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Influence of coronary calcification on hyperemic response during fractional flow reserve measurements

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ABSTRACT

Aim: During invasive fractional flow reserve (FFR) adenosine and nitrates are used to obtain maximal hyperemia. Severe coronary artery calcification (CAC) is associated with impaired vasodilation. We investigated the hyperemic response during FFR in vessels with severe versus mild CAC.
Methods and results: We retrospectively selected 236 patients who underwent both CAC scoring and invasive FFR. FFR was performed in 304 vessels with intermediate stenoses. Delta (Δ) FFR, the pressure gradient before the administration of adenosine minus FFR after the administration of adenosine, was used to investigate the hyperemic response. Mean age of the total population was 65 ± 10 years, 65% was male. Median CAC score was 510 (range 0 to 6141). Mean pressure gradient before the administration of adenosine was comparable in vessels with severe versus mild CAC. FFR was more often ≤0.80 in vessels with severe CAC ($p = 0.045$). Patients with a large Δ FFR were younger ($p = 0.05$). There was no association between Δ FFR and severity of calcifications. Regression analysis did not demonstrate an association between CAC score and the hyperemic response ($p = 0.49$).
Conclusion: We did not find an association between the severity of CAC and the hyperemic response during invasive FFR.

1. Introduction

Invasive fractional flow reserve (FFR) measurement is increasingly used to determine the functional significance of a coronary artery stenosis [1,2]. Maximal hyperemia is crucial for accurate FFR measurements and is usually induced by a combination of adenosine and nitroglycerin [3–5]. Increased coronary calcification is common in patients with coronary stenoses and is associated with impaired vasodilation. The extent of coronary calcification has been associated with impaired coronary flow reserve as assessed by positron emission tomography [6]. FFR is a macrovascular measurement, but is closely related to the vasodilator capacity of the microvasculature [7]. The hyperemic response during FFR, defined as the decrease in FFR compared to baseline pressure gradient, delta (Δ) FFR, may reflect the compensatory capacity of microvascular circulation [7]. Previous studies suggest that age, body mass index and hypercholesterolemia are independent predictors for Δ FFR in addition to angiographic lesion severity and lesion length [8]. Little is known about a possible relationship between coronary calcification and Δ FFR. It is suggested that a lower Δ FFR is associated with a worse prognosis and therefore this might have clinical implications [7,8]. We investigated whether the hyperemic response differs between vessels with mild versus vessels with severe calcifications.

2. Methods

2.1. Study population

This was a retrospective study in which we selected 236 consecutive patients with stable angina who underwent invasive coronary angiography with FFR measurements of intermediate coronary artery lesions and who had also undergone coronary artery calcification (CAC) score assessment by computed tomography (CT). CT and invasive FFR were performed in Isala hospital, Zwolle, the Netherlands between November 2009 and May 2014, the maximum interval between CT and invasive FFR was 6 months.

FFR measurements of visually estimated intermediate coronary lesions in different vessels in the same patient could be performed, resulting in 304 coronary artery stenoses that were assessed by FFR. Patients were prospectively enrolled in a registry, as previously described [9]. Retrospective analyses were performed. Because the participants of the registry were neither subject to research procedures nor were required to follow rules of behavior, the accredited Committee on Research Ethics of our hospital (Isala, Zwolle)

Abbreviations: Δ, delta; BMI, body mass index; CAC, coronary artery calcification; CT, computed tomography; Cx, circumflex artery; FFR, fractional flow reserve; LAD, left anterior descending artery; LM, left main artery; RCA, right coronary artery; QCA, quantitative coronary angiography.

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decided that the study did not fall under the scope of the medical research involving human subjects act.

2.2. Clinical information

Information regarding patients' age, gender, weight and height were collected by written questionnaires. Demographic information, medical history, cardiac risk factors and medical use were collected likewise. The data were verified and completed with information collected from medical records. Current smoking was defined as at least one cigar, cigarette or pipe a day. Diabetes was defined as hyperglycemia with HbA1c of 6.5% or more, or as current use of oral anti-diabetic medication or insulin. Hypertension was stated as a blood pressure measured higher than 140/90 mmHg for at least three times or the use of antihypertensive medication for the indication of hypertension. Hypercholesterolemia was stated as fasting total cholesterol ≥5.0 mmol/L or the use of lipid lowering drugs. A positive family history was defined as a first-degree family member <60 years of age with coronary artery disease.

2.3. Computed tomography-coronary artery calcification scan

The CT-based CAC score scans were performed using a 64-slice CT-scanner. Dedicated software (SmartScore, Advantage Windows 4.4; GE Heathcare) automatically calculated the CAC score as introduced by Agatston et al. [10]. The area of calcification (mm^2) of pixels with an intensity larger than 130 Houndsfield units is multiplied with a factor 1 to 4 depending on density, the cumulative value of all calcifications provides the Agatston score. Experienced operators manually assigned the calcifications to the vessels to ensure inclusion of all calcified regions and to exclude calcium depositions outside the coronary arteries. Total CAC scores as well as CAC scores on vessel level were calculated.

2.4. Coronary angiography

Invasive coronary angiography was performed by a radial or femoral approach using a 6Fr diagnostic or guiding catheter. The angiogram was repeated in the projection allowing the best possible visualization of the coronary stenosis. Two independent interventional cardiologists estimated the severity of the coronary artery disease visually. In case of discrepancies a third interventional cardiologist was asked. Visually a diameter stenosis <30% was interpreted as normal in the right coronary artery (RCA), the left anterior descending artery (LAD) and in the circumflex artery (Cx). Visual stenoses ≥30% and <70% were interpreted as being intermediate and stenoses ≥70% were considered anatomically significant. Left main artery (LM) stenoses were considered significant if diameter stenosis was ≥50%. Visual LM stenoses ≥30% to 50% were considered as being intermediate [2].

2.5. Pressure measurement

All patients underwent FFR measurements of at least one coronary stenosis. By invasive coronary angiography a 0.014 in. pressure monitoring wire (RADI Pressure wire, RADI Medical Systems AB, Uppsala, Sweden or Primewire PRESTIGE® Pressure guide wire, Volcano Inc., Rancho Cordova, California, USA) was advanced through a guiding catheter and positioned distal to the coronary artery stenosis. Maximal coronary blood flow was obtained by continuously infusion of adenosine (140 μg/kg/min) intravenously to achieve minimal distal coronary pressure. Nitroglycerin was administered routinely. FFR was calculated as the mean distal coronary pressure measured by the pressure wire, divided by the mean aortic pressure at the tip of the guiding catheter. FFR values ≤0.80 were considered functionally significant [1,11]. The decrease in pressure gradient after the administration of adenosine from baseline was defined Δ FFR (Pd/Pa rest minus Pd/Pa stress).

2.6. Data collection and statistical analysis

All data were stored in an IBM SPSS statistics 20.0 database. Absolute CAC scores were categorized into percentiles based on the distribution of CAC score based on gender and age [12]. Total CAC scores and CAC scores at vessel level were analysed. CAC scores on vessel level were used to analyse the potential influence of coronary calcium on the FFR measurement of the according artery.

CAC scores at vessel level were analysed as continuous variable and a dichotomous variable was made: a CAC score in the highest quartile was defined as ‘severe CAC’, the other quartiles were considered ‘mild CAC’. Δ FFR was analysed both as continuous variable and as categorical variable, with the ‘Δ FFR’ divided into quartiles. The highest quartile was defined as ‘large Δ FFR’, the remainder was defined ‘small Δ FFR’.

We used two previous studies after Δ FFR to perform a simple size calculation [7,8]. Based on the mean Δ FFR in these studies we assumed that the mean Δ FFR in our study would be 0.12 ± 0.05. We considered a difference in Δ FFR of 0.03 as a significant difference between the groups with severe versus mild CAC. With a power of 80% and α 0.05 we calculated that we needed a sample size of 44 patients to demonstrate a difference between both groups.

Statistical analysis was performed with IBM SPSS Statistics 20.0 (SPSS Inc. Chicago, Illinois, USA). Quantitative variables were reported as median with range or mean ± standard deviation. Categorical variables were reported as frequencies and percentage. Continuous variables were compared using an unpaired *t*-test or a nonparametric Mann-Whitney *U* test. Normal distribution was tested using the test of normality. In correlation analyses, categorical variables were analysed using Pearson's Chi-square test or Fisher exact test, as appropriate. Linear regression analyses and multivariate analyses were performed to study the relation between the severity of coronary calcifications, using CAC score of the according artery, and the Δ FFR. A p value <0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics and CAC scores

A total of 236 patients were included in this study. Mean age was 65 ± 10 years, 65% were male. 68% of the patients had hypertension and 57% had hypercholesterolemia. A positive family history of coronary artery disease was seen in 56% of the patients. Over 20% of the patients had diabetes mellitus and approximately 16% were current smokers. Median CAC score was 510, with a range from 0 to 6141. The CAC score was zero in two patients (0.8%). CAC score was ≥1000 in 76 patients (32%). 44% of the patients had a CAC ≥90th percentile based on age and gender. ‘Severe CAC’, defined as a CAC score in the highest quartile, were patients with CAC score ≥ 1341. These patients were more often older ($p = 0.001$). Current smokers had more often mild CAC ($p = 0.006$). Other baseline characteristics were comparable in both groups.

In Table 1, clinical characteristics on vessel level are demonstrated. Also on vessel level, severe CAC was associated with older age. Also hypercholesterolemia was seen more often in case of severe CAC. Other baseline characteristics were comparable.

3.2. FFR measurements

FFR measurements were performed in the RCA ($n = 54$), LM ($n = 13$), LAD ($n = 168$) and Cx ($n = 69$). Of all 304 FFR measurements 41% had a value ≤0.80. Mean pressure gradient before the administration of adenosine was comparable in vessels with severe versus mild CAC. FFR was more often ≤0.80 in vessels with severe CAC ($p = 0.045$). In the LAD, mean FFR value was 0.79. Mean Δ FFR in all vessels was 0.11 ± 0.06. Mean Δ FFR in the RCA was 0.10, in the LM 0.10, in the LAD 0.12 and in the Cx 0.10. Mean Δ FFR did not differ between vessels with mild versus severe CAC, this is displayed in Fig. 1.

Δ FFR ≥0.15 was defined ‘large Δ FFR’ (highest quartile). Table 2 displays the similarities and differences in clinical characteristics in patients with a small versus large Δ FFR. Patients with a large Δ FFR were more often younger ($p = 0.05$) and a large Δ FFR was seen more often in the LAD. Almost all vessels with a large Δ FFR had a corresponding FFR ≤0.80 (94%). We did not find an association between the

Table 1
Clinical characteristics at vessel level comparing mild CAC with severe CAC, $n = 304$.

Clinical characteristics	Mild CAC (%) $n = 229$	Severe CAC (%) $n = 75$	p[a]
Age, mean (years)	64.4 ± 10.1	66.9 ± 8.5	0.04*
Male gender	152 (66.4%)	51 (68%)	0.80*
BMI (kg/m^2)	27.6 ± 4.3	28.8 ± 4.7	0.07*
Current smoker	45 (19.8%)	7 (9.3%)	0.04*
Diabetes mellitus	42 (18.3%)	19 (25.3%)	0.19*
Hypercholesterolemia	128 (56.0%)	53 (70.7%)	0.02*
Hypertension	160 (70.0%)	49 (65.3%)	0.46*
Positive family history	135 (59.0%)	42 (56.0%)	0.65*
CAC score, median	402 (0–3446)	1853 (682–6141)	<0.001*
LAD location	126 (55%)	42 (56%)	0.88*
Pressure gradient before adenosine, mean	0.93 ± 0.07	0.92 ± 0.08	0.23*
FFR significant (≤0.80)	86 (37.6%)	38 (50.7%)	0.045*

Values are n (%), mean ± SD, or median with range. BMI, body mass index; CAC score, coronary artery calcification score; FFR, fractional flow reserve; LAD, left anterior descending artery.

[a] Based on a t-test for continuous normally distributed variables, for body mass index and CAC score the Mann-Whitney U test was used, and the χ^2 was used for dichotomous variables.

* p value <0.05.

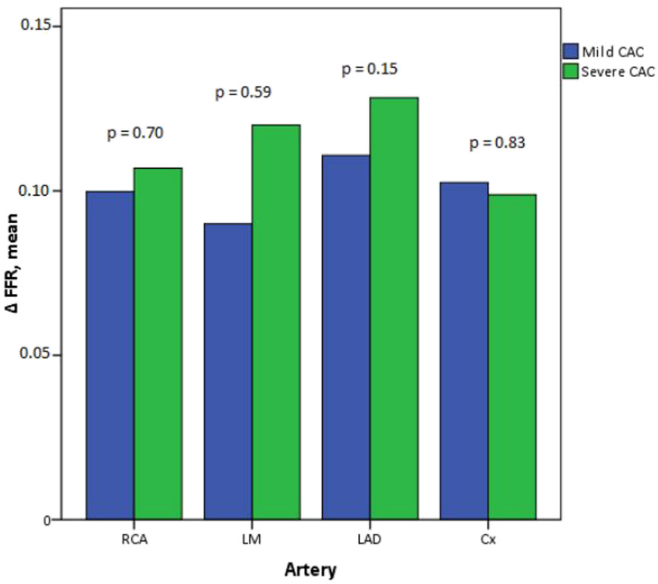

Fig. 1. Mean Δ FFR in coronary arteries with severe versus mild coronary artery calcifications.

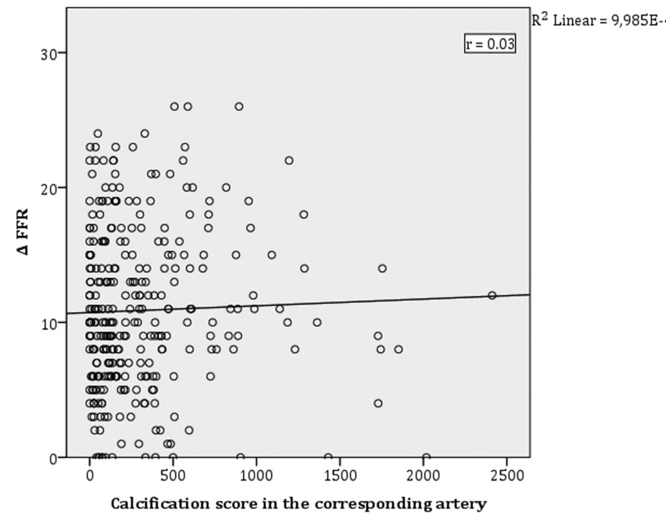

Fig. 2. Correlation between Δ FFR and the calcium score in the corresponding coronary artery.

absolute CAC scores and Δ FFR on patient level. Also on vessel level, we did not find a correlation between Δ FFR and the CAC score in the according vessel (Fig. 2). Linear regression analyses, adjusted for age, gender, pressure gradient before administration of adenosine and LAD lesion location did not show an association between Δ FFR and CAC score ($p = 0.49$). Multivariate analyses adjusted for age, gender, pressure gradient before adenosine and LAD lesion location did not display a relation between large Δ FFR and CAC score (odds ratio 1.00; 95% confidence interval 1.00–1.00). Also there was no relation between a large Δ FFR and severe CAC (odds ratio 0.63; 95% confidence interval 0.30–1.32).

4. Discussion

We did not find an association between the severity of coronary artery calcification and the influence on the hyperemic response during invasive FFR measurements in visually intermediate coronary artery stenoses which suggests that the hyperemic response is intact in the presence of severe coronary calcification.

Given the importance of FFR measurement in current daily practice and the increase of (severe) coronary calcification in an older population, potential influence of calcification on final FFR measurement is of major clinical relevance [2,13]. If severe coronary artery calcification impairs the hyperemic response, this might result in higher FFR values [14].

In our study, 41% of all FFR measurements had a value ≤0.80, this is consistent with other studies using FFR in intermediate coronary artery stenoses and represents daily practice [15–17]. Our finding that severe CAC does not impair the hyperemic response during FFR measurements is consistent with a study in dogs, suggesting that the vasodilator function of the microvasculature is preserved even in the presence of severe coronary artery stenoses [18]. Since adenosine mainly causes vasodilation in the coronary microvasculature, and coronary calcification occurs predominantly in the epicardial vessels [18–20], a possible association might have been only indirect.

In contrast, previous research demonstrated impaired nitroglycerin-induced vasodilation in severe coronary artery calcification [21,22]. We administered both adenosine and nitroglycerin and found no association. This might be explained by the fact that the relative magnitude of vessel dilation is inversely related to the vascular diameter, such that coronary microvessels dilate to a greater extent than epicardial vessels [18–20]. That coronary flow reserve demonstrated by positron emission tomography is impaired in patients with severe coronary artery calcification [6] might be explained by the fact that coronary flow reserve is influenced by both the microvascular and epicardial compartment.

Our findings that a larger Δ FFR is associated with younger age and LAD territories are consistent with the previous studies [7,8]. A possible explanation for a larger Δ FFR in younger patients, can be that younger patients have an intact microcirculation and a more pronounced hyperemic response. LAD territories can have a larger hyperemic response due to a larger myocardial mass [7,8].

4.1. Limitations

We have to keep in mind that we defined the hyperemic response as Δ FFR, which is also greatly influenced by diameter stenosis. However, we did not use quantitative coronary angiography (QCA) to determine the diameter stenosis, which could reduce some inter-cardiologist variability associated with visual assessment of diameter stenoses. However, QCA does not discriminate the functional severity of a coronary

Table 2
Baseline characteristics at vessel level, comparing small Δ FFR with large Δ FFR, $n = 304$.

Clinical characteristics	Small Δ FFR (%) $n = 222$	Large Δ FFR (%) $n = 82$	p^a
Age (years)	65.7 ± 10.0	63.3 ± 9.0	0.05*
Male gender	143 (64%)	60 (73%)	0.15*
BMI (kg/m^2)	28.0 ± 4.5	27.8 ± 4.2	0.76*
Current smoker	35 (16%)	17 (21%)	0.31*
Diabetes mellitus	45 (20%)	16 (20%)	0.88*
Hypercholesterolemia	136 (61%)	45 (55%)	0.31*
Hypertension	155 (70%)	54 (66%)	0.51*
Positive family history	133 (60%)	44 (54%)	0.33*
CAC score, median	545 (8–6141)	585 (0–3717)	0.62*
CAC score ≥ 1000	78 (35%)	29 (35%)	0.97*
LAD location	115 (52%)	53 (65%)	0.046*
FFR significant (≤0.80)	47 (21%)	77 (94%)	<0.001*
Δ FFR, mean	0.08 ± 0.04	0.19 ± 0.03	<0.001*

Values are n (%) or mean ± SD, or median with range. BMI, body mass index; CAC score, coronary artery calcification score; FFR, fractional flow reserve; LAD, left anterior descending artery.
[a] Based on a t-test for continuous normally distributed variables, for body mass index and CAC score the Mann-Whitney U test was used, and the χ^2 was used for dichotomous variables.
* p value <0.05.

stenosis and has an overall low concordance with FFR of only 61%, in patients with intermediate coronary artery stenoses [23–25]. We wanted our study to represent routine daily practice, and in clinical practice QCA is not frequently used [26]. Furthermore, QCA has low accuracy for the identification of coronary calcifications [27]. FFR measurements were performed only in case of visually intermediate coronary stenosis and by correcting for the pressure gradient before the administration of adenosine we tried to correct for the stenosis severity.

A second limitation is the sample size of the study. We performed a sample size calculation based on the Δ FFR in two previous studies [7,8]. However, the difference in mean Δ FFR in our two groups appeared to be smaller than assumed. More research appears warranted in a larger population to investigate the influence of coronary artery calcification on the hyperemic response during FFR.

At last, we did not perform coronary flow reserve measurements and did not measure the index of microcirculatory resistance for the assessment of microvascular coronary artery disease. Currently FFR is still routinely used, therefore potential influence of calcification on FFR measurements is of major clinical relevance. However, since coronary flow reserve measurements or index of microcirculatory resistance are more robust measurements to assess the microcirculation, future studies should investigate this in more detail.

5. Conclusion

In this study we did not find a relation between the amount of coronary artery calcification and the hyperemic response during FFR measurements in intermediate coronary artery stenoses. This suggests that the hyperemic response is in the presence of severe coronary calcifications, however more research appears warranted to investigate the potential influence of coronary artery calcification on the hyperemic response during FFR.

5.1. Impact on daily practice

We did not find an association between the severity of coronary calcification and the hyperemic response to adenosine and nitroglycerin. This suggests that the hyperemic response is intact in the presence of severe coronary calcifications.

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