distal coronary pressure values (reperfusion pressures) measured at the predefined stages in the early reperfusion period and peak CK-MB levels (immediately after reperfusion: r=0.653, P=0.002; at the 10th minute: r=0.597, P=0.007; and at the 20th minute: r=0.538; P=0.017) (Figure 6B).

DISCUSSION

In this pilot trial, we found that mechanically modulated myocardial reperfusion by stepwise reopening of the occluded IRA in STEMI was associated with significantly better preserved coronary microvascular perfusion and lower peak enzyme estimates of infarct size, compared with standard IS. We also obtained valuable insights on the temporal course of coronary hemodynamics in the first hour after successful pPCI. In this respect, our results revealed a progressive deterioration in microvascular perfusion in patients undergoing pPCI as per standard practice. These in vivo observations provide new evidence, obtained from the standpoint of coronary hemodynamics, on the development of microvascular injury associated with coronary reperfusion in patients with STEMI.

Microvascular injury associated with reperfusion constitutes one of the unmet needs in the management of patients with STEMI. There is ample evidence that this phenomenon, which occurs in up to 40% of patients undergoing successful pPCI, has major long-term prognostic implications.[1,2,15,16] Experimental models have revealed that the cardiac magnetic resonance (CMR) imaging findings correlating microvascular injury and obstruction is predominantly formed by

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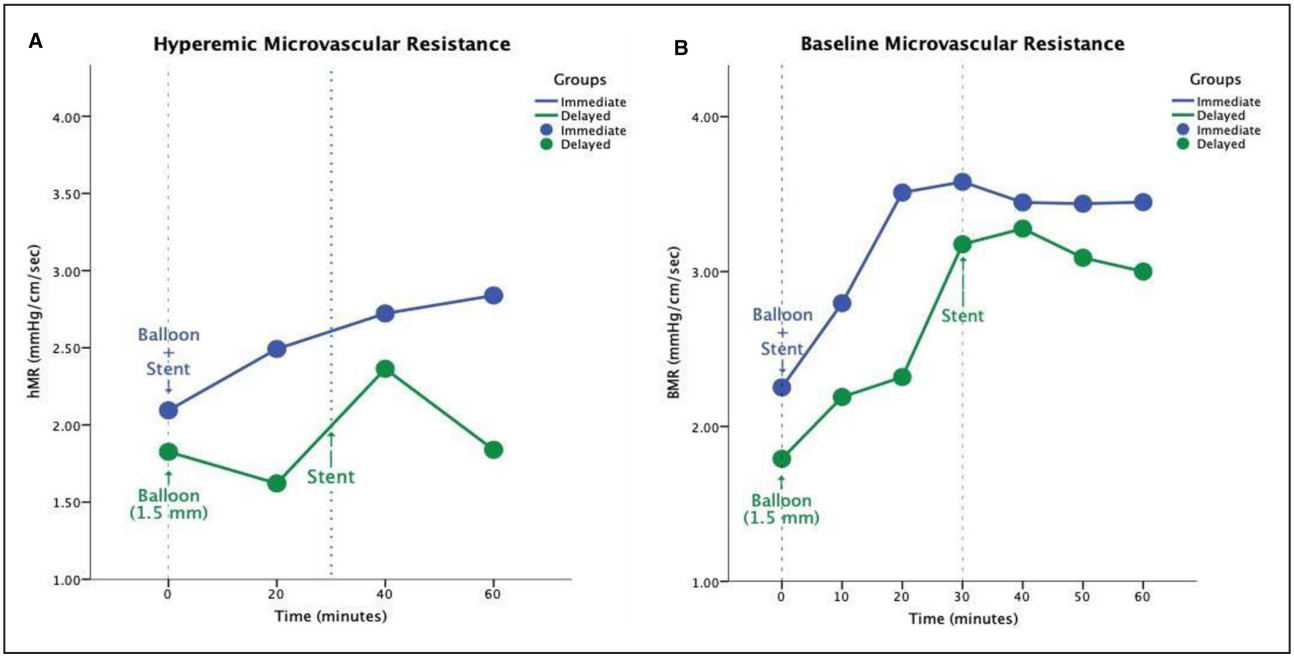


Figure 4. Temporal course of the baseline (resting) microvascular resistance (BMR) and hyperemic microvascular resistance (hMR) values during a 1-hour monitoring period (MP) after reperfusion.
A, Seven BMR values were measured with 10-minute intervals beginning from the initial reperfusion until the end of the 1-hour MP in the delayed (pressure-controlled reperfusion with delayed stenting [PCRDS]) and immediate stenting (IS) groups. In the IS group, when full-pressure reperfusion was established by stenting, the BMR value was at its lowest level. However, in the PCRDS group, the BMR value was close to its highest value when stenting was performed at the 30th minute of reperfusion (**B**) Four hMR values were measured with 20-minute intervals beginning from initial reperfusion until the end of the 1-hour MP in the PCRDS and IS groups. A progressive increase in hMR is seen in the IS group.

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erythrocyte extravasation with microvascular destruction[17] and not by intraluminal obstruction by thrombi. The latter finding explains why strategies aimed to prevent microembolization during pPCI fail in demonstrating clinical benefit in randomized trials.[3–5]

The rationale of performing controlled-pressure reperfusion of the IRA in patients with STEMI, aimed to preserve microvascular integrity, stems from previous research on the sequence of events associated with myocardial reperfusion injury. Arteriolar function downstream the occluded IRA, which controls myocardial blood flow by modulating microvascular resistance and protects the capillary network from excessive intraluminal pressure, is transiently lost (arteriolar stunning).[18,19] At the same time, capillary endothelium becomes vulnerable, fragile, and permeable because of hypoxia-induced damage.[12,13] Concurrently, venous drainage of the microcirculation can be blocked as a result of vascular insult caused by intraluminal microvascular obstruction and by free radicals generated during hypoxia. In the specific milieu described, the sudden and substantial rise in intraluminal pressure associated with abrupt coronary reopening[20] may be followed by the development of intramyocardial edema and hemorrhage formation. Of key importance for the treatment strategy of controlled reperfusion, myocardial blood flow in the area at risk is stabilized within ≈30 minutes of reopening the occluded coronary artery.[21,22] This implies that, in spite of an initial ischemic insult, coronary autoregulation in the reperfused myocardial territory might recover over 30 minutes after reperfusion starts. The treatment strategy tested in our trial aimed at protecting the coronary microcirculation from pressure overload until the above-described recovery of arteriolar control had taken place. Our approach is supported by experimental data in animal models showing that a gradual increase in intracoronary pressure at the time of initial reperfusion was associated with strikingly less interstitial edema and better ventricular function, as compared with abrupt and full-pressure myocardial reperfusion.[23]

The first set of observations made in the 2 arms of our study are aligned with the pathophysiological sequence outlined above. As Figures 3 and 4A show, in patients with STEMI, arteriolar resistance and baseline microcirculatory resistance shift in a significant manner over the next hour following vessel reopening, being lowest at the beginning and maximal at 30 to 40 minutes after reperfusion (increasing by 6 times for ARI and 1.9 times for baseline stenosis resistance, on average). The figures show the entirely different resistive environment in which full-pressure reperfusion took place

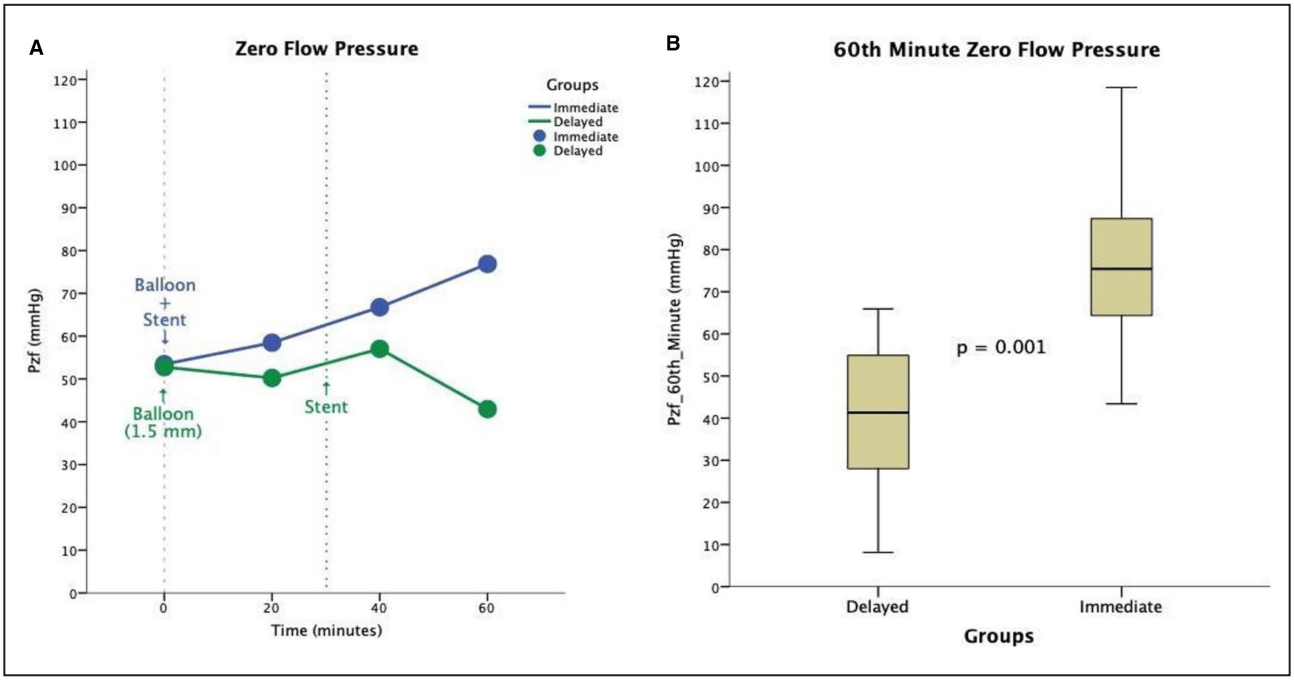


Figure 5. Temporal course of zero-flow pressure (Pzf) during a 1-hour monitoring period (MP) after reperfusion.
A, Four Pzf values were calculated 20 minutes apart beginning from initial reperfusion until the end of the 1-hour MP in the delayed (pressure-controlled reperfusion with delayed stenting [PCRDS]) and immediate stenting (IS) groups. In the IS arm, progressively increased Pzf values indicate progressively evolved external compression on microcirculation in this group of patients. (**B**) Comparison of the mean Pzf values at the end of the 1-hour MP between the study groups.

in the 2 treatment strategies: over the most vulnerable period (denoted by low ARI [Figure 3A] and baseline microvascular resistance [Figure 4A]), mean intracoronary pressure reached 90 mm Hg in the IS group, while it was kept below 75 mm Hg in the PCRDS group (Figure 2A). The second set of observations refers to the consequences of performing full-pressure reperfusion in the scenarios of impaired or recovered arteriolar control. After pPCI, the initial peak of edema associated with initial overperfusion (hyperfiltration) seems to occur rapidly, with IMH in 30% to 45% of patients with STEMI undergoing reperfusion.[24] Interstitial hemorrhage heralds the development of no-reflow perfusion defects, as shown in an animal model.[17,25,26] Critically, both edema and IMH may, in turn, decrease myocardial blood flow by creating an external compressive force on capillaries via increasing intramyocardial interstitial pressure.[11,27,28] As revealed in the above-mentioned experimental study,[23] initial reperfusion pressure is the main determinant of the myocardial edema developing after reperfusion. In our study, since we primarily aimed to limit the initial wave of edema and consequent IMH by modulating initial reperfusion pressure, Pzf was chosen as the primary end point. Because, first, from a conceptual standpoint, Pzf is the index that should better integrate the pathophysiological consequences of the process discussed above, which ultimately include IMH and edema exerting extravascular compression over collapsible elements of microcirculation (capillaries and venules)[28,29]; and, second, because previous studies have identified Pzf as an optimal index to establish the magnitude of microvascular injury after pPCI.[30,31] In patients undergoing PCRDS, values of measures of microvascular integrity (hyperemic coronary flow and microvascular resistance) displayed a rather stable course and were lower at all time points than in the IS group, which implies better-preserved microvascular structural integrity. However, we found that the IS strategy was associated with a steady increase of Pzf, potentially reflecting a time-dependent evolution of microvascular compression resulting from the above-described mechanisms (Figure 5A). Notably, in the whole study population (n=20), reperfusion pressure values measured at prespecified stages during the early reperfusion period (first 30 minutes of reperfusion) displayed robust associations with Pzf measured at 60 minutes and peak CK-MB levels (Figure 6). These findings strongly imply that, during pPCI, the magnitude of distal intracoronary repressurization in early reperfusion steps can be a pivotal determinant of microvascular integrity (Figure 7) and final infarct size and, therefore, modulation of distal reperfusion pressure with PCDRS may result in significantly improved patient outcome in the long term.

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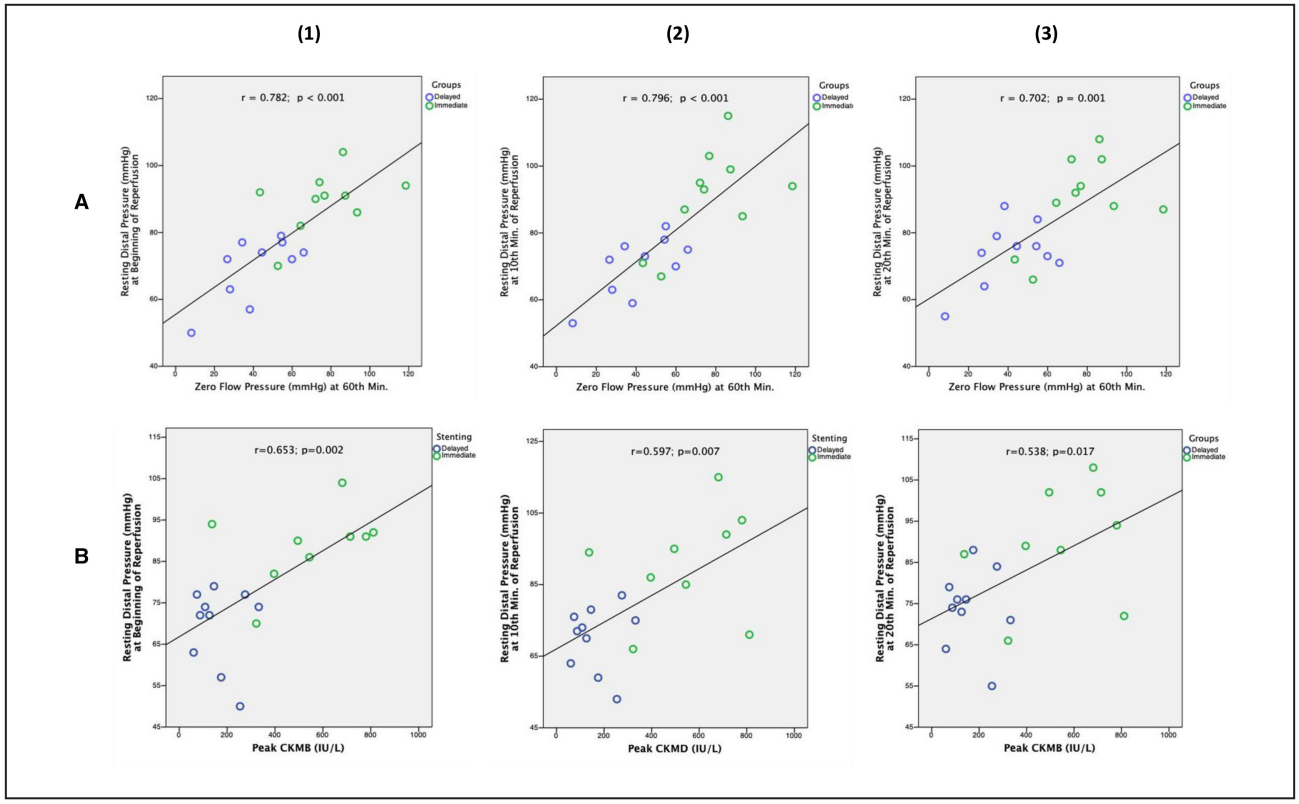


Figure 6. The relationship between initial reperfusion pressure (distal intracoronary pressure at the beginning of reperfusion) and zero flow pressure measured at the end of the 1-hour MP (primary endpoint) and peak CKMB values.
A, Correlations between resting distal intracoronary pressure values (reperfusion pressure) in the early reperfusion period: (1) immediately after reperfusion, (2) at the 10th minute, and (3) at the 20th minute after reperfusion; and zero flow pressure (Pzf) measured at the 60th minute of reperfusion in the study groups. **B**, Correlations between reperfusion pressure values in the early reperfusion period: (1) immediately after reperfusion, (2) at the 10th minute, and (3) at the 20th minute after reperfusion; and peak creatine kinase MB (CK-MB) levels.

The described pathophysiology mirrors extracardiac conditions, such as intracerebral hemorrhage after stenting of high-grade carotid stenosis,[32,33] compartment syndrome after abrupt reopening of the occluded limb arteries,[34,35] and pulmonary edema developing after pulmonary angioplasty performed for chronic thromboembolic pulmonary hypertension.[36] Most likely, these clinical scenarios share some background mechanisms with myocardial edema and IMH developing after abrupt reopening of the acutely occluded IRA. As a matter of fact, and similar to that proposed in our study, pressure-controlled or low-pressure reperfusion has also been shown to be beneficial in coronary artery bypass grafting,[37,38] solid organ transplantations,[39,40] pulmonary angioplasty for chronic thromboembolic pulmonary hypertension,[41] and in an acute cerebral ischemia model.[42]

Several limitations of our study should be noted. First, being a pilot trial, and because of the complexity of the study protocol, only 20 patients were enrolled. However, the robustness of the obtained data, sequentially acquired over the first hour of myocardial reperfusion with 2 treatment modalities, provide initial support to our hypothesis, supporting the design and launching of larger trials. Second, PCI operators could not be blinded to which arm patients were allocated. This could have potentially led to investigator bias. Third, CMR imaging was not performed as part of the study. However, the focus of our research was the temporal evolution of coronary hemodynamics over the 1 hour after reperfusion and this could not be addressed using CMR imaging. Fourth, although pressure-controlled (low pressure) reperfusion delivered under 70 mm Hg of distal perfusion pressure in the PCRDS group was shown to be associated with better microvascular protection than full-pressure reperfusion established immediately by standard pPCI, the value for distal perfusion pressure, which would be optimal for protecting capillaries from overpressurization without leading to re-ischemia remains unknown. Fifth, the degree of control over distal perfusion pressure provided by a small PCI balloon might be suboptimal; in future studies, better control of distal pressure may

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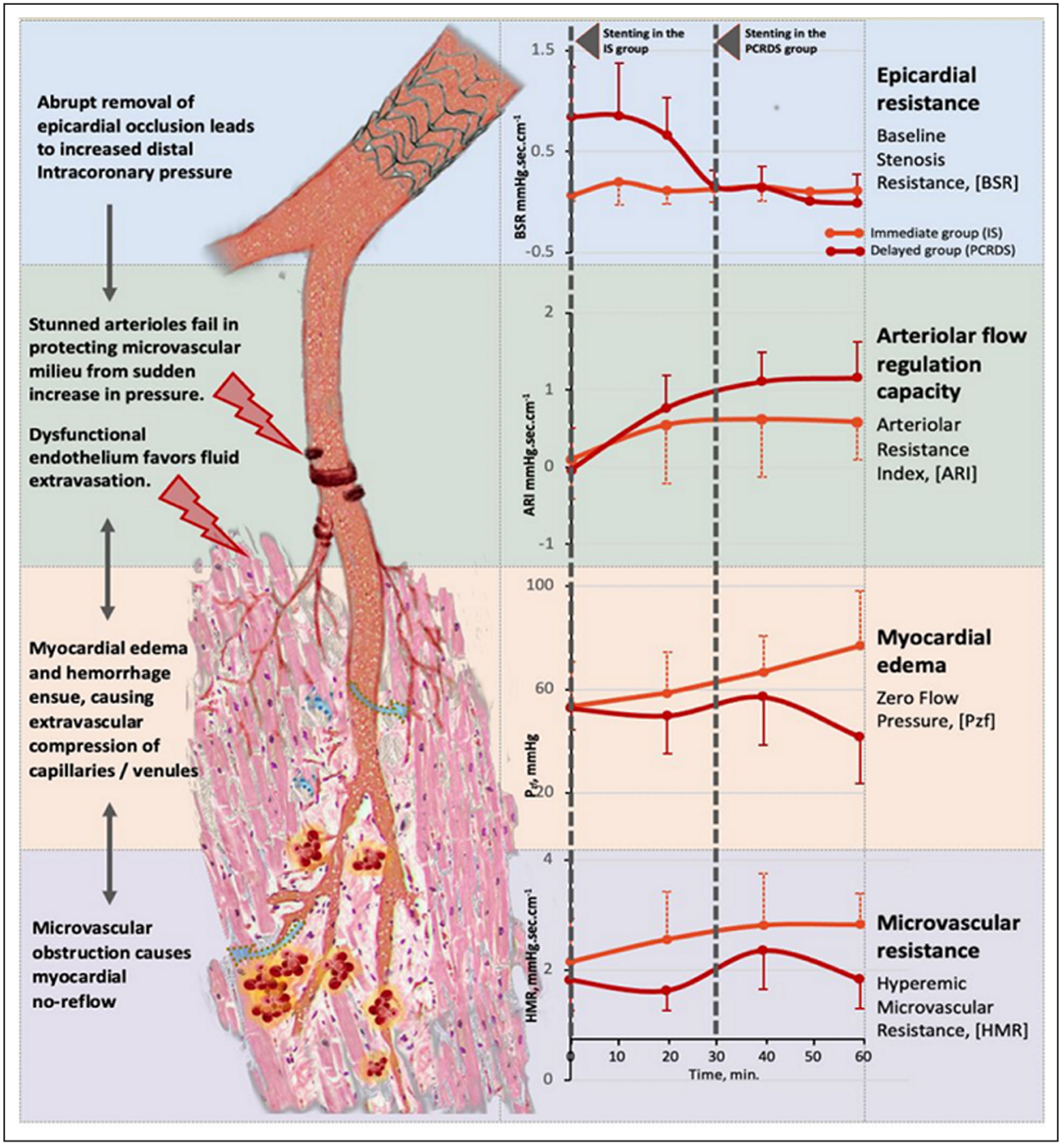


Figure 7. Coronary microcirculatory response to different myocardial reperfusion strategies: (1) immediate stenting (IS), and (2) pressure-controlled reperfusion with direct stenting (PCRDS).

be obtained with more sophisticated mechanical devices, which remains to be developed. Last, we used the peak values of cardiac enzymes to estimate final infarct size. Although high correlations were shown between peak level of troponin and CK-MB with single-photon emission computed tomographic infarct size (r>0.70),[43,44] scintigraphic infarct size remains a better correlate of 1-year mortality than either biomarker.[44] In addition, we were not able to show reflections of improved microvasculature on cardiac function by CMR imaging or echocardiography. This is a single-center study and unfortunately our center is not capable of performing CMR. Although echocardiographic evaluation was performed routinely in all patients and showed slightly better ejection fraction in the PCRDS group as compared with the IS group (P<0.05), we did not

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provide these data, which may be misleading, considering the limited number of patients included in this pilot study.

In conclusion, in patients with STEMI, abrupt reopening of the occluded IRA may paradoxically aggravate microvascular injury in patients undergoing pPCI. Immediate reconstitution of coronary blood flow by pPCI performed as per standard practice was associated with a progressive deterioration of the microvascular perfusion over the course of a 1-hour MP. Mechanical modulation of reperfusion pressure with delayed stenting was associated with significantly better-preserved microvascular integrity, as compared with standard pPCI. Modulation of initial reperfusion pressure might, therefore, prove to be a promising reperfusion strategy in order to limit vascular reperfusion injury.

ARTICLE INFORMATION

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Affiliations

Department of Cardiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey (M.S., B.U., Z.B., M.R.S., A.O., A.A., S.U.); Acibadem International Hospital, Istanbul, Turkey (M.S.); Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos, Universidad Complutense de Madrid, Madrid, Spain (J.E.); The Prince Charles Hospital, Chermside, Brisbane, Australia (C.J.B.); Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (I.O.); Marmara University, School of Medicine, Istanbul, Turkey (E.A.); Acibadem Atakent Hastanesi, Halkali, Istanbul, Turkey (Z.I.S.); Hammersmith Hospital, Imperial College London, London, United Kingdom (J.E.D.); and Radboud University Medical Center, Nijmegen, Netherlands (N.v.R.).

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Disclosures

None.

Supplemental Material

Figures S1–S4

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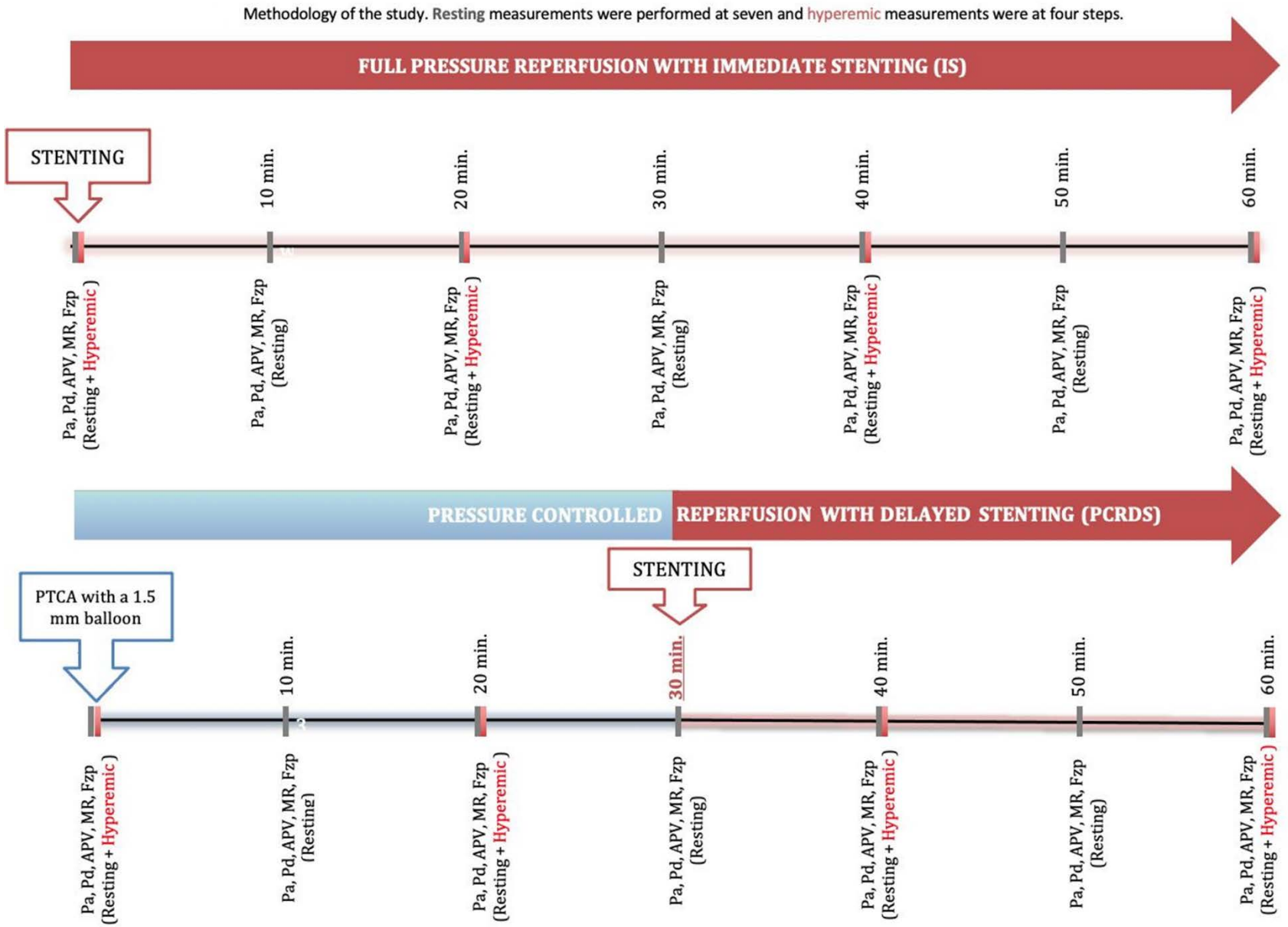
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Supplemental Material

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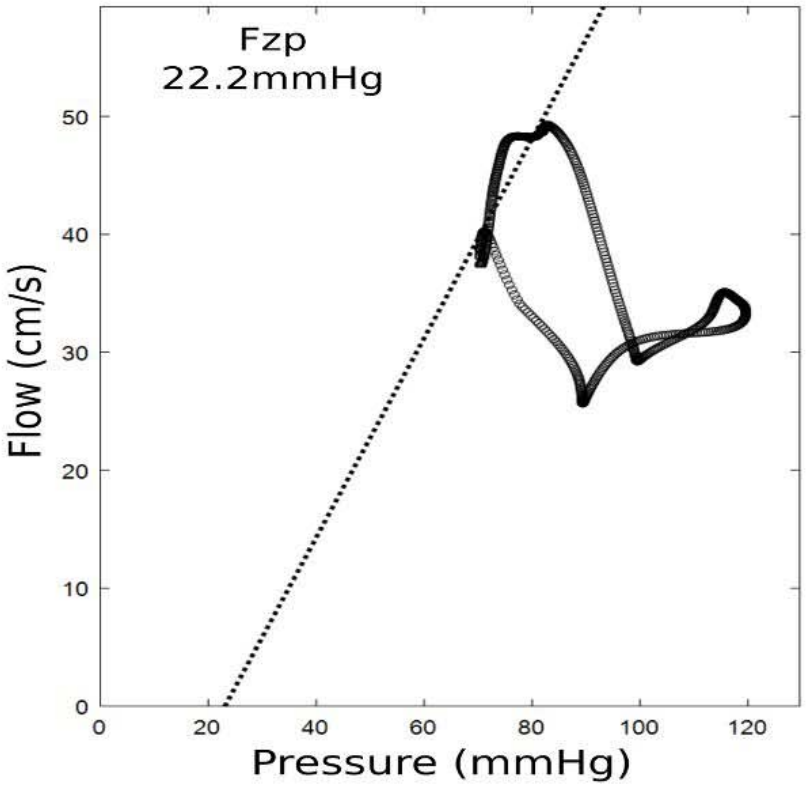
Figure S1. Hemodynamic measurements made at prespecified time points during the 1-hour MP in patients undergoing full pressure (IS) and controlled-pressure (PCRDS) reperfusion.



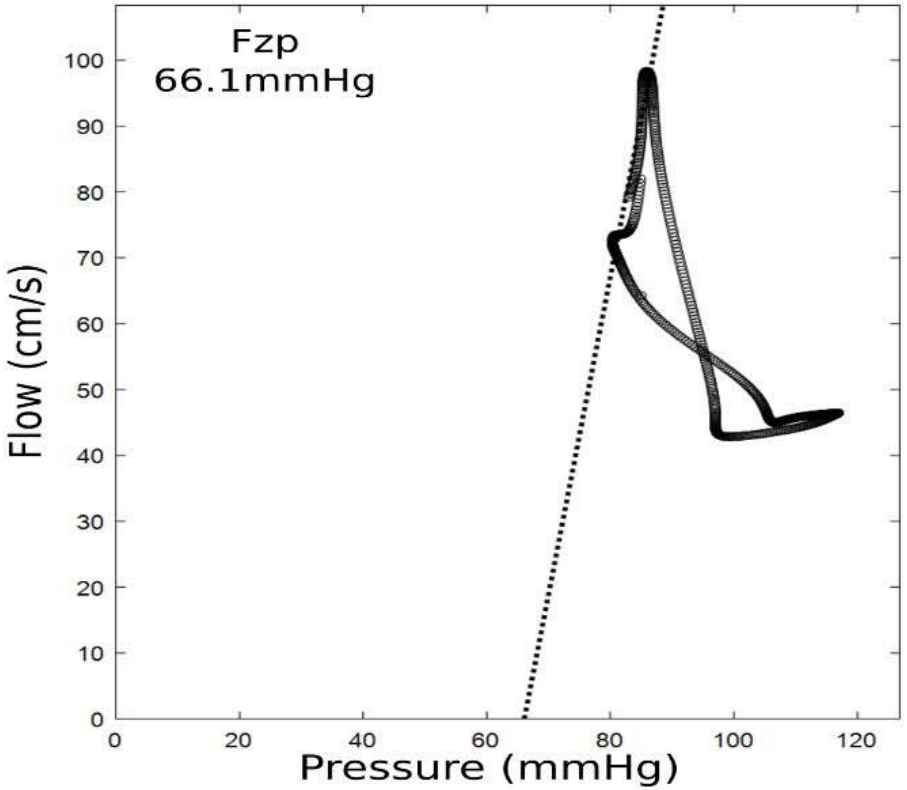
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Figure S2. Examples of zero flow pressure (Fzp) calculated in patients who randomized in PCRDS (22.2 mmHg) and in IS (66.1 mmHg) groups.

DELAYED STENTING



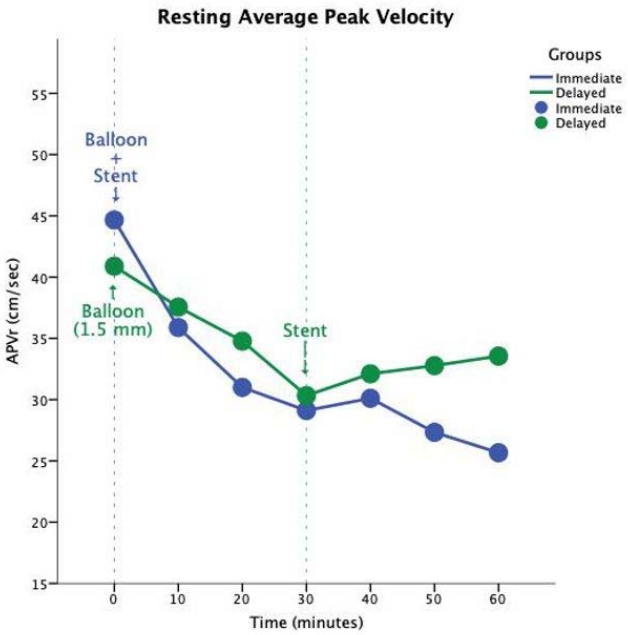
IMMEDIATE STENTING



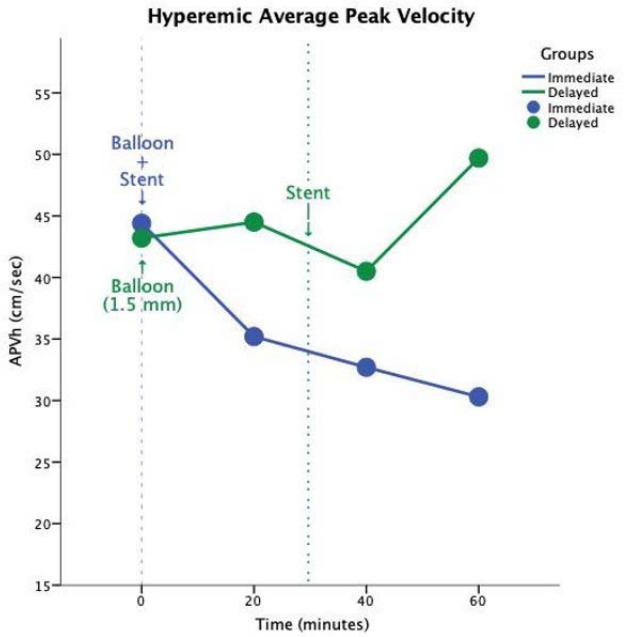
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Figure S3. Time course of the resting and hyperemic average peak velocity (APV) in PCRDS and IS groups during 1-hour MP.

(a)

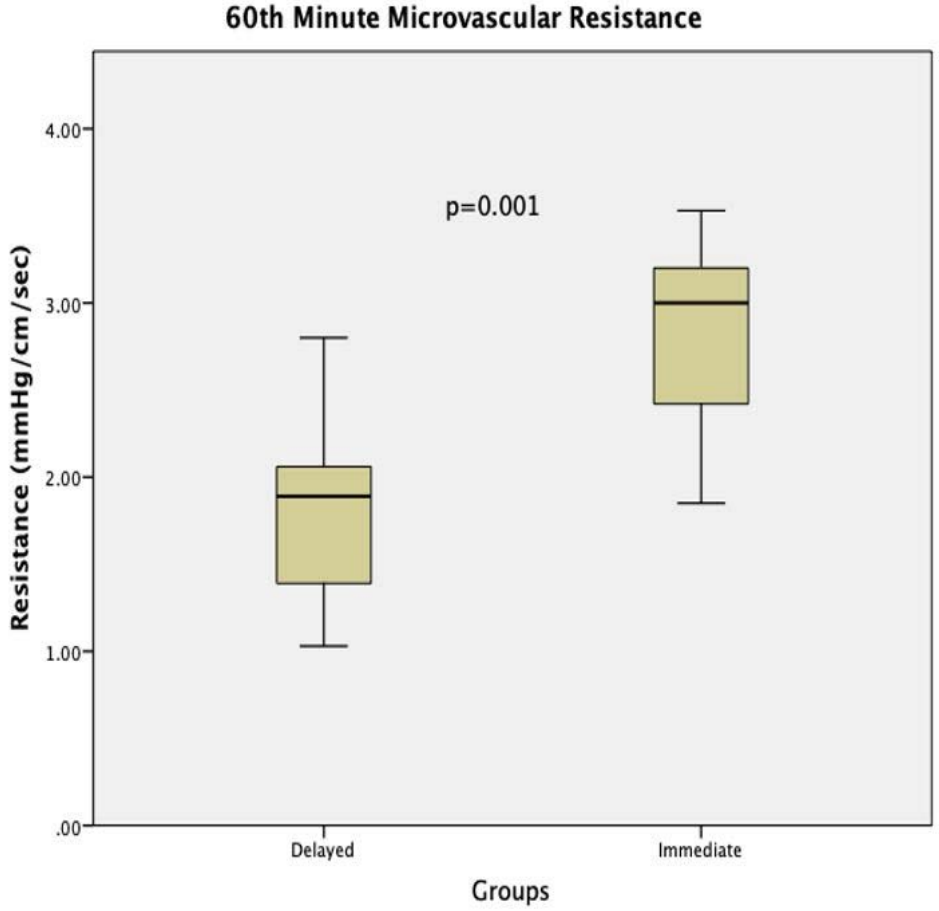


(b)



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Figure S4. Hyperemic microvascular resistance (hMR) measured at the end of the 1-hour MP in patients undergoing PCRDS and IS.



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