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Fractional Flow Reserve Guided PCI in Patients With and Without Left Ventricular Hypertrophy: a DANAMI-3-PRIMULTI Sub-study

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Running title
FFR-Guided PCI in Left Ventricular Hypertrophy.

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Conflicts of interest
The authors have no conflicts of interest to declare.

Abstract

Aims: To investigate the correlation between fractional flow reserve (FFR) and diameter stenosis in patients with STEMI with and without left ventricular hypertrophy (LVH), and the influence of LVH on complete FFR-guided revascularization versus culprit only, in terms of risk of clinical outcome.

Methods and results: In this DANAMI-3-PRIMULTI sub-study, 279 patients with STEMI had cardiac magnetic resonance (CMR) for assessment of left-ventricular-mass-index. Ninety-six patients had FFR evaluation of a non-culprit lesion. Diameter stenosis of the non-culprit lesion was determined with 2-dimensional quantitative-coronary-analysis. The diameter stenosis (56.9% vs. 54.3%, p=0.38) and FFR value (0.83 vs. 0.85, p=0.34) were significantly correlated in both groups (Spearmans ρ=-0.40 and -0.41 without LVH and with LVH, respectively; p<0.001) but was not different between patients without and with LVH (p for interaction =0.87). FFR-guided complete revascularization was associated with reduced risk of death, myocardial infarction or ischemia-driven revascularization for both patients without LVH (HR 0.42, 95%CI 0.20-0.85) and for patients with LVH (HR 0.50, 95%CI 0.17-0.47), with no interaction between the FFR-guided complete revascularization and LVH (p for interaction =0.82).

Conclusion: LVH did not interact with the correlation between diameter stenosis and FFR and did not modify the impact of complete revascularization on the occurrence of subsequent clinical events.

Classifications

Fractional flow reserve, STEMI, multiple vessel disease.

Condensed abstract

Fractional flow reserve guided (FFR) percutaneous coronary intervention (PCI) is becoming more common but has not been validated in patients with left ventricular hypertrophy (LVH). We investigated the interaction of LVH (measured with cardiac magnetic resonance) on the correlation between diameter stenosis and FFR in patients with STEMI randomized to complete revascularization or culprit only in the DANAMI-3-PRIMULTI trial. LVH showed no interaction with the effect of diameter stenosis on FFR. Moreover, LVH did not modify risk of clinical outcome related to treatment randomization. FFR-guided PCI of non-culprit lesions in patients with STEMI in DANAMI-3-PRIMULTI appears to be safe.

Abbreviations

ANCOVA=analysis of covariance

CFR=coronary flow reserve

CMR=cardiac magnetic resonance

FFR =fractional flow reserve

LVEF=left ventricular ejection fraction

LVH =left ventricular hypertrophy

LVM =left ventricular mass

LVMi=left ventricular mass index

QCA=quantitative coronary angiography

STEMI=ST-segment elevation myocardial infarction

Introduction

Fractional flow reserve (FFR) guided percutaneous coronary intervention (PCI) has not been validated in patients with left ventricular hypertrophy (LVH). FFR is a pressure-derived index used to assess the functional importance of coronary stenoses. FFR is defined as the ratio of distal coronary pressure to aortic pressure during maximal hyperaemia. An FFR value of 0.80 or less is considered physiologically significant. FFR-guided PCI has been validated extensively in randomized clinical trials of single and multivessel disease [1–3]. Moreover, FFR-guided complete revascularization is superior to medical treatment in patients with both stable coronary artery disease and ST-segment elevation myocardial infarction (STEMI) [4–6].

The impact of LVH on FFR measures has not been investigated in any of these trials. Moreover, it is not known if the current cut-off value for treatment applies in patients with LVH. Theoretically, a larger subtended myocardium is expected to contain a higher total capillary number, and thereby a decreased resistance to flow. This translates to greater hyperaemic flow, increasing the pressure-drop across a stenotic vessel, thereby lowering FFR. Contrarily, in patients with LVH factors such as extravascular compression, increased LV pressures and microvascular dysfunction may result in increased microvascular resistance, reduced hyperaemic flow and subsequently higher FFR value. The interplay between these factors and FFR is unknown. Furthermore, in severe cases of LVH, as in aortic stenosis, high intraventricular pressure in combination with (occasionally) low aortic pressure would be expected to skew FFR towards higher values independent of stenosis severity. In this study however, we only investigated LVH in patients with no valvular disease. In this sub-study of DANAMI in patients with STEMI and additional lesions in non-

culprit arteries, the utility of FFR was investigated in the presence of LVH to the extent which is found in a representative STEMI population. The prevalence of LVH in patients with STEMI has been reported to be 24% and associated with a higher risk of all-cause mortality and development of heart failure [7]. In patients with stable coronary disease the prevalence of LVH has been reported to be in the range of 16-50% [8–10].Therefore, it is important to investigate whether FFR-guided PCI in patients with STEMI is influenced by the presence of LVH and thereby affects clinical outcome compared to patients without LVH.

We investigated the correlation between the angiographically assessed diameter stenosis and FFR in STEMI patients with and without LVH and assessed the interaction of LVH with clinical outcome (composite of all-cause mortality, myocardial infarction or ischemia driven revascularization) in patients receiving culprit only versus complete revascularization. We hypothesized that patients with LVH, on average, had lower FFR at any given diameter stenosis, compared to patients without LVH.

Methods

Study population

This is a sub-study of the DANAMI-3-PRIMULTI trial [4], which was part of the DANAMI-3 trial program (clinicaltrials.gov identifier: NTC01435408) [11]. DANAMI-3 consisted of three different multicentre, randomized trials [4,12,13]. DANAMI-3-PRIMULTI investigated the effect of culprit only versus FFR-guided complete revascularization, on a composite of all-cause mortality, myocardial infarction or ischemia driven revascularization in patients with STEMI [4]. Out of 627

cases in DANAMI-3-PRIMULTI, 314 were randomized to full revascularization. As LVH was identified with cardiac magnetic resonance (CMR), we included only patients who had an index CMR done. CMR was only done in patients included in DANAMI-3-PRIMULTI at Rigshospitalet, Copenhagen. Patients were divided into two groups according to the presence of LVH. Enrolment was from March 2011 through February 2014.

Coronary angiography and FFR

Culprit lesion was treated with primary PCI in all patients. Patients randomized to complete revascularization underwent a second procedure with FFR-guided PCI of all lesions deemed suitable for PCI (angiographic diameter stenosis >50% in coronary artery branches with diameters ≥2 mm). The second procedure was performed at least 48 hours after the index procedure, but before discharge. FFR was not mandated in cases with a visually assessed diameter stenosis >90%. Intracoronary pressures were measured with a pressure wire (Abbott, Minneapolis, MN). Hyperaemia was induced with intravenous adenosine infusion at a rate of 140 μg/kg/min. FFR was assessed as the lowest recorded value during two minutes of continuous infusion.

Cardiac magnetic resonance

The CMR protocol has been described in detail elsewhere [7]. Briefly, CMR was performed during index admission following primary PCI, using a 1,5 Tesla scanner (Avanto;Siemens, Erlangen, Germany). Images were analysed by two independent observers, blinded to all clinical data, using Circle Cardiovascular Imaging Inc. (Calgary, Alberta, Canada). LV mass was measured from standard ECG-triggered

balanced steady-state free-precession cine images Endocardial and epicardial contours were traced manually, with the papillary muscles included in the ventricular cavity. Body surface area was calculated using the DuBois formula. LVH was defined as left ventricular mass indexed for body surface area (LVMi)>77 g/m^2 for men and 67 g/m^2 for women, based on CMR data from 44 healthy subjects [7].

Quantitative coronary analysis

Two-dimensional QCA was done offline using Medis, QAngio XA7.3.82.0. The contrast-filled guide catheter was used as a distance calibration standard. QCA was done by two independent investigators. Angiographic views with optimal stenosis delineation, contrast filling and least degree of foreshortening, were chosen. Measurements were performed on end-diastolic frames. Manual correction of edge detection and reference diameter was done whenever necessary. QCA parameters were diameter stenosis, lesion length and area stenosis.

Statistical analysis

Normality of data was evaluated with histograms. Differences in continuous variables were analysed using Student's t-test or Mann-Whitney's U test when data was not normally distributed. Differences between proportions were assessed with the χ^2-test or Fisher's exact test. Spearman's rank correlation coefficient was used to assess the correlation between diameter stenosis and FFR in each group. The interaction between LVH on the correlation between diameter stenosis and FFR was evaluated with an analysis of covariance (ANCOVA) model. Linear regression was used to assess the association between FFR and indexed left ventricular mass when corrected for

diameter stenosis. We used Cox regression analysis to calculate hazard ratios for the primary outcome. The assumption of proportionality of hazards was evaluated with partial residual plots (Schoenfeld residuals test). Evaluation of the assumption of linearity was not relevant as no continuous variables were included in the model. Interaction between the prognostic implications of treatment allocation, and the presence of LVH was tested in the Cox model. We used cumulated incidence rate curves to show differences between groups according to randomized treatment and LVH. Statistical analyses were done using IBM SPSS Statistics version 22. We considered p-values <0.05 to be significant.

Results

Baseline characteristics

All patients with available index CMR were included in the study and evaluated for long-term outcome (n=279, Figure 1). Of these, 71(25%) patients had LVH and 208(75%) had normal LVM. For the comparison between FFR and diameter stenosis on lesion-level in patients with and without LVH, all patients with at least one FFR measurement and index CMR were included, totalling 96 of the 314 cases randomized to FFR-guided full revascularization (Figure 1). The discrepancy between the number of cases with an FFR measurement (n=184) and the number of randomized cases (n=314) is explained in Figure 1. Of the 96 cases, 25 had LVH and 71 had normal LVM, corresponding to 34 and 100 lesions, respectively. Patients with and without LVH differed significantly in the frequency of posterior infarction, infarct size, LVEF and Killip class at discharge. All baseline characteristics are listed in Table 1.

Diameter stenosis, indexed left ventricular mass and FFR

There was no difference in the QCA parameters (diameter stenosis, area stenosis, lesion length) and FFR between groups (Table 2). The distributions of lesions in the major coronary branches were comparable. Differences in median, interquartile range, minimum and maximum values for diameter stenosis and FFR are shown in box-plots (Figure 2). Diameter stenosis was significantly associated with FFR in both groups (Spearmans ρ=-0.40 and -0.41 without LVH and with LVH, respectively; p<0.001 for both groups). LVH showed no interaction with this correlation in an ANCOVA model (p=0.87, Figure 3). Left ventricular mass index, as a continuous variable, was not significantly associated with FFR when corrected for diameter stenosis (β-coefficient 0.18, p=0.054). The correlation between area stenosis and FFR was comparable to that of diameter stenosis and FFR (Spearmans rho=0.40 for no-LVH and 0.41 for LVH, p<0.001 and p=0.016 respectively).

Outcome analysis

Median follow-up time was 23.4 months (interquartile range 16.5-33.0 months). In the present patient population hazard ratio was 0.44 (95%CI 0.24-0.80, p=0.007) for the primary outcome when randomized to FFR-guided complete revascularization, which is in line with the findings of the original study [4]. Figure 4 shows cumulated incidence rate curves according to LVH and treatment strategy (FFR-guided complete revascularization and culprit only). The hazard ratio was 0.50 (95%CI 0.17-1.47) for patients with LVH and 0.42 (95%CI 0.20-0.85) for patients without LVH favouring

FFR-guided complete revascularization, with no interaction between revascularization strategy and the presence of LVH (p=0.82).

Discussion

Findings

The main findings of this DANAMI-3-PRIMULTI sub-study was that LVH did not influence the correlation between FFR and diameter stenosis as assessed by QCA, nor the risk of clinical outcome following FFR-guided complete revascularization versus culprit only in patients with STEMI, although LVH in itself appears to impair prognosis, as demonstrated in another DANAMI-3 sub-study [7]. Thus, from a clinical perspective, the presence of LVH should not affect the interpretation and clinical use of FFR in stable non-culprit territories in patients with STEMI. The hazard ratio of 0.44 (95%CI 0.24-0.80, p=0.007) in this subpopulation was comparable to that reported for the entire DANAMI-3-PRIMULTI population (HR 0.56, 95%CI 0.38-0.83, p=0.004) [4]. This does not preclude the possibility of a different (higher) cut-off value for treatment when LVH is present, but perhaps suggests that it does not differ much from the current cut-off value.

Potential pathophysiological mechanisms

Hemodynamic theory poses that a large myocardium subtended by a stenotic vessel imposes a lower FFR at a given stenosis severity when compared to a smaller myocardium [14]. Theoretically this would mean that if the subtended myocardium has a mass of 50g and FFR in the stenotic vessel is 0.80, the same myocardium should, at an increase in mass to for example 60g, yield a lower FFR of for example 0.70

(Figure 5). An inverse relationship between the amount of myocardium subtended by a given stenotic vessel and FFR has been suggested [15]. In the study by Leone and colleagues, data was in accordance with theory, but patients with acute coronary syndrome and severe LVH were excluded [15]. This limits the comparability to our study as differences in size of subtended myocardium may still be within physiological range in their population. Another study of 84 patients compared correlations of diameter stenosis and FFR in matched vessels in patients with normal and increased LV mass, measured using contrast ventriculography [16]. They found no difference in FFR and no interaction of LVH on the relationship between diameter stenosis and FFR, which is in line with the findings in our study. Our study adds to previous observations, as LV mass was measured using CMR and provides information regarding clinical outcome following revascularization strategy in patients with LVH. The finding that the presence of LVH does not impact correlation between diameter stenosis and FFR can be explained by several factors: 1) LVH is associated with microvascular dysfunction and decreased coronary flow reserve [17–19]. 2) LVH is often accompanied by diastolic dysfunction, with increased levels of extravascular compression of the intramyocardial microcirculation. 3) The prevalence of smoking and diabetes, which both promote macrovascular disease but also impair microcirculatory function by decreasing nitric oxide production and bioavailability [20,21], is considerable. All these factors could antagonize the effect of an increase in functionally subtended myocardium. In other words, the absence of differing results may indicate that the influence of increased myocardium size on FFR is counter-balanced by decreased coronary flow reserve (microvascular dysfunction) and increased extravascular resistance. Consequently, existing data including results from

the present study show that the presence of LVH does not influence the correlation between the FFR value and diameter stenosis severity in patients with STEMI.

Future studies

One way to clarify how LVH modulates FFR would be to measure i) coronary flow reserve to assess microvascular dysfunction ii) absolute volumetric flow indexed to LV mass to assess baseline vasodilation (although capillary density would be a confounder) and iii) index of microvascular resistance and left ventricular end-diastolic pressure to assess total vascular resistance including the extravascular compressive component. In endurance athletes, physiological LVH is characterized by conserved capillary density, representing a "balanced" model of increased subtended myocardium size. A comprehensive physiological work-up as outlined above, may yield interesting findings, if performed in LVMi-matched subjects with pathological LVH and exercise-induced LVH. In addition, pathological LVH from different patient categories, for example, hypertension, aortic stenosis may be different and should be examined. However, in the present setting LVH did not indicate a need for change in decision making, as it did not affect clinical outcome.

Limitations

This is a retrospective study and non-prespecified sub-analysis. CMR was only done at one site (Rigshospitalet). Thus, CMR data was available for only 279 of the total 627 (45%) patients in DANAMI-3-PRIMULTI. However, the hazard ratio for clinical outcomes was comparable to that of the original study [4]. STEMI causes myocardial edema in the infarct area, which could have influenced the CMR estimation of LVM

and thus LVH [7]. Patients with LVH had significantly larger infarct size which may have influenced FFR in non-culprit arteries. QCA should ideally have been performed by a core laboratory. There was a weak correlation between diameter stenosis and FFR. However, this is not unique for our study and has been shown previously in several studies [22,23]. An effect of LVH on the relation between diameter stenosis and FFR (type 2 error) cannot be excluded as the number of cases with data on both CMR and FFR was small. The number of lesions for analysis was limited because FFR was not measured in the culprit-only arm of DANAMI-3-PRIMULTI. Moreover, the lack of FFR measurement in vessels with diameter stenosis >90% constrained FFR values to a narrow range (Table 2). This likely made it harder to detect differences in the correlation between diameter stenosis and FFR, which may have been more pronounced at greater stenosis severity. However, any potential difference between groups was likely small as clinical outcome was not affected by LVH, although this may also be due to a negligible impact of FFR values near 0.80 on prognosis [24]. Non-hyperaemic pressure measurements were not available for analysis. Finally, an effect of LVH on FFR in severe hypertrophic patients such as those with aortic stenosis cannot be excluded based on the findings in this study.

Conclusions

In the DANAMI-3-PRIMULTI population of patients with STEMI, presence of mild to moderate LVH did not influence the correlation between FFR value and diameter stenosis. The advantage of FFR-guided complete revascularization compared to culprit lesion only, was similar between patients with and without LVH.

Impact on daily practice

FFR-guided PCI has become widespread but has not been validated in patients with left ventricular hypertrophy (LVH). In this retrospective study of the DANAMI-3-PRIMULTI trial we showed that LVH (measured with cardiac magnetic resonance), in patients with STEMI randomized to complete FFR-guided or culprit only PCI, does not interact with the correlation between diameter stenosis and FFR. Importantly, the advantage of FFR-guided complete revascularization compared to culprit lesion only was similar between patients with LVH and without LVH.

Funding

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Figure legends

Figure 1. Title: Venn diagram illustrating how data was obtained.

Legend: FFR was done in 184 cases of the 314 cases randomized to full FFR-guided revascularization. In 81 cases FFR was not measured due to diameter stenosis > 90% [25]. In 35 cases FFR data was not available as the procedure was performed at another site. In the remaining 14 cases FFR was not measured due to technical issues (n = 8), periprocedural complications (n = 3), logistical and other reasons (n = 3). CMR was done in 279 cases. FFR and CMR were performed in 96 of the total 314 cases.

Figure 2. Title: Diameter stenosis and FFR in patients with and without LVH.

Legend: Boxplots showing the median, interquartile range, minimum and maximum values for diameter stenosis (left) and FFR (right). There were no significant differences between groups for either variable.

Figure 3. Title: Correlation between diameter stenosis and FFR in patients with and without LVH.

Legend: Trendlines for each group are shown. Trendlines were not significantly different when analysed in an ANCOVA model (p for interaction = 0.87).

Figure 4. Title: Cumulated incidence rate curves of patients randomized to treatment of culprit only or complete revascularization. Legend: patients are grouped according to presence of LVH. There was a significant difference between treatment groups (p = 0.007), but no difference between treatment groups when grouped according to LVH (p for interaction = 0.82).

Figure 5. Title: **S**implified theoretical relationship between size of subtended myocardium and FFR at a given stenosis severity. Legend: an increase in subtended myocardial mass at an arbitrarily chosen diameter stenosis is expected to result in a lower FFR. P_a indicates aortic pressure; P_d, distal coronary pressure; FFR, fractional flow reserve; LV, left ventricle; DS, diameter stenosis.

Table 1. Baseline and periprocedural characteristics

Variable	No LVH	LVH	p-value
	(n =208)	(n = 71)	
Age, y	61 (±11)	61 (±11)	0.97
Male sex	170 (82)	63 (89)	0.35
Medical history			
Diabetes mellitus	17 (8)	6 (8)	0.95
Smoking	111 (53)	41 (58)	0.54
Hypertension	69 (33)	32 (45)	0.15
Previous stroke	11 (5)	5 (7)	0.84
Previous MI	7 (3)	2 (3)	>0.999
STEMI parameters			
Anterior infarct on ECG	68 (33)	30 (45)	<0.001*
Inferior infarct on ECG	130 (63)	37 (52)	
Posterior infarct on ECG	10 (5)	2 (3)	
Percutaneus coronary intervention			
Trombectomy	117 (56)	36 (51)	0.39
Arteries treated per patient	1 (1-2)	1 (1-2)	0.62
Implanted stents	1 (1-2)	1 (1-2)	0.91
Stent diameter, mm	3.0 (2.6-3.5)	3.1 (2.9-3.5)	0.30
Total stent length, mm	23 (15-39)	23 (18-41)	0.94
Stent type			
No stenting	12 (6)	3 (4)	0.85
Bare metal	2 (1)	2 (3)	

Drug-eluting	194 (93)	66 (93)	
Use of glycoprotein IIb/IIIa Inhibitor	51 (25)	16 (23)	0.81
Use of bivalirudin	141 (68)	56 (79)	0.15
CMR parameters			
LVMi, g/m^2	61.4 (55.9-66.9)	84.1 (79.0-86.4)	
Concentric hypertrophy Eccentric hypertrophy	- -	33 (46) 38 (54)	-
Infarct size, % of LV mass	13.0 (6.8-22.2)	21.8 (13.0-31.8)	<0.001
LVEF, %	53 (46-59)	46 (38-52)	<0.001
Medication at discharge			
Antiplatelet drug			
Aspirin	204 (98)	71 (99)	0.95
Clopidogrel	17 (8)	4 (6)	0.50
Prasugrel	163 (78)	52 (72)	
Ticagrelor	27 (13	14 (19)	
Statin	208 (100)	71 (99)	0.23
ACE inhibitors/ARB	70 (34)	43 (61)	0.03
β-blocker	190 (91)	64 (90)	0.91
Aldosteron receptor antagonist	4 (2)	3 (4)	0.39
Calcium antagonist	16 (8)	10 (14)	0.26
Clinical status at discharge			
Killip class II-IV	3 (1)	7 (10)	0.01

Table 1. Baseline characteristics. Data are presented as mean±SD, median (interquartile range) or n (%). LVH indicates left ventricular hypertrophy; MI, myocardial infarction; LV, left ventricle; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement;

LVMi, left ventricular mass indexed to body surface area; CMR, cardiac magnetic resonance imaging; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. Chi-square test was calculated, unless stated otherwise. *Significant difference in frequency of posterior infarction.

Table 2. Lesion characteristics

Variable	No LVH	LVH	p-value
	n lesions = 100	n lesions = 34	
Diameter stenosis (by QCA), (%)	56.90 (49.4-64.1)	54.30 (49.40-60.3)	0.38
Area stenosis (by QCA), (%)	81.4 (74.4-87.1)	79.1 (74.4-84.2)	0.65
FFR	0.83 (0.75-0.89)	0.85 (0.80-0.89)	0.34
Reference diameter, mm	2.42 (2.10-2.80)	2.53 (2.09-2.94)	0.42
Minimal lumen diameter, mm	1.00 (0.77-1.32)	1.12 (0.88-1.40)	0.18
Stenosis length, mm	9.67 (7.09-13.53)	10.71 (7.01-14.54)	0.54
Artery			
Left main (%)	3 (3)	1 (3)	
Left anterior descending (%)	37 (37)	10 (29)	0.53
Right coronary artery (%)	11 (11)	5 (15)	
Left circumflex artery (%) (proximal, middle and OM1)	32 (32)	12 (35)	
Others (%)	17 (17)	6 (18)	

Table 2. Lesion characteristics. Data are presented as median (interquartile range) or n (%). P-values were calculated using Mann-Whitney test. OM1 indicates obtuse marginal artery 1.