Quantitative contrast stress echocardiography in assessment of restenosis after percutaneous coronary intervention in stable coronary artery disease

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Aims Quantitative contrast stress echocardiography (CSE) can assess regional myocardial perfusion. The aim of this study was to evaluate the performance of quantitative CSE in the detection of restenosis after percutaneous coronary intervention (PCI).

Methods and results Thirty-three patients with stable coronary artery disease, scheduled for PCI, underwent CSE and quantitative coronary angiography (QCA) before and 9 months after PCI. Regional myocardial perfusion was analysed blinded to QCA results. QCA identified 38 significant stenoses (≥50% diameter reduction). Before PCI, perfusion during stress was significantly reduced in regions supplied by stenotic arteries; blood flow velocity (Db) = 3.9 (±9.0 to 0.5) s⁻¹, perfusion rate (DA×b) = 175.0 (±518.0 to 58.5) s⁻¹, and refilling time (Drt) = 210 (±22 to 452) ms, compared with the perfusion increase seen in regions supplied by non-stenotic arteries; Db = 1.6 (±0.7 to 4.4) s⁻¹, DA×b = 151.7 (±67.0 to 300.5) s⁻¹, and Drt = 47 (±195 to 89) ms, all P < 0.05. At follow-up, regional stress-induced perfusion improved in 29 regions with successful PCI; Db = 0.1 (±2.7 to 3.6), DA×b = 30.5 (±133.3 to 232.1), and Drt = 99 (±247 to 125), all P < 0.01, although there was no improvement in nine regions with restenosis; Db = 0.9 (±1.5 to 5.3), DA×b = 65.7 (±40.8 to 412.6), and Drt = 79 (±268 to 163), P = NS.

Conclusion Quantitative CSE has the potential to detect angiographically significant coronary artery stenoses as well as angiographic success after PCI.

Trial registration: ClinicalTrials.gov Identifier: NCT00354081.

Introduction

Myocardial perfusion can be visualized by contrast echocardiography, where contrast replenishment in the myocardium reflects myocardial blood flow. Regional perfusion parameters such as myocardial blood flow velocity, total blood volume, perfusion rate, and refilling time can be quantified from contrast replenishment curves expressing contrast intensity over time. Assessment of regional myocardial perfusion during stress is important in pre-intervention management of patients with stable coronary artery disease (CAD). Current guidelines recommend documentation of ischaemia by non-invasive testing before percutaneous coronary intervention (PCI) in stable CAD. Contrast stress echocardiography (CSE) has documented high sensitivity but low specificity for the detection of angiographic coronary artery stenosis, and a recent publication demonstrated excellent feasibility of quantitative stress echocardiography in detecting angiographic coronary artery stenosis. From clinical practice, it is well known that some patients develop restenosis after PCI or experience progression of atherosclerosis resulting in the development of new significant coronary artery stenoses that may be difficult to diagnose non-invasively.

The aim of the present study was to assess regional perfusion by quantitative CSE to identify angiographic restenosis or significant disease progression in CAD patients after PCI.

Methods

Study population

A total of 37 patients with symptomatic stable angina and significant CAD diagnosed by quantitative coronary angiography (QCA) were
invited to participate in the present quantitative contrast echocardiography study assessing regional myocardial perfusion before and 9 months after PCI. The patients were selected for inclusion in the study on the basis of angiographic findings with at least one angiographically significant stenosis eligible for PCI with bare metal stents, and non-obstructive atherosclerotic disease detected by invasive angiography in at least one other main coronary artery and follow-up angiography at 9 months was planned at inclusion. All patients underwent the pre-PCI test, although only 33 patients attended the planned re-examination by quantitative CSE and QCA 9 months after PCI. One patient was lost to follow-up because of cerebral haemorrhage, one patient had PCI converted to coronary artery bypass grafting because of procedural complications. Two patients were excluded from further participation one because of diagnosis of hypertrophic cardiomyopathy with resting outflow-tract gradient 60 mmHg and the second because of an anaphylactic reaction during contrast infusion which resulted in incomplete imaging. The present study population consists of the 33 patients who completed both baseline and follow-up testing. All patients gave written informed consent to participate and the study protocol was approved by the Regional Ethical Committee.

Contrast stress echocardiography

CSE was performed before and 9 months after PCI, using an Acuson Sequoia C256 (Siemens, Mountain View, CA, USA) echocardiograph. Pharmacological stress was induced following a standardized high-dose dobutamine/atropine stress protocol. Stress level was defined as high if ≥85% of maximum age predicted heart rate was achieved, and as intermediate if ≥75% of maximum age predicted heart rate or a doubling of basal heart rate was achieved. Assessment of regional myocardial perfusion was obtained by non-destructive real-time imaging with low mechanical index (0.14) in apical two-, three-, and four-chamber views at rest and peak stress. Sonovue (Bracco, Milan, Italy) ultrasound contrast agent was administered intravenously as an initial 1 mL bolus followed by continuous infusion of 60 mL/h using a rotating infusion pump, Vueject (Bracco, Milan, Italy).1 Contrast microbubble destruction was induced by a high-energy ultrasound burst and contrast replenishment assessed at rest and peak stress. Ten cardiac cycles of contrast replenishment at rest and peak stress in each of the three apical views were stored on magnetic optical discs for off-line analysis at a working station (TomTech Imaging system, Munich, Germany).

Quantification of myocardial perfusion

Myocardial perfusion may be explored by the measurement of myocardial contrast signal intensity plotted against time obtaining contrast replenishment curves fitting the exponential function: \[ y(t) = A(1 - e^{-\beta t}) + C \], where \( y \) is the signal intensity at any time during contrast replenishment reflecting regional myocardial perfusion.10-12 In this equation, \( A \) is the plateau signal intensity reflecting the total blood volume, \( \beta \) is the rate of signal intensity rise reflecting myocardial blood flow velocity, and \( C \) is reflecting the background intensity level. Myocardial perfusion was assessed in operator-specified myocardial regions of interest (ROI) by contrast replenishment curves expressing myocardial blood flow velocity \((\beta)\), total blood volume \((A)\), myocardial perfusion rate \((A \times \beta)\), and refilling time \((rt)\), constructed by a contrast quantification software, Qontrast (Bracco, Milan, Italy).12 The software is fully automatic except for operator-dependent definition of a left ventricular template, frames of interest, and ROI. The refilling time was measured by the software as the time from burst until \( A \) has reached the plateau level. Perfusion parameters for each of the typical distribution areas of the coronary arteries—left anterior descending (LAD), circumflex (CX), and right coronary artery (RCA)—were calculated using a 17-segment left ventricular (LV) model, assigning the ROI to the typical distribution territories of the three main coronary arteries independent of coronary artery dominance.13 In two patients with previous myocardial infarction and fixed perfusion abnormalities at rest, the specific regions were excluded from the analysis and regarded as infarct scarring. Quantification of myocardial perfusion was performed by an experienced single operator (M.T.L.) blinded to the QCA results. Intraobserver reproducibility of perfusion parameters was assessed by RHO from two independent blinded readings of the same peak stress echocardiography images.

Quantitative coronary angiography

Contrast angiograms performed before PCI and at follow-up, 9 months after PCI, were stored for off-line CQA analysis. All coronary arteries were evaluated by digitalized QCA edge-detecting program, Quantor (QCA V5.0, Pie Medical Imaging, Maastricht, The Netherlands). Stenoses with a lumen diameter reduction of ≥50% by QCA were considered significant. QCA was performed by an experienced single operator (E.S.) blinded to the quantitative CSE results.

Statistics

Statistical analysis was performed using the SPSS statistical program, version 15.0 (SPSS Inc., Chicago, IL, USA). Patients’ characteristics and regional perfusion parameters were expressed as median and quartiles or numbers and percentages. Correlation between continuous variables not normally distributed was evaluated by Spearman correlation coefficient. Comparison of perfusion parameters in groups of patients was performed by non-parametric statistical tests (Wilcoxon, Kruskal–Wallis tests) as appropriate. The performance of quantitative CSE in detecting significant coronary artery stenosis by perfusion parameters was evaluated by receiver–operator characteristic (ROC) curves and area under the curve (AUC). Optimal cut-off values were calculated. A \( P \)-value < 0.05 was considered statistically significant.

Results

Patients

All patients had symptomatic CAD and five (15%) had previous myocardial infarction treated by PCI at least 12 months before the current procedure (Table 1). LV function was well preserved; only two patients (6%) had LV ejection fraction < 50% by biplane Simpson’s method.13 Five

<table>
<thead>
<tr>
<th>Table 1 Patients characteristics</th>
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<tbody>
<tr>
<td>n = 33</td>
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<tr>
<td>Age (years), mean (range)</td>
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<tr>
<td>Women, n (%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
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<tr>
<td>Anti-anginal medication, n (%)</td>
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<tr>
<td>β-Blockers, n (%)</td>
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<tr>
<td>Ejection fraction, % ± SD</td>
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<tr>
<td>LV mass index, g/m² ± SD</td>
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<tr>
<td>Previous myocardial infarction, n (%)</td>
</tr>
<tr>
<td>Anterior wall, n (%)</td>
</tr>
<tr>
<td>Inferior wall, n (%)</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
</tr>
<tr>
<td>LAD, n (%)</td>
</tr>
<tr>
<td>CX, n (%)</td>
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<tr>
<td>RCA, n (%)</td>
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</tbody>
</table>

LAD, left anterior descending artery; CX, circumflex artery; RCA, right coronary artery.
patients had LV hypertrophy as calculated by Devereux’s formula. At follow-up, four patients (12%) had recurrent stable angina pectoris.

Quantitative coronary angiography and percutaneous coronary intervention

At baseline, single-vessel disease was present in 19 (58%) and multi-vessel disease in 14 (42%) of the patients. The mean degree of stenoses was 69 ± 20%. A total of 38 significant stenoses were eligible for PCI and successfully treated—12 in LAD, 12 in CX, and 14 in RCA (Table 1). At 9 month follow-up, significant restenosis (average degree 73 ± 17%) had developed in 9, whereas no significant restenosis was detected in the other 29. Nine new significant stenoses (average degree 58 ± 7%) due to disease progression were also detected at follow-up.

Myocardial contrast stress echocardiography

During CSE at baseline, three patients developed severe angina and one non-sustained ventricular tachycardia was observed, whereas no symptoms or arrhythmia occurred during CSE at 9 month follow-up. All 33 patients underwent a complete stress protocol, and stress level before and after PCI was comparable, with a mean increase in heart rate during stress of 46 ± 14 b.p.m. before PCI and 50 ± 16 b.p.m. at follow-up (P = NS). Two (6%) patients obtained high stress level, 29 (87%) patients intermediate stress level, and 2 (6%) patients less than intermediate stress level at the pre-PCI test, compared with 4 (12%) patients obtaining high, 29 (87%) patients intermediate stress level, and 2 (6%) patients less than intermediate stress level at 9 month follow-up.

Quantitative myocardial perfusion parameters by contrast stress echocardiography

Intraobserver reproducibility yielded RHO 0.95 (95% CI 0.90–0.98) for β, RHO 0.91 (95% CI 0.82–0.96) for A, RHO 0.78 (95% CI 0.58–0.89) for A × β, and RHO 0.84 (95% CI 0.68–0.92) for rt at peak stress.

Perfusion parameters before percutaneous coronary intervention

Before PCI, there were no significant differences in regional perfusion at rest between myocardial regions supplied by stenotic and non-stenotic coronary arteries (Table 2). At peak stress, however, we observed a significant difference in perfusion parameters between stenotic and non-stenotic regions. During dobutamine stress, blood flow velocity [Δβ = −3.9 (−9.0 to 0.5) s⁻¹] and perfusion rate [ΔA × β = −175.0 (−518.0 to 58.5) s⁻³] declined and refilling time [Δrt = 210 (−22 to 452) ms] increased in myocardial regions supplied by stenotic arteries compared with an increase in blood flow velocity [Δβ = 1.6 (−0.7 to 4.4) s⁻¹] and perfusion rate [ΔA × β = 151.7 (−67.0 to 300.5) s⁻³] as well as a reduction in refilling time [Δrt = 47 (−195 to 89) ms] in non-stenotic regions (all P < 0.05). The ratio between perfusion during peak stress and at baseline for blood flow velocity and perfusion rate was also significantly different in stenotic and non-stenotic regions, β peak/β baseline: 0.5 (0.2; 1.3) and 1.4 (0.8; 2.0), respectively, P < 0.01, and A × β peak/A × β baseline: 0.6 (0.2; 1.3) and 1.5 (0.8; 2.0), respectively, P < 0.01.

Correlation between perfusion and degree of stenosis before percutaneous coronary intervention

Comparing QCA degree of stenosis and perfusion quantified by CSE, a weak but statistically significant association was found between degree of stenosis by QCA and regional blood flow velocity (r = −0.34, P < 0.01), perfusion rate (r = −0.36, P < 0.01), and refilling time (r = 0.35, P < 0.05) at peak stress. The correlation between the ratio of stress and baseline blood flow velocity and ratio of stress and baseline perfusion rate and angiographic degree of stenosis was almost identical, with a Spearman correlation [(r = −0.31, P < 0.05) and (r = −0.28, P < 0.05), respectively].

Perfusion parameters 9 months after percutaneous coronary intervention

At 9 month follow-up, there was no significant difference in myocardial perfusion between myocardial regions supplied by stenotic and non-stenotic coronary arteries at rest. Furthermore, at peak stress, the absolute values of perfusion parameters at 9 month follow-up did not differ significantly between regions with successful PCI and regions developing restenosis (Table 3). In addition, in five regions supplied by coronary arteries not amenable for intervention because of peripheral disease or borderline stenosis, there was no significant change in myocardial perfusion during follow-up. However, comparing findings in tests before and after PCI, perfusion response to dobutamine stress in regions with successful PCI had improved with increase in blood flow velocity and perfusion rate and reduction in refilling time (all P < 0.05) (Table 3). In contrast, no significant improvement in perfusion response to dobutamine stress was found in the

Table 2 Perfusion parameters [median (25–75 percentile)] before percutaneous coronary intervention in non-stenotic and stenotic regions, respectively

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Peak</th>
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<tr>
<td></td>
<td>No stenosis</td>
<td>Stenosis</td>
</tr>
<tr>
<td>A (%)</td>
<td>66.0 (60.3–69.5)</td>
<td>61.8 (53.3–68.9)</td>
</tr>
<tr>
<td>β (s⁻¹)</td>
<td>5.6 (3.0–10.7)</td>
<td>8.1 (3.8–13.8)</td>
</tr>
<tr>
<td>A × β (s⁻¹)</td>
<td>340.9 (187.3–679.8)</td>
<td>478.8 (237.4–785.8)</td>
</tr>
<tr>
<td>rt (ms)</td>
<td>279 (212–501)</td>
<td>252 (140–402)</td>
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</table>

A, total blood volume (percentage of cavity contrast intensity); β, blood flow velocity (s⁻¹); A × β, perfusion rate (s⁻³); rt, refilling time (ms).
Table 3  Perfusion [median (25–75 percentile)] at peak stress during quantitative contrast stress echocardiography at baseline (pre-percutaneous coronary intervention) and 9 months post-percutaneous coronary intervention in regions with successful percutaneous coronary intervention, restenosis, or new stenosis defined by quantitative coronary angiography at 9 months post-percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Successful PCI (n = 29)</th>
<th>P-value</th>
<th>Restenosis (n = 9)</th>
<th>P-value</th>
<th>New stenosis (n = 9)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>9 months</strong></td>
<td></td>
<td><strong>Baseline</strong></td>
<td><strong>9 months</strong></td>
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<tr>
<td>A peak (%)</td>
<td>70 (62.4 to 74.1)</td>
<td>62.1 (58.5 to 74.2)</td>
<td>NS</td>
<td>69.5 (64.9 to 81.9)</td>
<td>72.6 (63.6 to 76.5)</td>
</tr>
<tr>
<td>β peak (s⁻¹)</td>
<td>3.7 (2.3 to 4.8)</td>
<td>4.5 (2.3 to 8.2)</td>
<td>0.05</td>
<td>4.0 (2.7 to 13.7)</td>
<td>4.8 (2.6 to 8.9)</td>
</tr>
<tr>
<td>A × β peak (s⁻¹)</td>
<td>258.0 (150.3 to 351.2)</td>
<td>313.4 (154.7 to 526.7)</td>
<td>NS</td>
<td>275.5 (177.7 to 1066.4)</td>
<td>329.2 (165.7 to 657.1)</td>
</tr>
<tr>
<td>A rt peak (ms)</td>
<td>462 (317 to 649)</td>
<td>303 (234 to 646)</td>
<td>NS</td>
<td>430 (243 to 628)</td>
<td>407 (228 to 560)</td>
</tr>
<tr>
<td>ΔA (s⁻¹)</td>
<td>5.9 (1.6 to 12.2)</td>
<td>5.5 (1.7 to 14.3)</td>
<td>0.01</td>
<td>10 (1.5 to 17.8)</td>
<td>9.7 (2.7 to 11.8)</td>
</tr>
<tr>
<td>Δβ (s⁻¹)</td>
<td>–3.8 (–9.5 to –0.4)</td>
<td>0.1 (–2.7 to 3.6)</td>
<td>0.01</td>
<td>2 (–3.1 to 3.6)</td>
<td>0.8 (–1.3 to 5.3)</td>
</tr>
<tr>
<td>Δ A × β (s⁻¹)</td>
<td>–175.0 (–561.0 to 232.1)</td>
<td>30.5 (–133.3 to 141)</td>
<td>&lt;0.01</td>
<td>165 (–40.8 to 67)</td>
<td>140 (–407 to 407)</td>
</tr>
<tr>
<td>Δ rt (ms)</td>
<td>259 (–24 to 493)</td>
<td>–99 (–247 to 125)</td>
<td>&lt;0.01</td>
<td>8 (–91 to 253)</td>
<td>–79 (–268 to 163)</td>
</tr>
</tbody>
</table>

A, total blood volume (percentage of cavity contrast intensity); β, blood flow velocity (s⁻¹); A × β, perfusion rate (s⁻¹); rt, refilling time (ms); ΔA, stress-induced change in total blood volume (%); Δβ, stress-induced change in blood flow velocity (s⁻¹); Δ A × β, stress-induced change in perfusion rate (s⁻¹); Δrt, stress-induced change in refilling time (ms).
restenosis could be identified by a lack of improvement in stress-induced perfusion during CSE.

By definition, successful revascularization with PCI should result in the normalization of myocardial perfusion in the region supplied by the treated artery. As demonstrated by our results, there was a significant improvement in stress-induced regional myocardial perfusion after successful PCI, including significant increased blood flow velocity and perfusion rate and a reduced refilling time during stress comparable to stress response found in myocardial regions supplied by non-stenotic arteries. Our findings are in accordance with results from a longitudinal study by Manyari et al.\textsuperscript{17} assessing perfusion by SPECT following PCI. In their study, perfusion defects gradually resolved in patients without angiographic restenosis during 6 months of follow-up. In another study by Versaci et al.,\textsuperscript{18} no patients had perfusion defects by SPECT imaging 6 months after angiographic successful PCI with stent implantation.

In general, \~30\% of patients develop restenosis after PCI with bare metal stent implantation, and \~50\% of restenosis are asymptomatic. Another 7\% of patients experience disease progression, resulting in the development of new significant coronary artery stenosis during the first 3–9 months of follow-up.\textsuperscript{19} Thus, our finding of restenosis by QCA in nine (27\%) patients, symptomatic in four, is as expected, although the finding of new significant coronary artery stenosis in nine (27\%) patients is higher than expected and may be explained by the use of post-interventional QCA for the detection of restenosis or disease progression irrespective of symptoms.

The present study, performed in patients with stable CAD, demonstrates improvement of regional myocardial perfusion after PCI in the majority of patients. However, in patients developing restenosis, quantitative CSE demonstrated lack of improvement in stress-induced perfusion response. The lack of post-PCI improvement of regional perfusion was mainly associated with restenosis, and a deterioration of previous normal regional perfusion was associated with the development of new significant stenosis. However, as demonstrated by our results, the absolute values of perfusion parameters at post-PCI testing were not able to distinguish between successful revascularization and development of restenoses or new stenosis. This could partly be explained by the relatively high interindividual variation in regional perfusion. Therefore, comparing regional myocardial perfusion before and after PCI and calculating stress-induced change in perfusion was necessary to diagnose restenosis or disease progression in the present study.

Our study demonstrates that pre-PCI quantitative CSE was able to distinguish between stenotic and non-stenotic regions by stress-induced perfusion changes, although there were no significant differences in myocardial perfusion in stenotic vs. non-stenotic myocardial regions at rest. This is in accordance with previous studies demonstrating that resting myocardial perfusion is relatively unaffected by coronary artery stenosis <80–85\%.\textsuperscript{20} In our study population, the mean degree of coronary stenosis before PCI was 69\%. Experimental studies have demonstrated that metabolic changes in chronic ischaemia lead to the activation of myocardial circulatory auto-regulation, including vasodilatation of resistance vessels and capillary derecruitment distal to a haemodynamic significant stenosis, resulting in the maintenance of perfusion pressure at rest.\textsuperscript{20,21} These perfusion changes are typical in chronic stable CAD, avoiding resting ischaemia but resulting in reduced coronary flow reserve and decreased hyperaemic response to stress-induced increase in oxygen demand.\textsuperscript{20}

During pre-PCI testing, quantitative contrast echocardiography at peak stress showed a significant reduced regional perfusion in myocardial regions supplied by significant QCA-verified coronary artery stenoses, in accordance with the reduced coronary flow reserve demonstrated in experimental coronary artery stenosis.\textsuperscript{22} In contrast, stress-induced increase in myocardial perfusion was found in myocardial regions supplied by non-stenotic arteries. The sensitivity of CSE for detecting myocardial ischaemia by quantitative perfusion analysis was 72\% and specificity 62\% for both blood flow velocity and perfusion rate in our study. The low specificity for detecting significant angiographic coronary stenosis has also been reported previously by others.\textsuperscript{7} This may be explained by the many factors other than artery diameter reduction that influences myocardial perfusion. The weak but statistically significant association between degree of stenosis by QCA and perfusion parameters found in the present study is in accordance with previous reports.\textsuperscript{23–26} The multiple factors beyond stenosis diameter reduction per se that influence myocardial microcirculation, including individual variation in coronary anatomy, stenosis length, activation of coronary flow auto-regulation, development

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|}
\hline
 & \multicolumn{2}{l|}{\beta \text{ peak cut-off}} & \multicolumn{2}{l|}{\times \beta \text{ peak cut-off}} & \multicolumn{2}{l|}{\times \beta \text{ baseline cut-off}} \\
 & \multicolumn{1}{|l|}{5.4 \text{ s}^{-1}} & \multicolumn{1}{|l|}{379 \text{ s}^{-1}} & \multicolumn{1}{|l|}{341 \text{ ms}} & \multicolumn{1}{|l|}{75 \text{ (0.65–0.81)}^*} & \multicolumn{1}{|l|}{77 \text{ (0.66–0.84)}^{**}} & \multicolumn{1}{|l|}{73 \text{ (0.62–0.84)}^{**}} \\
AUC (95\% CI) & 0.74 (0.63–0.84)^{**} & 0.71 (0.61–0.83)^* & 0.75 (0.65–0.81)^* & 0.77 (0.66–0.84)^{**} & 0.73 (0.62–0.84)^{**} \\
Accuracy (\%) & 74 & 71 & 75 & 77 & 73 \\
Sensitivity (\%) & 72 & 72 & 72 & 72 & 72 \\
Specificity (\%) & 62 & 57 & 62 & 70 & 70 \\
Ppv (\%) & 63 & 61 & 63 & 65 & 65 \\
Npv (\%) & 70 & 69 & 69 & 71 & 70 \\
\hline
\end{tabular}
\caption{The accuracy, sensitivity, specificity, and positive and negative predictive values for the different perfusion parameters blood flow velocity ($\beta$), perfusion rate ($\times \beta$), and refilling time (rt) at peak stress by the optimal cut-off values derived from receiver–operator characteristics curves described by area under the curve (95\% CI) and P-values.}
\end{table}

Ppv, positive predictive value; Npv, negative predictive value.
\*P < 0.05.
\**P < 0.01.
of collateral circulation and retrograde filling of sub-totally or totally occluded coronary arteries as well as haemodynamic factors like heart rate, diastolic blood pressure, stroke volume, and left ventricular filling pressure, can explain the weak association. In addition, small-vessel disease and endothelial dysfunction not visualized by angiography may interfere with myocardial microcirculation. The multifactorial regulation of coronary microcirculation may also explain the large inter-individual variation in regional perfusion parameters found in our study, as also reported previously by Malm et al. in healthy individuals. Applying the optimal cut-off values derived from ROC curves on the basis of the pre-PCI tests detected only five of nine restenoses at post-PCI testing. Sensitivity for the detection of significant stenoses after intervention was reduced to 62%, and specificity reduced to only 35%. Consequently, detection of normal regional myocardial perfusion on post-PCI testing could be used to exclude restenosis or disease progression with a negative predictive value of 71%, although a reduction in regional myocardial perfusion could not distinguish between stenotic and non-stenotic arteries 9 months after PCI, as the positive predictive value was only 27%. This contrasts previous reports using SPECT to assess myocardial perfusion after PCI. However, myocardial hypoperfusion in the absence of angiographic restenosis is a well-known phenomenon after revascularization, caused by a combination of micro-emboli, microthrombi, microvascular spasm, and reperfusion injury, in addition to microvascular disease and endothelial dysfunction not assessable by QCA. Theoretically, this can explain our finding of reduced regional myocardial perfusion in the absence of significant coronary artery stenoses by QCA. Assessment of microvascular function after PCI has been shown to have prognostic implications, and detection of regional myocardial hypoperfusion is useful in the detection of area at risk, restenosis, and disease progression.

Study limitations

This is a small study performed in patients with known significant coronary artery stenosis, and its findings need confirmation in larger trials. In particular, more optimal cut-off values may probably be derived from larger series of CSE in post-PCI patients who undergo angiographic follow-up. Contrast echocardiography visualizes myocardial microcirculation. Anatomically, the relation between stenoses by QCA and microvascular perfusion is complex. However, coronary angiography is still regarded as the gold standard in the diagnosis of CAD, and was therefore chosen as the comparator in our study. Furthermore, the main purpose of this study was to evaluate the use of quantitative CSE in the diagnosis of restenosis after PCI in patients with stable CAD.

Conclusion

Quantitative CSE has the potential to detect angiographically significant coronary artery stenoses as well as angiographic success after PCI. However, identification of successful revascularization and restenosis after PCI is dependent on serial assessment before and after intervention. Compared with pre-treatment assessment, a lack of improvement in regional stress-induced perfusion 9 months after PCI could indicate development of restenosis in contrast to the improvement demonstrated in regions after successful PCI. However, optimal cut-off values for the diagnosis of restenosis after coronary interventions need to be derived from larger trials.

Acknowledgement

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Conflict of interest: none declared.

References