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Research Article

In Acute ST-Segment Elevation Myocardial Infarction, Coronary Wedge Pressure Is Associated with Infarct Size and Reperfusion Injury as Evaluated by Cardiac Magnetic Resonance Imaging

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Background. Coronary collateral flow influences patient prognosis in the setting of acute myocardial infarction. However, few data exist about the relation between coronary collaterals, infarct size, and reperfusion injury. The angiographic Rentrop score is prone to subjectivism and to the inherent limitations of angiographic images. Its prognostic value is controversial in the setting of acute myocardial infarction. The invasive measurement of coronary wedge pressure (CWP) represents an alternative to Rentrop score for the evaluation of coronary collateralization. Our study evaluates pre-revascularization CWP as a predictor of infarct size and reperfusion injury as evaluated by cardiac magnetic resonance imaging. *Methods*. Patients with acute ST-elevation myocardial infarction underwent preprocedural CWP measurement and primary percutaneous coronary intervention. Infarct size, microvascular obstruction, intramyocardial edema, and intramyocardial hemorrhage were evaluated by cardiac magnetic resonance imaging. *Results*. Mean CWP was inversely associated with infarct size ($p = 0.01$), microvascular obstruction ($p = 0.02$), intramyocardial edema ($p = 0.05$), and intramyocardial hemorrhage ($p = 0.01$). An excellent association was found between mean CWP and an infarct size ≥24% of left ventricular mass (AUC = 0.880, $p = 0.007$), with an optimal cutoff value ≤24.5 mmHg. Both intramyocardial edema ($p = 0.02$) and hemorrhage ($p = 0.03$) had a larger extent in patients with coronary wedge pressure ≤24.5 mmHg. Rentrop grade <2 was associated with larger infarct size ($p = 0.03$), but not with the extent of edema, microvascular obstruction, or intramyocardial hemorrhage. *Conclusions*. Pre-revascularization CWP was a predictor of infarct size and was significantly associated with a larger extent of intramyocardial edema and intramyocardial hemorrhage. Rentrop grade <2 was associated with a larger infarct size, but had no influence on reperfusion injury. The clinical trial is registered with NCT03371784.

1. Introduction

The long-term prognosis after an acute ST-segment elevation myocardial infarction (STEMI) is influenced by the extent of infarct size and reperfusion injury [1–3].

Infarct size depends on total ischemic time, on the debated presence and extent of collateralization, and on the development of microvascular obstruction (MVO) [3, 4]. The semiquantitative Rentrop angiographic grade is the most widely used method for the evaluation of coronary collateralization. However, it is prone to subjectivism and to the inherent limitations of an angiographic image. Its prognostic value is controversial in the setting of acute myocardial infarction [4–7]. An alternative to Rentrop

grading system is represented by the invasive measurement of coronary wedge pressure (CWP). CWP represents the distal coronary pressure when the vessel is completely occluded. A CWP value <25 mmHg was found in patients with complete absence of collateral flow, both in clinical and animal studies [8–10]. The absence of angiographic collateralization was reflected on the prognosis of patients with acute myocardial infarction [11]. Still, literature data is scarce about the exact relation between coronary collateral flow, infarct size, and reperfusion injury, as evaluated by cardiac magnetic resonance (CMR) imaging [2, 3]. An early, quantitative, and easily determined predictor of infarct size and reperfusion injury could open a much needed therapeutic window for intracoronary, cardioprotective therapies. CMR, the current gold standard in the evaluation of myocardial necrosis, MVO, intramyocardial edema, and intramyocardial hemorrhage (IMH) has the major disadvantage of being performed only days after the primary percutaneous coronary intervention (PCI), which reduces the chance for early intracoronary cardioprotection.

The aim of this study was to evaluate pre-revascularization CWP as a predictor of infarct size and reperfusion injury in patients with acute STEMI undergoing primary PCI.

2. Methods

This was a prospective, observational, single-center trial. During six months, consecutive patients referred for a first episode of acute STEMI were screened for inclusion. The inclusion criteria were typical ongoing ischemic pain ≤12 hours and ST-segment elevation in two contiguous electrocardiographic leads, according to the Fourth Universal Definition of Myocardial Infarction [11]. The exclusion criteria were previous myocardial infarction or coronary revascularization, left bundle branch block, thrombolysis, Killip class III or IV, active bleeding, or known contraindications for CMR. The research protocol was approved by the Local Ethics Committee and all patients gave written informed consent. The study protocol conformed to the principles outlined in the Declaration of Helsinki.

All patients underwent coronary angiography either through radial or femoral access. The culprit lesion was crossed with a pressure wire (Verrata Pressure Guide Wire, Volcano Corporation, San Diego, CA) and CWP was measured directly, distal to the lesion, if Thrombolysis in Myocardial Infarction (TIMI) flow remained 0. In the situation of initial TIMI >0 flow or in case of distal flow restoration following wire crossing, CWP was measured and recorded during balloon inflation. The rationale for the pre-revascularization CWP measurement was the exclusion of intraprocedural embolism, a process that leads to MVO and increases distal pressure values [5].

All the procedures were performed during normal working hours by experienced operators. A mean two-minute increase in procedural time was noticed because of CWP measurement.

Following CWP measurement, primary PCI was performed according to current practice. All patients underwent revascularization with drug-eluting stents and received double antiplatelet and anticoagulant therapy according to the most recent guidelines. Secondary prevention measures were applied in all cases as recommended by the current standard of care [12].

TIMI flow was evaluated at the beginning and at the end of the procedure. Angiographic collateralization grade was evaluated during the diagnostic injections as originally described by Rentrop [13].

Total ischemic time (TIT) was defined as the time from the onset of symptoms to balloon inflation.

High-sensitivity cardiac troponin T levels were determined at the time of admission and at 24 and 48 hours after reperfusion.

2.1. CMR Imaging. CMR was performed between three and seven days after the index event. Image acquisition was made on a 1.5 T scanner (Siemens Magnetom Avanto Tim) and comprised late gadolinium enhancement for the evaluation of infarct size and MVO and T2-weighted imaging for the assessment of edema and IMH. Left ventricular ejection fraction (LVEF), mass, and left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were also measured.

Complete details regarding CMR protocol are largely described in the Supplementary Materials (available here).

2.2. Statistical Methods. Data distribution was assessed using Kolmogorov–Smirnov and D'Agostino tests. Quantitative continuous data were summarized as mean ± standard deviation whenever data proved normally distributed; otherwise, median and interquartile range ($Q1$–$Q3$) were used. Groups were compared with Student's t-test, Mann–Whitney, or Wilcoxon rank-sum test, as appropriate. Categorical data were presented as percentages. Linear regressions were used to model the relation between variables of interest.

Receiver Operating Characteristic (ROC) curves were constructed to evaluate the association between CWP and CMR parameters. The area under the curve (AUC) was reported as a scalar measure of performance. The ROC curve analyses were performed with SPSS version 25.0 (IBM, Chicago, IL, USA).

All other statistical analyses were performed with MedCalc (v. 19.0.3, MedCalc Software, Ostend, Belgium). A two-sided p value <0.05 was considered statistically significant.

All authors had full access to all the data in the study. They all take responsibility for its integrity and for the data analysis.

3. Results

3.1. Patient Characteristics. A cohort of thirty-five patients was included in the analysis. Baseline patient characteristics are presented in Table 1. Left anterior descending coronary artery was the culprit vessel in 65.71% of patients. Pre-procedural TIMI 0 flow was observed in 48.57% of the cases,

Table 1: Clinical and angiographic patient characteristics.

Parameter	Value ($n = 35$)
Age (years), mean ± SD	60.11 ± 11.97
Males, n (%)	19 (54.28)
Smokers, n (%)	16 (45.71)
Arterial hypertension, n (%)	17 (48.57)
Diabetes mellitus, n (%)	11 (31.42)
Dyslipidemia, n (%)	9 (25.71)
BMI (kg/m^2), median ($Q1$–$Q3$)	26.59 (24.97–31.21)
Infarct localization, n (%)	
Anterior	23 (65.71)
Inferior	8 (22.85)
Lateral	2 (5.71)
Inferolateral	5 (14.28)
Total ischemic time (min), median ($Q1$–$Q3$)	300 (180–480)
CWP (mmHg), mean ± SD	31.02 ± 10.29
TIMI flow before the index procedure, n (%)	
0	17 (48.57)
1-2	7 (20)
3	12 (34.28)
TIMI flow at the end of the index procedure, n (%)	
0	0 (0)
1-2	9 (25.71)
3	26 (74.28)
Rentrop grade, n (%)	
0	17 (48.57)
1	11 (31.42)
2	5 (14.28)
3	2 (5.71)
Troponin T (ng/ml), median ($Q1$–$Q3$)	
Admission value	0.17 (0.08–0.36)
Peak value	2.57(1.86–3.88)

*BMI = body mass index; CWP = coronary wedge pressure; n = number; $Q1$ = 1st quartile; $Q3$ = 3rd quartile; SD = standard deviation; and TIMI = thrombolysis in myocardial infarction.

while at the end of the procedure, TIMI 3 flow was recorded in 74.28% of the study group.

3.2. CMR Findings in the Study Population. Evaluable myocardial edema on T2-weighted acquisitions was present in all patients, while MVO and IMH were detectable in 65.71% and 37.14% of them, respectively. Mean infarct size reached 14.57 ± 9.34% of LV mass. The CMR data is presented in Table 2.

Infarct size, MVO, intramyocardial edema, and IMH were each positively correlated with peak troponin T value ($r = 0.72$, $p < 0.001$ for infarct size, $r = 0.42$, $p = 0.02$ for MVO, $r = 0.45$, $p = 0.01$ for edema, and $r = 0.52$, $p = 0.004$ for IMH, resp.).

3.3. The Association between Mean CWP, CMR Parameters, and Angiographic Collateralization. On univariate linear regression analysis, mean CWP was inversely associated with infarct size ($r^2 = 0.18$, $p = 0.01$) (Figure 1(a)), MVO ($r^2 = 0.14$, $p = 0.02$), intramyocardial edema ($r^2 = 0.10$, $p = 0.05$) (Figure 1(b)), and IMH ($r^2 = 0.17$, $p = 0.01$), respectively. As expected, infarct size was positively associated with MVO ($r^2 = 0.34$, $p < 0.001$), intramyocardial edema ($r^2 = 0.57$, $p < 0.001$), and IMH ($r^2 = 0.35$, $p = 0.004$).

ROC curve analysis showed an excellent association between mean CWP and an infarct size ≥24% of LV mass (AUC = 0.880, $p = 0.007$) (Figure 2). A CWP cutoff value ≤24.5 mmHg could estimate infarct size with a sensitivity of 80% and a specificity of 89.7%.

Patients with Rentrop grade 0 or 1 had a significantly lower mean CWP value ($p = 0.05$) (Figure 3). Infarct size was two times greater in patients with Rentrop score 0 or 1 as compared to those with Rentrop score 2 or 3 (15.79 vs. 7.57%, $p = 0.03$) but the extent of MVO, edema, and IMH did not significantly differ between these two categories ($p = 0.57$, 0.47, and 0.86 resp.).

3.4. Group Comparison. Patients were divided into two groups based on the 24.5 mmHg mean CWP cutoff for the prediction of an infarct size ≥24% of LV mass. Infarct size was two times larger in the group with low CWP (22.32 ± 9.89 vs. 12.17 ± 7.90 %, $p = 0.005$), while the extent of MVO was more than twice the one measured in patients with CWP >24.5 mmHg ($p = 0.21$). Both IMH and edema had a significantly greater extent in patients with CWP ≤24.5 mmHg ($p = 0.03$ for IMH and 0.02 for edema, resp.) (Table 3).

At the multivariate linear regression analysis, however, infarct size was associated with intramyocardial edema independent of mean CWP value ($R^2 = 0.53$, $p < 0.001$). An increase of 1% in infarct size was associated with a 0.9 % increase in edema. The same observation was made for the association between infarct size and MVO or IMH. Infarct size was associated with MVO and IMH independent of mean CWP value ($R^2 = 0.35$, $p < 0.001$ and $R^2 = 0.37$, $p < 0.001$, resp.). An increase of 1% in infarct size was associated with a 0.24% increase in MVO, while an increase of 1% in infarct size was associated with a 0.07% increase in IMH.

4. Discussion

In this study, we investigated the relationship between prerevascularization CWP, angiographic collateral flow, and the CMR parameters of postmyocardial infarction prognosis: infarct size, MVO, intramyocardial edema, and IMH. Significant inverse associations were identified between mean CWP on one side and infarct size, MVO, intramyocardial edema, and IMH on the other. What is more, a CWP ≤24.5 mmHg predicted an infarct size ≥24% of LV mass with a sensitivity of 80% and a specificity of 89.7% and could differentiate patients with regard to the presence of intramyocardial edema and IMH. Both intramyocardial edema and IMH represent severe forms of MVO [2]. In a large meta-analysis, a 24% infarct size cutoff was demonstrated as a clinically useful parameter for the prediction of post-STEMI mortality [14]. Regarding CWP, the 24.5 mmHg calculated cutoff is close to the 25 mmHg value described by former clinical and experimental research as a limit for the absence of functional collaterals [8–10].

Table 2: CMR characteristics, three to seven days after the index procedure.

Parameter	Value ($n = 35$)
LVESV (ml), mean ± SD	75.42 ± 28.75
LVEDV (ml), mean ± SD	144.57 ± 40.16
LVEF (%), mean ± SD	48.69 ± 10.02
Left ventricular mass/BSA (g/m^2), mean ± SD	64.69 ± 14.21
Edema, *n* (%)	35 (100)
Edema (% of left ventricular mass), mean ± SD	30.81 ± 12.12
MVO, *n* (%)	23 (65.71)
MVO (% of left ventricular mass), median (*Q*1–*Q*3)	0.36 (0.00–1.57)
IMH, *n* (%)	13 (37.14)
IMH (% of left ventricular mass), median (*Q*1–*Q*3)	0.00 (0.00–0.57)
Necrosis, *n* (%)	35 (100)
Necrosis (% of left ventricular mass), mean ± SD	14.57 ± 9.34

*BSA = body surface area; IMH = intramyocardial hemorrhage; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MVO = microvascular obstruction; *n* = number; *Q*1 = 1st quartile; *Q*3 = 3rd quartile; and SD = standard deviation.

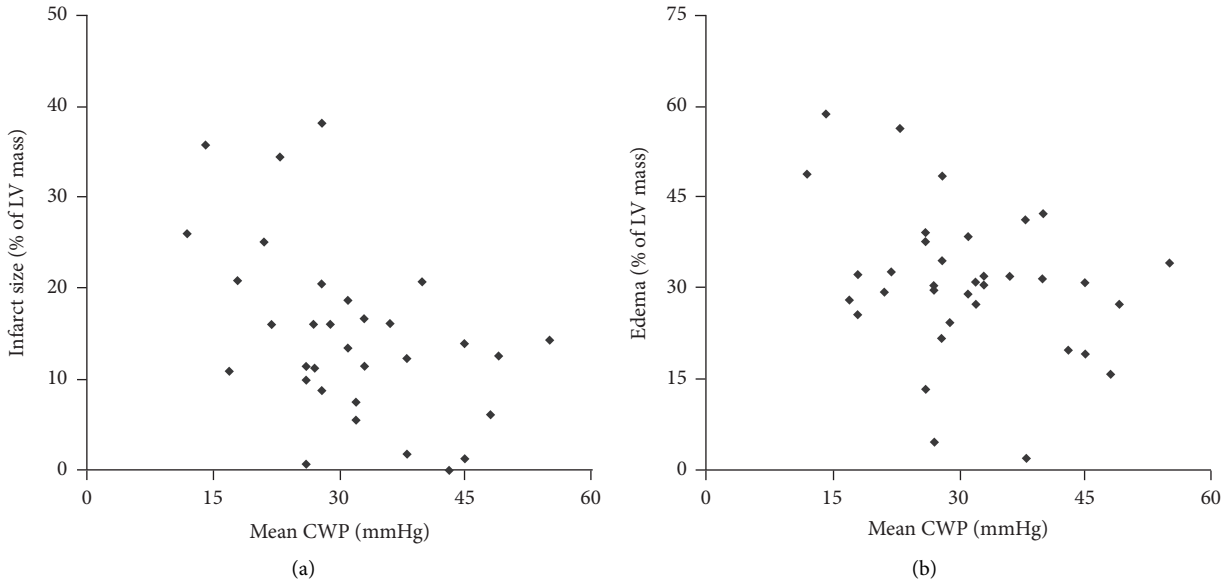

Figure 1: The association between mean CWP, infarct size, and intramyocardial edema. (a) An inverse, statistically significant association was identified between mean CWP and infarct size, expressed as percentage of left ventricular mass ($p = 0.01$). (b) An inverse, statistically significant association was identified between mean CWP and intramyocardial edema, expressed as percentage of left ventricular mass ($p = 0.05$). CWP = coronary wedge pressure and LV = left ventricle.

The extent of infarct size per se was associated with larger areas of edema and IMH, independent of mean CWP value. The most powerful association regarded intramyocardial edema, as each 1% increase in infarct size led to an almost 1% increase in the extent of edema. It has already been demonstrated that infarct size is significantly associated with the extent of MVO, intramyocardial edema, and IMH [15, 16]. Necrosis has a centrifuge extension in the myocardium, and its extension is directly associated with the dimensions of the area at risk. The need for collateral supply to the salvageable borders of the infarcted territory increases with the increase in myocardial edema. The larger the area of edema, the greater the required amount of collateral flow and diffusion supply from adjacent normally perfused areas. In the setting of a large area of edema, the contribution of collateral flow to limiting infarct size extension diminishes.

In our study, CWP proved to be a more powerful predictor of infarct size as compared to Rentrop grade, and it was also associated with reperfusion injury. A Rentrop grade <2 was associated with a larger extent of necrosis, but it had no value in the prediction of reperfusion injury as defined by the presence of MVO, intramyocardial edema, and IMH. The utility of Rentrop angiographic grade as a predictor of post-STEMI prognosis is controversial. In a large meta-analysis, Rentrop grade was correlated with better outcomes only in the setting of stable coronary artery disease, while in acute mechanically reperfused STEMI patients the risk reduction did not reach statistical significance [17]. On the contrary, in a recently published study, the presence of a Rentrop collateralization grade of 1 or 2 was associated with better in-hospital and 5-year mortality rates following STEMI [18]. Another research showed that the presence of

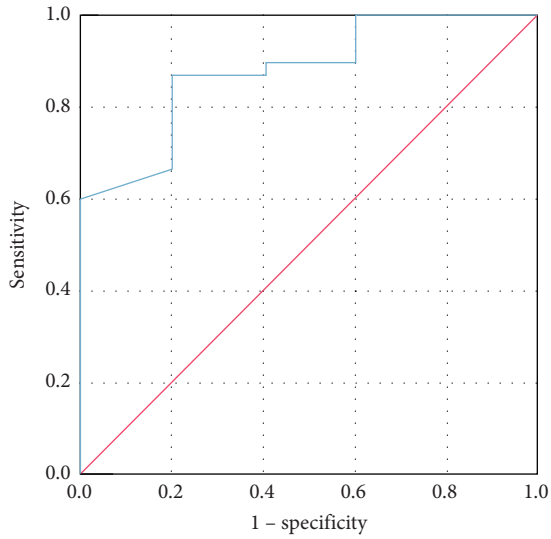

Figure 2: ROC curve analysis. ROC curve analysis for the association between mean CWP and an infarcted area ≥24% of left ventricular mass (AUC = 0.880, $p = 0.007$). A CWP value ≤ 24.5 mmHg was found as the optimal cutoff value to predict an infarct size ≥24% of left ventricular mass. AUC = area under the curve; CWP = coronary wedge pressure; and ROC = receiver operating characteristic.

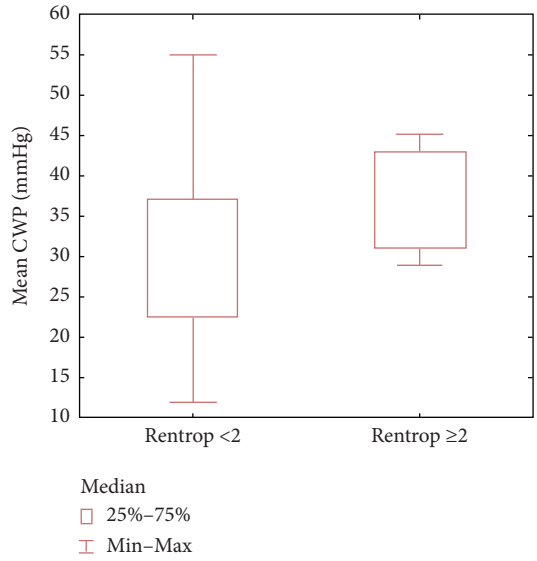

Figure 3: The association between mean CWP and Rentrop collateralization grade. Mean CWP was significantly lower in patients with Rentrop collateralization grade <2 ($p = 0.05$). CWP = coronary wedge pressure.

angiographically detectable collaterals had a protective effect on enzymatic infarct size in STEMI patients undergoing primary PCI [19]. Literature data is also conflicting with regard to the correlation between Rentrop angiographic grade and quantitative assessment of collateral flow through invasive physiology indices. Lee et al. found a weak correlation between pressure-derived collateral flow index (CFIp) and angiographic collateral grade and observed larger infarct sizes in the lower CFI group [7]. Meisel et al. demonstrated that both CWP and CFIp values are strongly correlated with angiographic collateralization in the setting of STEMI [20]. Still, none of these studies used the gold standard of CMR for the exact quantification of infarct size, MVO, intramyocardial edema, and IMH. Only recently, Greulich et al. used CMR to demonstrate the importance of Rentrop collateralization in infarct size and MVO, but the quantitative collateral flow evaluation was missing [3].

In our study, pre-revascularization CWP emerged as a predictor of both infarct size and severe reperfusion injury. Reperfusion injury is linked to the development of left ventricular adverse remodeling in STEMI survivors. A reliable pre-revascularization marker of adverse remodeling could open a therapeutic window for an early targeted cardioprotective strategy. High-risk STEMI patients defined by low CWP could benefit from intracoronary glycoprotein IIb/IIIa inhibitors, intracoronary thrombolytics, or postconditioning. There is an increasing interest in the intracoronary fibrinolytic therapy during primary PCI. Two

Table 3: Patients' characteristics according to the mean CWP 24.5 mmHg cutoff for infarct size.

Parameter	CWP ≤24.5 mmHg ($n = 8$)	CWP >24.5 mmHg ($n = 27$)	p value
Age (years), mean ± SD	54 ± 18.63	60.11 ± 9.14	0.39
Males, n (%)	6 (75)	13 (48)	0.18
Smokers, n (%)	4 (50)	12 (44.44)	0.79
BMI (kg/m^2), median ($Q1$–$Q3$)	25.64 (24.40–29.49)	26.79 (25.25–31.24)	0.51
Arterial hypertension, n (%)	2 (25)	15 (55.55)	0.13
Systolic BP, mean ± SD	125.12 ± 25.35	135.37 ± 20.37	0.36
Diastolic BP, mean ± SD	78.75 ± 16.42	80.62 ± 18.04	0.78
Heart rate (beats/min), mean ± SD	75 ± 11.30	78.66 ± 11.93	0.44
Diabetes mellitus, n (%)	3 (37.50)	8 (29.60)	0.70
Glycaemia (mg/dl), median ($Q1$–$Q3$)	140.50 (123.25–206.25)	143.30 (119–223)	0.86
Peak troponin T value (ng/ml), median ($Q1$–$Q3$)	3.63 (2.01–5.13)	2.38 (1.56–3.72)	0.19
Total ischemic time (min), median ($Q1$–$Q3$)	300 (195–300)	300 (180–540)	0.54
Rentrop grade <2, n (%)	8 (100)	20 (77.14)	0.01
Left ventricular mass/BSA, mean ± SD	60.41 ± 9.24	65.95 ± 15.28	0.33
Infarct size (% of LV mass), mean ± SD	22.32 ± 9.89	12.17 ± 7.90	0.005
Edema (% of LV mass), mean ± SD	38.92 ± 13.45	28.41 ± 10.82	0.02
MVO (% of LV mass), median (Q–$Q3$)	0.50 (0.01–6.17)	0.19 (0.00–1.36)	0.21
IMH (% of LV mass), median ($Q1$–$Q3$)	0.86 (0.00–3.00)	0 (0.00–0.02)	0.03
LVESV (ml), mean ± SD	84.82 ± 28.67	72.63 ± 28.70	0.31
LVEDV (ml), mean ± SD	159.12 ± 24.43	140.25 ± 43.16	0.13
LVEF (%), mean ± SD	47.51 ± 12.49	49.03 ± 9.41	0.75

*BMI = body mass index; BP = blood pressure; BSA = body surface area; IMH = intramyocardial hemorrhage; LV = left ventricle; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MVO = microvascular obstruction; n = number; $Q1$ = 1st quartile; $Q3$ = 3rd quartile; and SD = standard deviation.

ongoing trials will hopefully bring new data with regard to low-dose intracoronary thrombolytics administration (STRIVE-NCT03335839; RESTORE-MI-ACTRN12618000778280). The timely administration of dedicated molecules like neprilysin inhibitors could also be beneficial for the improvement of long-term prognosis in this patient subgroup [21, 22]. The PARADISE-MI trial (NCT02924727) is currently investigating the efficacy of sacubitril/valsartan on left ventricular structure and function after myocardial infarction. In a recently published review, an area of edema >30% of LV mass was recommended as criterion for the selection of patients who would most likely benefit from cardioprotective therapies [23]. In our study, in patients with a mean CWP ≤24.5 mmHg, the mean extent of intramyocardial edema reached 38.9% of LV mass.

4.1. Study Limitations. The main limitation of this study is represented by the small sample size. The exclusion of patients with primary pharmacological reperfusion, the most frequently applied strategy in the geographical region the center covers, led to a reduced number of study participants. Despite the relatively small cohort, the study did show several significant associations between CWP, infarct size, and reperfusion injury. Larger cohort studies are needed to confirm these results.

The analysis is also limited by the lack of a six-month CMR follow-up examination for the evaluation of left ventricular adverse remodeling. However, the strong association between CWP and infarct size is an indirect argument in favor of CWP's value as a potential marker of adverse remodeling.

5. Conclusions

In this study, coronary collateral flow as assessed by pre-revascularization CWP was associated with both infarct size and reperfusion injury. A mean CWP ≤24.5 mmHg predicted an infarct size ≥24% of LV mass and was associated with a larger extent of intramyocardial edema and IMH. Angiographic Rentrop grade was associated with infarct size but had no influence on the extent of reperfusion injury. Although larger-scale studies are needed to confirm these results, CWP emerges as an early, quantitative, and easily measured predictor of an adverse postmyocardial infarction prognosis. Such a parameter could open a much needed window for the timely administration of cardioprotective therapies.

Data Availability

Data supporting the conclusions of the study will be made available on request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Supplementary Materials

Detailed cardiac magnetic resonance imaging protocol and STROBE checklist. (*Supplementary Materials*)

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