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The impact of left ventricular ejection fraction on fractional flow reserve: Insights from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) trial

Yuhei Kobayashi [a,b], Pim A.L. Tonino [c], Bernard De Bruyne [d], Hyoung-Mo Yang [a,e], Hong-Seok Lim [a,e], Nico H.J. Pijls [c], William F. Fearon [a,b,*], on Behalf of the FAME Study Investigators:

[a] Stanford University Medical Center, Stanford, CA, USA
[b] Stanford Cardiovascular Institute, Stanford, CA, USA
[c] Catharina Hospital, Eindhoven, the Netherlands
[d] Cardiovascular Center Aalst, Aalst, Belgium
[e] Ajou University School of Medicine, Suwon, Republic of Korea

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ABSTRACT

Background: Fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) significantly improves outcomes compared with angio-guided PCI in patients with multivessel coronary artery disease. However, there is a theoretical concern that in patients with reduced left ventricular ejection fraction (EF) FFR may be less accurate and FFR-guided PCI less beneficial.

Methods: From the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) trial database, we compared FFR values between patients with reduced EF (both ≤40%, n = 90 and ≤50%, n = 252) and preserved EF (>40%, n = 825 and >50%, n = 663) according to the angiographic stenosis severity. We also compared differences in 1 year outcomes between FFR- vs. angio-guided PCI in patients with reduced and preserved EF.

Results: Both groups had similar FFR values in lesions with 50–70% stenosis (p = 0.49) and with 71–90% stenosis (p = 0.89). The reduced EF group had a higher mean FFR compared to the preserved EF group across lesions with 91–99% stenosis (0.55 vs. 0.50, p = 0.02), although the vast majority of FFR values remained ≤0.80. There was a similar reduction in the composite end point of death, nonfatal myocardial infarction, and repeat revascularization with FFR-guided compared to angio-guided PCI for both the reduced (14.5% vs. 19.0%, relative risk = 0.76, p = 0.34) and the preserved EF group (13.8 vs. 17.0%, relative risk = 0.81, p = 0.25). The results were similar with an EF cutoff of 40%.

Conclusion: Reduced EF has no influence on the FFR value unless the stenosis is very tight, in which case a theoretically explainable, but clinically irrelevant overestimation might occur. As a result, FFR-guided PCI remains beneficial regardless of EF.

1. Introduction

Left ventricular dysfunction is present in as many as 10–30% of patients undergoing percutaneous coronary intervention (PCI) and has been shown to be a predictor of increased mortality [1–4] and medical costs [2] in these patients. Fractional flow reserve (FFR) is an invasive index to assess the functional severity of epicardial coronary artery disease (CAD), originally validated in patients with preserved left ventricular ejection fraction (EF) [5]. The FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) trial demonstrated the superiority of FFR-guided PCI over angiography-guided PCI in patients with multivessel CAD [6–8].

However, data remain limited on the use of FFR in patients with reduced left ventricular EF. There is a theoretical concern that FFR may be less accurate and FFR-guided PCI less effective in patients with reduced EF because of the effect of elevated left ventricular end diastolic pressure, venous pressure and nonviable left ventricular myocardium on maximal flow down a vessel and the resultant FFR. Accordingly, the primary goal of the present study is to investigate the impact of reduced EF on FFR and FFR-guided PCI in patients enrolled in the FAME trial.

Abbreviations: CAD, coronary artery disease; FAME, Fractional flow reserve versus Angiography for Multivessel Evaluation; FFR, fractional flow reserve; MACE, major adverse cardiac event(s); MI, myocardial infarction; P_a, mean proximal coronary pressure; P_d, mean distal coronary pressure; P_v, mean central venous pressure; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography.

* Corresponding author at: Division of Cardiovascular Medicine, Stanford University Medical Center, 300 Pasteur Drive, H2103, Stanford, CA 94305-5218, USA.
E-mail address: wfearon@stanford.edu (W.F. Fearon).

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2. Methods

2.1. Study design and patient population

The detailed study protocol has been published previously [6,8,9]. In brief, the FAME trial is a prospective, randomized, controlled, multicenter trial investigating the superiority of FFR-guided PCI over angiography-guided PCI in patients with multivessel CAD (NCT00267774). In patients with multivessel CAD amenable to PCI, the investigators indicated which lesions had at least 50% diameter stenosis and were thought to require PCI. Thereafter, patients were randomly assigned to either FFR-guided or angiography-guided PCI. In patients assigned to FFR-guided PCI, only functionally significant lesions with FFR ≤ 0.80 were treated with PCI, whereas in patients assigned to angiography-guided PCI, all indicated lesions were treated without the measurement of FFR.

Patients with ST-segment elevation myocardial infarction (MI) could be enrolled if the infarction had occurred at least 5 days before PCI. On the other hand, patients with unstable angina or non-ST-segment elevation MI were allowed to be enrolled earlier than 5 days if the peak creatinine kinase was <1000 IU. Patients were excluded if they had significant left main coronary artery disease, previous coronary artery bypass surgery, cardiogenic shock, or extremely tortuous or calcified coronary arteries. Patients were further excluded from the present substudy if the EF value was not available. This study was approved by an institutional review committee of each participating site and informed consent was obtained from all patients.

2.2. FFR measurement and treatment

PCI was performed according to standard coronary interventional techniques primarily with drug-eluting stents. FFR was measured with a 0.014 in. pressure sensor guidewire (St. Jude Medical, Uppsala, Sweden). After equalization to the guide catheter pressure with the sensor positioned at the ostium of the coronary artery, the pressure guidewire was advanced down the target coronary artery. To induce maximal hyperemia, intravenous adenosine was administered at 140 μg/kg/min through a central vein. Simultaneous measurement of the mean proximal coronary pressure with the guide catheter and the mean distal coronary pressure with the pressure guidewire was performed. FFR was calculated as the ratio of the mean distal to proximal coronary pressure at hyperemia. All patients received dual antiplatelet therapy with aspirin and clopidogrel for at least 1 year after PCI [6,8,9].

2.3. End points

An independent clinical events committee whose members were blinded to treatment strategy adjudicated all events. The primary endpoint of this reanalysis was same as that of the original FAME trial: major adverse cardiac events (MACE, defined as a composite of all-cause death, MI, or any repeat revascularization), and its components (all-cause death, MI, repeat revascularization, and death or MI) at 1 year after the index procedure in the preserved and reduced EF groups with the cutoff value of 50%. To date, preserved EF is variably defined as an LVEF >40%, >45%, or 50% in the context of patients with heart failure [10]. In this substudy, we found that the 25th percentile of the EF value was 50% and therefore we chose this cutoff value to investigate the effect of any degree of left ventricular dysfunction. Secondary goals of this reanalysis were to assess the impact of EF on FFR values and compare FFR values between patients with preserved and reduced EF according to the angiographic stenosis severity. The above mentioned analyses were repeated with an EF cutoff of 40% to test whether the results of this substudy can be applied to the patients with more severe LV dysfunction.

2.4. Statistical analysis

All patients were included in the reanalysis of the present study according to the intention-to-treat principle, as long as the EF value was available. Categorical variables, including the primary endpoint and its individual components, are presented as counts and percentages. Pearson's χ [2] test or Fisher's exact test was used for comparisons of categorical variables, as appropriate. The interaction between EF and treatment strategy was analyzed with a Breslow–Day test [11]. Continuous variables are presented as mean and standard deviation. Normality of the continuous variables was confirmed with a Shapiro–Wilk test. Depending on the result of a Levene test for homoscedasticity, variables with normal distribution were compared with a Student *t*-test or a Welch *t*-test, as appropriate. If the normality test failed, variables were compared with a Mann–Whitney *U* test. The Spearman's correlation coefficient (ρ) between FFR values and EF was obtained. Kaplan–Meier curves are shown for the time-to-event distributions of MACE in all enrolled patients stratified by EF group and treatment strategy. Patients were censored at 1 year (365 days) or when events occurred. Lesions with FFR measurements were divided into the 4 quadrants using cutoff values of FFR = 0.80 and %diameter stenosis = 50%, and were demonstrated on the scatter-plot graphic. An overall difference of EF among subgroups was determined by one-way ANOVA test, and differences between individual subgroups were estimated using a Games–Howell test. A two-sided p value of <0.05 was considered statistically significant. All analyses were performed using SPSS 21 software® (SPSS Inc., Chicago, Illinois).

3. Results

An EF value was available in 915 out of 1005 patients from the FAME trial database. Overall the mean EF was 57.3 ± 10.9%, ranging from 20 to 80%. The assessment method was unknown in 14 patients and included EF calculated from left ventriculography (n = 461), echocardiography (n = 289), or scintigraphy (n = 79), and visually estimated from any of these modalities (n = 72) in the other 901 patients. Accordingly, we performed reanalysis of the 915 patients, consisting of 458 patients in the FFR-guided PCI arm and 457 patients in the angiography-guided PCI arm.

3.1. Comparisons of baseline data between the preserved vs. the reduced EF group

Comparisons of clinical, angiographic, and procedural characteristics between the preserved (EF > 50%) and reduced (EF ≤ 50%) EF groups are summarized in Table 1. Mean EF values of the preserved and reduced EF groups were 62.5 ± 7.0 and 43.0 ± 8.8%, respectively (p < 0.001). Baseline patient clinical characteristics including age, sex, and risk factors were similar between two groups, except for the higher incidence of hypertension and current cigarette smoking in the reduced EF group (69.0 vs. 61.7%, p = 0.04 and 33.7 vs. 27.0%, p = 0.045, respectively). A history of MI was significantly more frequent in the reduced EF group than the preserved EF group (55.2 vs. 30.2%, p < 0.001).

The number of lesions intended to treat and the total number/length of stents used were similar between the two groups. The complexity of CAD as assessed by the SYNTAX score tended to be higher in the reduced EF group than the preserved EF group (15.7 ± 9.8 vs. 14.2 ± 8.3, p = 0.07). In the reduced EF group, procedure time was significantly longer (72.5 ± 38.0 vs. 69.6 ± 45.3 min, p = 0.03), and the volume of contrast agent used during the procedure tended to be higher (297.6 ± 127.5 vs. 284.1 ± 135.0 ml, p = 0.08).

3.2. Clinical outcomes

Comparisons of outcomes at 1 year between the preserved and reduced EF patients are summarized in Table 2. The primary endpoint of