Measurement, comparison, and application of FFR and non-hyperemic Pd/Pa to estimate prognosis in non-culprit vessels of patients with acute coronary syndrome

PhD thesis

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1. INTRODUCTION

Functional assessment of coronary lesions has been well investigated and proved to be beneficial in chronic coronary syndrome. In ACS patients there is also evidence that FFR guidance of revascularization in non-culprit vessels can improve clinical outcome mainly by a decreased need for urgent revascularization later. On the other hand, there is limited and equivocal data regarding the use of resting indexes in non-culprit vessels of ACS cases. It is not completely clarified if resting indexes can be used to determine significance of non-culprit lesions in ACS and if it is safe to defer revascularization based on a negative value.

2. OBJECTIVE

Our objective was to determine the correlation of FFR and resting Pd/Pa in non-culprit vessels in patients immediately after successful primary PCI for STEMI, and to compare the respective power of FFR and resting Pd/Pa to predict vessel-related untoward events.

3. METHODS

3.1. Patients

The Compare-Acute trial enrolled STEMI patients with multivessel disease within 12 hours of symptom onset. Two groups were randomized in a 1:2 fashion to infarct-related artery only (IRA-only) and FFR-guided complete revascularization, immediately after the successful and uncomplicated primary percutaneous intervention of the infarct-related artery. FFR and resting Pd/Pa of all non-culprit vessels with at least 50% diameter stenosis were measured in all patients. In the complete revascularization group, non-culprit revascularization was decided by FFR (cut-off $\leq$0.80), whereas in the other arm, resting Pd/Pa and FFR values were measured but concealed and all non-culprit lesions were left without revascularization. We compared FFR and resting Pd/Pa in the non-culprit vessels and their respective power to predict 3-year MACE. Resting Pd/Pa and FFR were measured using commercially available pressure wires (St. Jude Medical, now Abbott). Intravenous infusion or intracoronary

boluses of adenosine at standard doses were used to achieve hyperemia. A total of 885 patients were randomized in the study, 295 to the FFR-guided complete revascularization arm and 590 to the IRA-only group. To assess the relative prognostic power of FFR and resting Pd/Pa to predict 3-year MACE, we included only patients from the IRA-only group (n=517) who had both FFR and resting Pd/Pa measured in the non-culprit vessels (target vessels in this evaluation).

3.2. Endpoints

Target vessel-related MACE included target vessel myocardial infarction (TVMI) and target vessel revascularization (TVR) at 36 months in this analysis. Cardiovascular death was not included as an endpoint, because it is hard to relate it to a specific vessel.

We compared the respective power of FFR and resting Pd/Pa in predicting target vessel-related MACE with special attention to cases with discrepant FFR and Pd/Pa values. The Clinical Event Committee reviewed all reported non-fatal myocardial infarction (MI) events and

assigned them to a target or a non-target vessel. In case the event (non-fatal MI or non-target vessel revascularization) was related to a non-target vessel, it was not counted as an event.

4. RESULTS

4.1. Patients, vessels, and physiology parameters

517 patients and 665 target vessels were included in our assessment. 282 (42.4%) were left anterior descending (LAD), 221 (33.2%) were left circumflex (Lcx) and 162 (24.4%) were right coronary artery (RCA). The distribution of FFR and resting Pd/Pa values is shown in **Figure 1**. Median FFR was 0.83 (interquartile range, 0.14), and median resting Pd/Pa was 0.92 (interquartile range, 0.10).

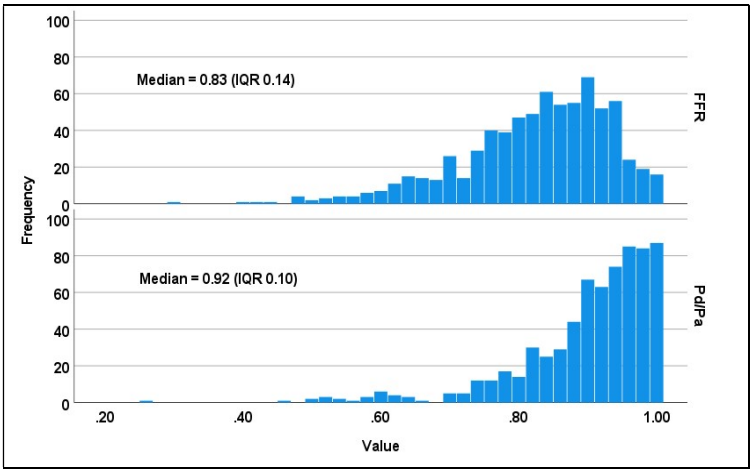

Figure 1. Distribution of fractional flow reserve (FFR) and resting full cycle distal coronary to aortic pressure ratio (Pd/Pa) values. IQR indicates interquartile range.

(Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 5.)

4.2 Correlation of FFR and resting Pd/Pa

The scatter plot of FFR and resting Pd/Pa is shown in **Figure 2**. There was a linear correlation between FFR and resting Pd/Pa with a Pearson R2 of 0.84 (P<0.01). The area under the ROC curve (C statistic) to predict an FFR≤0.80 was 0.894 for resting Pd/Pa indicating a good correlation [**Figure 3**].

Based on ROC curve analysis, the optimal cut-off value of resting Pd/Pa to predict an FFR≤0.80 was 0.905 (Youden index 0.620). 301 vessels (45%) had an FFR >0.80 and a resting Pd/Pa >0.91 [true negatives, **Figure 2**, quadrant B], 232 (35%) had an FFR≤0.80 and a resting Pd/Pa≤0.91 [true positives, **Figure 2**, quadrant C]. 85 (13%) had an FFR >0.80 and a resting Pd/Pa≤0.91 [false positives, **Figure 2**, quadrant D] and 47 (7%) had an FFR≤0.80 and a resting Pd/Pa>0.91 [false negatives, **Figure 2**, quadrant A]. Altogether 132 vessels (20%) had discrepant FFR and resting Pd/Pa values. The overall sensitivity, specificity, positive and negative predictive value of Pd/Pa≤0.91 versus FFR≤0.80 were 83.15%,

77.98%, 73.19%, and 86.49%, respectively, and the overall diagnostic accuracy was 80.15%.

To achieve a diagnostic accuracy of 90%, 95%, and 99%, adenosine was needed in 24.1%, 31.4%, and 74.9% of the lesions, respectively.

Of the 132 vessels with discrepant FFR and resting Pd/Pa, 57 (43%) were left anterior descending, 34 (26%) were left circumflex and 41 (31%) were right coronary arteries. Resting and hyperemic measurements of coronary physiology of the target vessels were discrepant in 20% in the left anterior descending (57/282), 15% in the left circumflex (34/221), and 25% in the right coronary artery (41/162). The level of diagnostic agreement between FFR≤0.80 and resting Pd/Pa≤0.91 had a kappa of 0.60 (SE 0.031, P<0.001), indicating a moderate level of agreement.

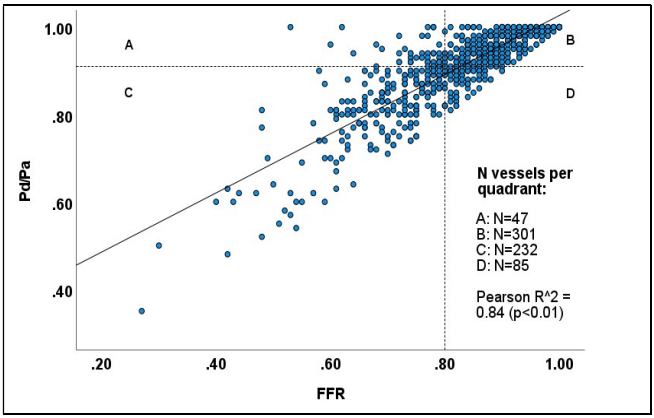

Figure 2. Scatter plot of fractional flow reserve (FFR) and resting full cycle distal coronary to aortic pressure ratio (Pd/Pa). (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 5.)

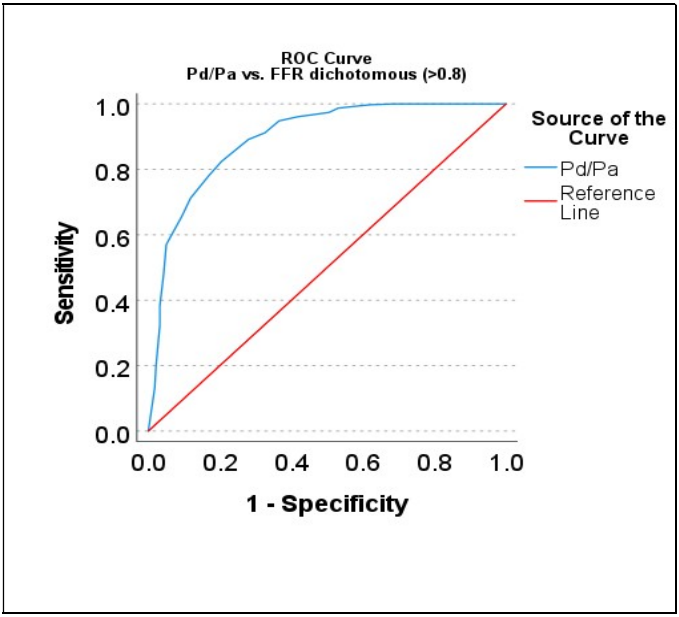

Figure 3. Receiver-operating characteristic (ROC) curve for resting full cycle distal coronary to aortic pressure ratio (Pd/Pa). FFR indicates fractional flow reserve.
(Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 6.)

4.3 Endpoints, the predictive power of FFR versus resting Pd/Pa

130 target vessel revascularizations (57 LAD, 43 Lcx, and 30 RCA) and 14 target vessel-related myocardial infarctions (4 LAD, 7 Lcx, and 3 RCA) occurred in 36 months. 132 vessels were related to an endpoint (TVR and/or TVMI). 82 of the 279 (29.4%) target vessels with an FFR≤0.80 had an endpoint compared with 50 of 386 (13.0%) with an FFR >0.80. FFR had a sensitivity, specificity, and overall diagnostic accuracy of 62%, 63%, and 63%, respectively. 81 of the 317 (25.6%) target vessels with a resting Pd/Pa ≤0.91 had an endpoint compared with 51 of 348 (14.7%) with a resting Pd/Pa of >0.91. Resting Pd/Pa had a sensitivity, specificity, and overall diagnostic accuracy of 61%, 56%, and 57%, respectively.

The ROC curves of FFR and resting Pd/Pa in predicting 36-month TVMI and/or TVR are shown in **Figure 5**. The AUC for FFR and resting Pd/Pa were 0.630 (95% CI, 0.578–0.682) and 0.608 (95% CI, 0.556–0.661), respectively (*P*=0.20). Based on ROC analysis, the best

cut-off values of FFR and resting Pd/Pa to predict 36-month TVMI and/or TVR were 0.815 and 0.935, respectively.

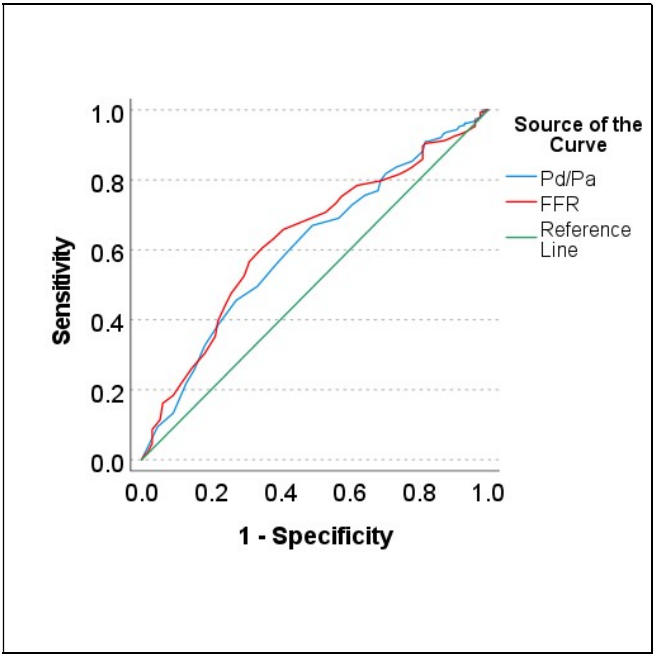

Figure 5. Receiver-operating characteristic curves of fractional flow reserve (FFR) and resting full cycle distal coronary to aortic pressure ratio (Pd/Pa) in predicting 36-month target vessel myocardial infarction and/or target vessel revascularization. (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of

Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 8.)

4.4 Outcome of vessels with discrepant FFR and resting Pd/Pa values

The outcome was analyzed in vessels with discrepant Pd/Pa and FFR (i.e., FFR≤0.80 and Pd/Pa>0.91 or FFR>0.80 and Pd/Pd≤0.91) [quadrants A and D in **Figure 2**]. In these cases, revascularization decisions of non-culprit vessels would have been different. There was a discrepancy in the resting (Pd/Pa) and hyperemic (FFR) measurements in 132 of the 665 vessels (20%). In 105, no TVMI or TVR occurred, of these, 72 had negative FFR and positive Pd/Pa, and 33 had positive FFR and negative Pd/Pa [**Figure 6a**]. In 27, TVMI and/or TVR occurred, of these 13 had negative FFR and positive Pd/Pa and 14 had positive FFR and negative Pd/Pa [**Figure 6b**]. FFR was better than resting Pd/Pa (P=0.048) to identify which nIRA could be safely deferred. The event-free survival

curves of the 4 concordant and discordant groups are shown in **Figure 7**.

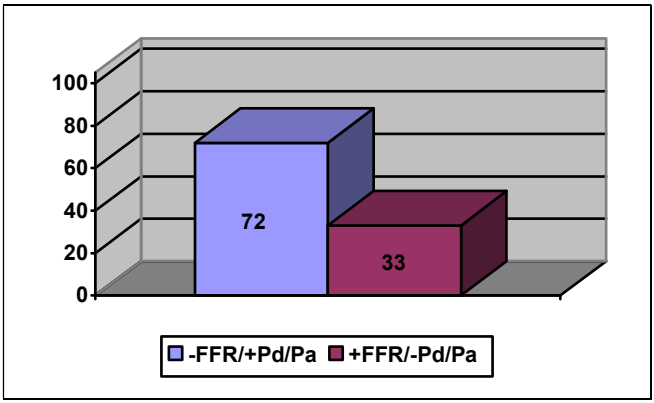

Figure 6a. Non-culprit vessels with discrepant functional indexes and no target vessel myocardial infarction (TVMI) and/or target vessel revascularization (TVR).

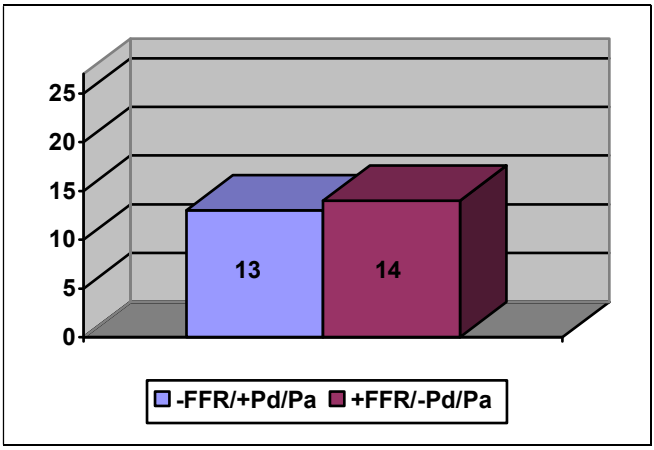

Figure 6b. Non-culprit vessels with discrepant functional indexes with target vessel myocardial infarction (TVMI) and/or target vessel revascularization (TVR).

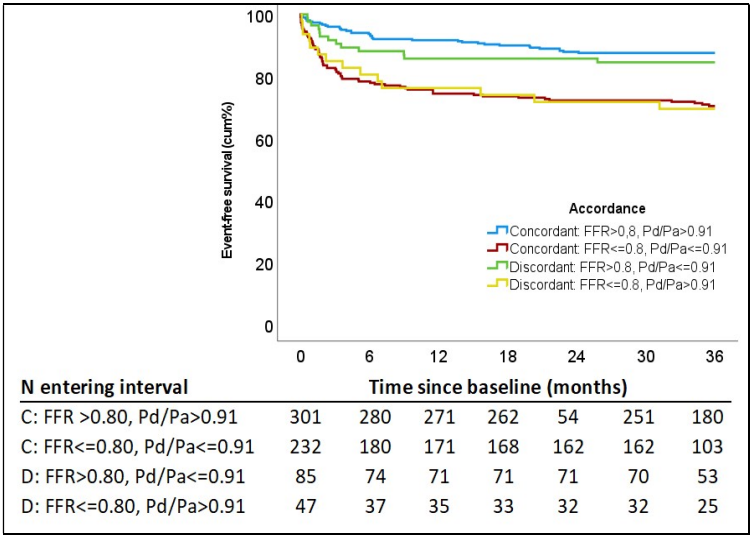

Figure 7. Event-free survival curves of the 4 groups according to the concordance of fractional flow reserve (FFR) and resting full cycle distal coronary to aortic pressure ratio (Pd/Pa). (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 8.)

5. CONCLUSIONS

In STEMI patients and multivessel disease, the functional assessment of non-culprit vessels immediately after successful primary PCI showed that resting Pd/Pa had an 80% diagnostic accuracy compared with FFR. In this analysis, the best cut-off value of resting Pd/Pa to predict an FFR≤0.80 was 0.905. FFR was not significantly better than resting Pd/Pa to predict major adverse cardiovascular events, but in case the two indexes were discrepant, FFR was superior in identifying which non-culprit lesions could be safely deferred.

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   *Dr Piróth and Dr Fülöp were both primary authors.
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