Comparison of myocardial perfusion study and invasive hemodynamic measurement of the significance of non-infarct-related residual stenoses in ST elevation myocardial infarction patients

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Background. Nearly 50% of ST elevation myocardial infarction (STEMI) patients have multivessel coronary artery disease. The optimal selection of non-culprit lesions for complete revascularization is a matter of current debate. Little is known about the predictive value of myocardial perfusion study (MPS) in this scenario.
Methods. We enrolled 49 STEMI patients (61.5 ± 10.3 years) with at least one major non-culprit lesion (50–90%) other than left main coronary artery lesions. Overall 63 non-infarct- related artery (IRA) stenoses (65.2 ± 11.9%) were recommended for further evaluation using Fractional Flow Reserve (FFR) measurement as is standard in our institution. Prior to FFR, all patients were scheduled for non-invasive MPS using single-photon emission computed tomography (SPECT). Both FFR and MPS were performed 4–8 weeks after STEMI with MPS preceding FFR within no more than 48 hours. An FFR value of ≤0.80 was considered significant and guided the final revascularization strategy. The results of MPS were correlated to FFR as well as to the clinical and angiographic characteristics of both culprit and non-infarct-related lesions.
Results. Based on FFR, 30 out of 63 stenoses (47.6%) in 27 patients were considered hemodynamically significant (FFR 0.69 ± 0.08, range 0.51–0.79) compared to residual 33 stenoses considered negative (FFR 0.87 ± 0.04, range 0.81–0.96). The MPS revealed abnormal myocardium (23.6% average, range 5–56%) in 21 patients (42.8%). Among those patients, only 9 showed the evidence of ischemic myocardium (average 10.8%, range 4–18%) with low sensitivity of MPS in predicting positive FFR. Besides that, higher proportion of patients (71.4% vs. 42.9%, *P*=0.047) with overall lower FFR values (0.73 vs. 0.80, *P*=0.014, resp.) in non-IRAs as well as higher proportion of patients with more severely compromised flow in IRAs (*P*=0.048) during STEMI had MPS-detected abnormal myocardium.
Conclusion. In STEMI patients with multivessel coronary artery disease, we observed rather weak correlation between MPS using SPECT and invasive hemodynamic measurement using FFR in ischemia detection.

Key words: atherosclerosis, acute ST elevation myocardial infarction (STEMI), multivessel coronary artery disease (CAD), infarct related artery (IRA), complete revascularization, coronary flow, fractional flow reserve (FFR)

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INTRODUCTION

Both acute coronary syndromes and stroke are the major causes of morbidity, mortality as well as disability in westernized countries[1]. During acute cardiac presentation, abrupt deterioration of coronary flow following complete or near-complete coronary obstruction may lead to ST segment elevation myocardial infarction (STEMI) with a large proportion of myocardium jeopardized by ischemia. Primary percutaneous coronary intervention (PCI) allows timely restoration of coronary flow minimizing the adverse events related to transmural scarring and decreased cardiac output[2,3]. Owing to the diffuse nature of atherosclerosis, almost 50% of STEMI patients have significant non-infarct related artery (IRA) lesions universally defined as ≥ 50% stenosis in any major epicardial coronary artery[4,5]. Since the majority of these lesions represent incidental (and potentially stable) findings, one must be very cautious offering the patient routine completion of revascularization taking into account the limited possibilities to fine-estimate the vulnerability of the lesions as well as the absence of guidelines to obtain and evaluate such information. Indeed, several large-scale trials so far failed to prove clear mortality benefit in routine revascularization of non-IRA lesions in STEMI patients provided that the selection of lesions was based on angiographic or invasive hemodynamic evaluation[6-11]. On the other hand, it is unquestionable that some patients did benefit from reduced need for future revasculatizations. Fractional flow reserve (FFR) evaluation, which is considered the gold standard and most accurate invasive method for estimating the lesion severity in stable coronary artery disease (CAD) patients, has failed to show additional value in the selection of STEMI non-IRA lesions

compared to visual angiographic estimation[10]. Myocardial perfusion study (MPS) has very robust prognostic data[12] but little is known about its additional value in patients with STEMI and multivessel disease. For this reason, we focused on such patients and provide the real-world comparison of the hemodynamic measurement with invasive FFR and non-invasive MPS.

MATERIALS AND METHODS

Study design

We enrolled all adult patients with STEMI as the first manifestation of CAD. The major inclusion criterion was at least one 50–90% residual stenosis in major non-IRA (diameter ≥ 2.5 mm) provided that the culprit lesion was successfully revascularized (Thrombolysis In Myocardial Infarction "TIMI" score at least 2 following PCI). Table 1 summarizes the key exclusion criteria. Patients with stable CAD symptoms prior to STEMI were strictly excluded allowing one to consider the residual lesions as silent or incidental. All patients gave written informed consent to the study protocol. The study was performed in accordance with the latest Declaration of Helsinki of the World Medical Association and the local ethics committee approved the study protocol.

Angiographic evaluation of stenosis severity

Both culprit and non-IRA lesions were evaluated by the primary operator in terms of the severity of stenosis (percentage) but also in more details regarding both angiographic and clinical characteristics including (but not inclusive of): 1) localization, proximity and severity of all stenoses, 2) caliber of the artery in stenosed segment, 3) estimated delay from the onset of symptoms to the recanalization of the culprit lesion and 4) TIMI flow score before and after PCI.

Myocardial perfusion study

All patients were scheduled for the MPS within 4–8 weeks after the index PCI procedure. A single-photon emission computed tomography (SPECT) study was performed in a standardized two-day protocol. In order to induce stress, physical exercise using stationary bicycle was strongly preferred. The objective was to achieve the highest tolerated workload reaching a minimum of 85% of the maximum of predicted heart rate based on the patient's age. If achieving this target was not possible (or in case of left bundle branch block) a pharmacological stress agent was administered (Regadenoson at a dose of 440 μg). At the peak stress moment or 20-30 seconds after the administration of the pharmacological stress agent, the radioisotope (99mTc MIBI) was injected in a standardized dosage (2MBq/kg for the stress and 6MBq/kg for the rest examination) and in case of exercise test, the patient was motivated to continue exercise for another 1–2 min. The following data were collected for subsequent analysis: left ventricular ejection fraction before and after stress, the percentage of abnormal myocardium (fixed or reversible perfusion defect), the percentage of ischemia and both Summed Stress Score (SSS) and Summed Difference Score (SDS).

Table 1. Key exclusion criteria.

- Hemodynamic instability requiring complete revascularization during culprit procedure
- Residual lesions considered unstable and requiring immediate treatment
- Inability to perform hemodynamic evaluation of stenosis severity (anatomical or medical)
- Non-IRA stenosis > 90% or occlusion
- Non-IRA stenosis in left main coronary artery
- Non-IRA stenosis in vascular bed considered as non-relevant (small distal territory)
- Valvular disease considered hemodynamically significant
- Pregnancy
- Probable non-compliance with treatment strategy

Hemodynamic evaluation of the stenosis severity and completion of the revascularization

The invasive hemodynamic evaluation of all eligible non-IRA lesions was performed within no more than 48 hours after MPS and in the majority of patients the second day of hospitalization in order to minimize the length of hospital stay and maximize patients' comfort. The hemodynamic measurement was performed using FFR – an invasive technique using dedicated pressure wire allowing one to compare the difference between prestenotic (using guiding catheter) and poststenotic pressure in real-time. The greater is the poststenotic pressure drop during maximal vasodilation, the more hemodynamically relevant is the stenosis. Indeed, FFR is currently considered the gold standard for the assessment of the hemodynamic significance of borderline stenoses (50–90%) in the case of the absence of non-invasive measurement of the extent of ischemia[13]. Albeit available, we used no other means of hemodynamic measurement such as resting full-cycle ratio ("RFR") or the instantaneous wave-free ratio ("iFR") in order to comply with the design of the pioneering studies. All operators were well-experienced in FFR use and followed a standardized protocol including the application of adenosine. A dedicated pressure wire (PressureWire AERIS™, Abbott) was used in all patients. A universally accepted cut-off value of 0.80 or less during maximal vasodilation was considered significant. In such case, the choice of optimal revascularization method was based on the operator's recommendation. Drug eluting stents were the first-line choice during PCI and all patients were discharged with guideline-recommended optimal medical therapy.

Statistical analysis

A statistical software IBM™ SPSS Statistics version 23 (Armonk, NY: IBM Corp.) was used for the statistical analysis. Standard descriptive statistics were used to summarise the data. Categorical variables were reported as numbers and relative frequencies (percentages) and con-

tinuous variables as the mean ± standard deviation. Mann-Whitney U test, chi-square Fisher's exact test, Spearman's correlation and Kruskal-Wallis with post-hoc Dunn test were used for detailed analysis with P value < 0.05 considered statistically significant in all cases.

RESULTS

A total of 56 patients were enrolled over the period of 2 years, but only 49 patients (61.5 ± 10.3 years) completed the study. Their baseline characteristics are summarized in Table 2. None of the patients had experienced any adverse clinical event during the time period between culprit lesion PCI and subsequent invasive measurement, however, seven patients declined further participation preferring only one-day PCI procedure in the time of the Covid-19 pandemia. In the study group, a total of 63 non-IRA stenoses were recommended for hemodynamic measurement (comprising 10 patients with two-vessel and 2 patients with three-vessel disease). Subsequently, all study patients underwent successful hemodynamic measurement of all eligible stenoses. Overall, 30 stenoses (47.6%) in 27 patients were considered hemodynamically significant and recommended for revascularization (average FFR value 0.69 ± 0.08, FFR range 0.51–0.79). The remaining 33 lesions in 22 patients were FFR negative (average FFR value 0.87 ± 0.04, FFR range 0.81– 0.96). In patients with two-vessel disease or three-vessel disease, the lowest value of FFR was utilized for further analysis. Prior to FFR, pharmacological stress MPS was performed in 21 patients (42.9%) with the remaining 28 undergoing physical exercise only. In 28 patients (57.1%), the study was evaluated as negative indicating normal myocardium with no evidence of abnormal perfusion. Of the remaining 21 patients, abnormal myocardium pattern was detected averaging 23.6% of the left ventricle and ranging from 5% to 56% comprising 17 patients with signs of permanent scarring corresponding to IRA territory and 4 patients with reversible defect only. Moreover, a total of 9 patients (18.4%) with 11 lesions showed evidence of reversible perfusion defect averaging 10.8% and ranging from 4% to 18% (Fig. 1). Table 3 summarizes the comparison of SPECT results and FFR values with respect to residual lesion territory.

Table 2. Patients' baseline characteristics.

Age (years)	61.5 ± 10.3
Male sex	40 (81.6%)
Hypertension	29 (59.2%)
Diabetes mellitus	10 (20.4%)
Current smoking	17 (34.7%)
Peripheral arterial disease	1 (2%)
Creatinine (μmol/L)	82.2 ± 28.3
Total cholesterol (mmol/L)	5.0 ± 1.3
LDL-c (mmol/L)	3.3 ± 1.3
Location of MI	
anterior	13 (26.5%)
inferior	32 (65.3%)
lateral	4 (8.2%)
Residual non-IRA with stenoses	
single	35 (71.4%)
double	12 (24.5%)
triple	2 (4.1%)

In the subgroup of patients with abnormal myocardium, significantly lower FFR values were observed in non-IRAs compared to patients with residual negative MPS study (0.73 vs. 0.80, P=0.014) (Fig. 2). Indeed, significantly higher proportion of patients with abnormal myocardium had FFR value ≤ 0.80 (71.4% vs. 42.9%, P=0.047). If the cut-off value was lowered to 0.75, the correlation would be even more significant (57.1% vs. 25%, P=0.022). We also observed a relationship between the presence of abnormal myocardium and the proportion of myocardial flow in the culprit lesion. In patients with TIMI 0 or 1

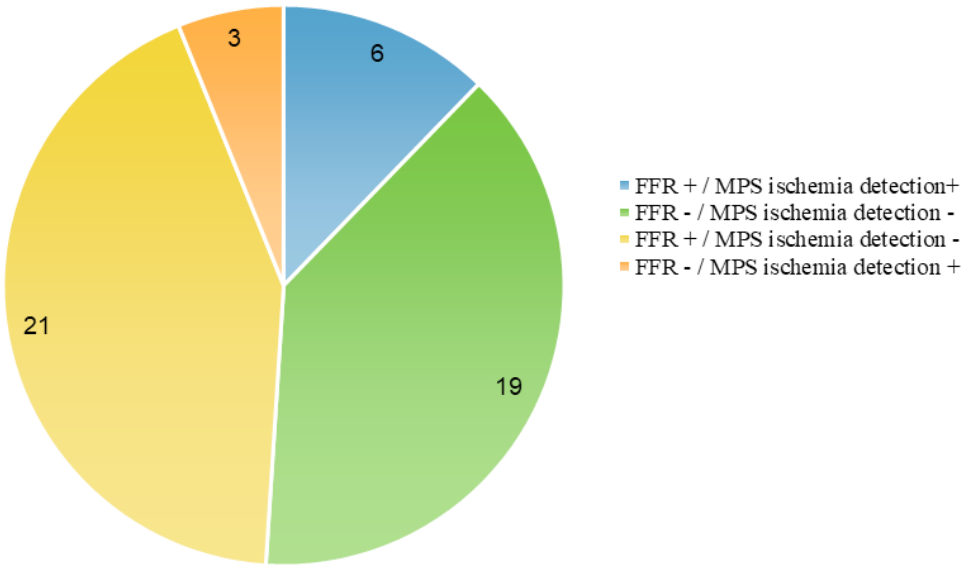

Fig. 1. Correlation/discrepancy of FFR and MPS.

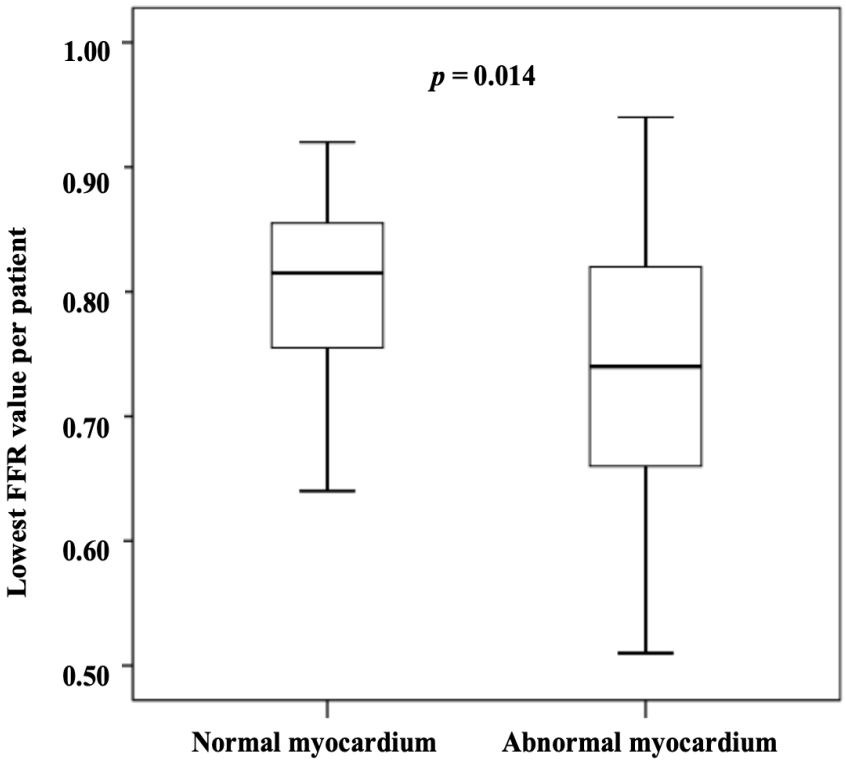

Fig. 2. Comparison of FFR values and presence of abnormal myocardium at MPS.

Table 3. SPECT to FFR comparison with respect to residual lesion territory (per lesion).

	Residual left anterior descending artery lesion		Residual non-left anterior descending artery lesion	
SPECT	Ischemia – (28 lesions)	Ischemia + (5 lesions)	Ischemia – (24 lesions)	Ischemia + (6 lesions)
FFR positive	17 lesions (60.7%)	4 lesions (80%)	6 lesions (25%)	3 lesions (50%)
Average FFR value	0.76 ± 0.09 (range 0.56–0.91)	0.64 ± 0.12 (range 0.51–0.82)	0.84 ± 0.09 (range 0.60–0.96)	0.81 ± 0.10 (range 0.66–0.94)

flow in IRA (complete or near complete occlusion) there was a significantly higher likelihood of detecting SPECT perfusion abnormality compared to patients with initial TIMI 2 or 3 ((near) normal) culprit flow (81% vs. 50%, P=0.026). Of the remaining angiographic and anatomical characteristics including culprit lesion location and estimated caliber of the artery in the stenotic segment, stenosis proximity as well as the delay of revascularization, there was no significant correlation to MPS study in terms of abnormal myocardium. Moreover, there was no significant correlation between the clinical and anatomical parameters and the extent of detected ischemia or resting left ventricular ejection fraction. Overall, we found a very low sensitivity and specificity for MPS in predicting the positivity of FFR (cut-off value ≤ 0.80) measurement with the values of 22% and 86% respectively (positive and negative predictive value of 48% and 67%). Conversely, the optimal FFR cut-off value to detect the presence of stress-induced myocardial ischemia was calculated as low as 0.686 with a sensitivity and specificity of 56% and 85% respectively.

DISCUSSION

Given that atherosclerosis is a diffuse process mostly affecting larger arteries, it is not surprising that nearly 50% of STEMI patients had multivessel CAD universally defined as at least 50% stenosis in at least one major artery other than the culprit lesion[4,5]. Historically, these stenoses were treated conservatively due to the increased rate of adverse events including mortality, but over time, this has changed with the improvement of procedural safety and efficacy[14-17]. Indeed, the current guidelines recommend that such lesions should be treated with the aim of complete revascularization[3]. The rationale for such an approach is the results of the pioneering randomized trials such as PRAMI, CvLPRIT, DANAMI-3 PRIMULTI and COMPARE-ACUTE comparing initial invasive to initial conservative strategy[6-9]. In summary, these trials failed to confirm difference in hard endpoints such as mortality or myocardial infarction, however, there was a clear benefit in lower need for future revascularization in favor of initial invasive strategy. One must, however, keep in mind

the heterogeneity of these studies in terms of the length of follow-up (12–27 months), timing of revascularization completion and, most importantly, lesion severity criteria (≥50%, ≥70% or FFR guided).

The Complete Revascularization with Multivessel PCI for Myocardial Infarction (COMPLETE) trial published in 2019 aimed to overcome several pitfalls of the pioneering trials[11]. The major inclusion criterion was at least ≥70% stenosis based on angiography or 50–69% stenosis with FFR value ≤0.80. Patients were randomized following culprit lesion PCI to either no further revascularization or complete revascularization of all significant non-culprit lesions irrespective of stable CAD symptoms prior to STEMI. Even though more than 4000 patients were included, the COMPLETE found no difference in mortality rate over the median follow-up of 3 years, but with significantly lower incidence of future revascularizations as well as lower incidence of new myocardial infarction (non-STEMI of uncertain significance defined by the increase of cardiac markers; no difference in STEMI) in favor of complete revascularization.

In 2021, Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction (FLOWER-MI) trial was published evaluating the difference between angiography-driven (≥50% stenosis) or FFR-driven complete revascularization in STEMI patients over the period of 12 months[10]. The primary outcome was a composite of death from any cause, non-fatal myocardial infarction or unplanned hospitalization leading to urgent revascularization. The mean number of stents used per patient for non-culprit lesions was 1.01 ± 0.99 in the FFR-guided group, and 1.50 ± 0.86 in the angiography-guided group, consistent with a well-documented general practice of a more restrictive approach to revascularization with FFR (ref.[13,14]). The primary outcome event occurred in 32 of 586 patients (5.5%) in the FFR-guided group and in 24 of 577 patients (4.2%) in the angiography-guided group. Therefore, the authors concluded that FFR-guided strategy was not superior to angiography-guided strategy in STEMI patients requiring completion of revascularization.

FFR is a well-established and widely used invasive method of determining the functional significance of coronary obstruction. It is based on pressure-flow analysis of a stenosis during maximum flow - the greater is the poststenotic pressure drop during maximum coronary vasodilation, the more likely is the stenosis susceptible to induce ischemia during stress. In a landmark report, Pijls and co-workers[18] validated the FFR index in a group of patients with single moderate coronary artery stenosis using three different non-invasive stress tests (exercise test, thallium scan and stress echocardiogram) of which at least one needed to be positive. The authors proposed a cut-off FFR value of 0.75 as a threshold for discrimination between ischemia-inducible and non-inducible lesions. An FFR value of 0.75–0.80 is considered a grey-zone in which some of the patients likely benefiting from revascularization may fall due to technical aspects of FFR investigation, therefore the majority of FFR trials set a cut-off value of 0.80. It has been well documented in large scale trials such as DEFER and FAME I + II (ref.[19-21]) that revascularization may safely be deferred in patients with FFR above 0.80 while patients with lower FFR values have higher risk of developing adverse cardiac outcomes, particularly driven by the need for future revascularization. One may also view FFR as a non-binary but rather a continuous prognostic tool with indirect relationship between its numeric value and adverse cardiac outcomes. It is, however, of utmost importance to take into consideration that most of the data come from patients with stable CAD symptoms referred for PCI. On the other hand, SPECT is a widely used imaging technique based on the detection of gamma rays emitted by radioisotope ("tracer") delivered into the target organ such as heart through the injection into the bloodstream. Together with stress echocardiography, it is considered a well-established and readily available non-invasive technique for evaluation of CAD providing very robust prognostic data[12]. The tracer uptake in ischemic myocardium is lower than that in normal myocardium, but this relative difference is lost after rest. This is called a "reversible defect" and it is a hallmark of ischemia. Irreversible defect (reduced or absent uptake of the tracer at rest) represents myocardial scar. Imaging is usually performed with ECG gating, which allows assessment of both global and regional left ventricular function and left ventricular size.

In our study, we primarily focused on STEMI patients with strictly incidental finding of multivessel CAD and applying the diagnostic strategy for stable CAD patients. So far, there is a lack of data providing comparison of SPECT and FFR in such patients. We found a significantly lower rate of patients with SPECT detected ischemia compared to FFR. As a collateral finding, we observed a rather high percentage of patients with STEMI and residual normal myocardial finding (57.1%). Moreover, the presence of abnormal residual myocardial perfusion was more likely in patients with lower FFR values in the residual lesions and in patients with no or minimal flow in the IRA during culprit procedure.

All patients with significant residual lesions safely underwent staged PCI with the completion of revascularization postponed up to 8 weeks after culprit-lesion PCI and no adverse event was reported within this time window. Together with the above-described large-scale study finding of limited benefit in "hard outcomes" related to an early invasive treatment, we advocate that completion of revascularization might be postponed for 4–8 weeks provided that such lesions are strictly incidental and lack any angiographic signs of vulnerability. We cannot recommend such an approach in patients with left main stenosis or tight >90% lesions because these patients were excluded from our study. Considering the advance of the current potent lipid-lowering agents, it is of utmost importance to focus on the highest risk patients. We provide an insight into the real-world comparison of SPECT and FFR techniques in selected patients with STEMI and residual lesions. Whether SPECT may further help in the selection of such patients for complete revascularization remains to be answered in a large-scale trial.

CONCLUSION

A large proportion of patients with STEMI have residual stenoses in non-culprit territories with unknown potential of the development of future adverse events. Based on the available data, it is questionable to support routine PCI of such (≥50%) lesions in order to reduce the rate of hard outcomes, however, it is likely to reduce the risk of future unplanned PCI procedures. The optimal selection strategy for the completion of revascularization and its optimal timing in STEMI patients with strictly incidental residual lesions in major coronary arteries exclusive of left main lesions remains unknown. In our study, we safely postponed the decision to up to 4–8 weeks after the culprit procedure and observed more restrictive results in terms of SPECT detected ischemia compared to the gold standard of FFR. Whether SPECT can play a role in selection of such patients remains to be answered.

ABBREVIATIONS

CAD, Coronary artery disease; ECG, Electrocardiogram; FFR, Fractional flow reserve; IRA, Infarct related artery; MPS, Myocardial perfusion study; PCI, Percutaneous coronary intervention; SDS, Summed difference score; SPECT, Single photon emission computed tomography; SSS, Summed stress score; STEMI, ST elevation myocardial infarction; TIMI, Thrombolysis in myocardial infarction.

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