**Effect of contrast application on interpretability and diagnostic value of dobutamine stress echocardiography in patients with intermediate coronary lesions: comparison with myocardial fractional flow reserve**


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**Aims**

Poor image quality remains a limitation of dobutamine stress echocardiography (DSE). This study aimed at investigating the effects of transpulmonary contrast application on endocardial border delineation and diagnostic yield of DSE in patients with intermediate coronary stenoses. The invasively measured fractional flow reserve (FFR) served as the reference standard.

**Methods and results**

Seventy patients with an intermediate coronary stenosis entered the study. Cineloops were recorded during DSE before and after contrast application at rest and peak stress. Two observers blinded to angiography assessed wall motion. FFR was measured in the target vessel during repeat angiography and an FFR $\leq 0.75$ was considered pathological. Abnormal FFR findings were seen in 41% of the patients. Native DSE was abnormal in 36% and contrast-enhanced DSE in 50% of the patients. Luminal diameter narrowing measured by quantitative angiography was not significantly different between patients with normal and abnormal FFR. After contrast application, the number of non-interpretable segments [median (25–75th percentile)] decreased from 2 (1–3) to 0 (0–0) at rest and from 1 (0–3) to 0 (0–0) at stress (both $P < 0.001$). Compared with native imaging, sensitivity and accuracy increased with transpulmonary contrast from 48 [% (confidence interval) 40–57%] to 83% (76–91%) and from 62 (CI 56–69%) to 77% (71–82%), respectively (both $P = 0.05$).

**Conclusion**

Transpulmonary contrast application improves the interpretability and diagnostic yield of DSE in patients with intermediate coronary lesions.

**Keywords**

Transpulmonary contrast echocardiography • Dobutamine stress echocardiography • Intermediate coronary artery stenosis • Myocardial fractional flow reserve

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Introduction

Dobutamine stress echocardiography (DSE) is an established non-invasive diagnostic method for the assessment of myocardial ischaemia. Its interpretation is based on comparing left ventricular (LV) wall thickening and motion at rest and during stress. Despite progress in imaging quality due to new ultrasound techniques such as harmonic imaging, a substantial number of patients are still considered unsuitable for stress echocardiography because of inadequate visibility of endocardial borders.1−3 Obviously, application of a second-generation transpulmonary ultrasound contrast agent renders the images more interpretable.4 However, it is unknown whether the improvement of endocardial border delineation (EBD) may also increase the diagnostic yield of DSE regarding the detection of haemodynamically relevant coronary artery disease (CAD).

In diagnostic studies the choice of the reference standard is crucial. Angiography bears limitations regarding the valid estimation of the haemodynamic relevance of coronary lesions,4,5 particularly in diffuse disease or intermediate stenoses. Therefore, we employed the pressure-derived myocardial fractional flow reserve (FFR) as reference standard for the present study. The FFR is an index of the functional severity of coronary lesions. It has been validated in different patient groups and is not influenced by heart rate, blood pressure or contractility.5–8 FFR measurements also account for the presence of collaterals, which is an important feature of the studies thus providing an option for superior evaluation of the diagnostic potential of functional non-invasive tests such as native and contrast-enhanced DSE.9

The aim of the present two-centre clinical study was to investigate the diagnostic utility of transpulmonary contrast enhancement during DSE on EBD in patients with intermediate coronary lesions in whom reliable testing of the haemodynamic significance is of particular clinical importance. We hypothesized that contrast enhancement would improve the interpretability and diagnostic yield of DSE.

Methods

Study protocol

The study protocol was designed to conform to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients prior to inclusion into the study. Approval was obtained from the local ethics committees of the Universities of Munich and Würzburg.

Irrespective of the native echocardiographic image quality, consecutive patients with chest pain in the presence of an angiographically intermediate stenosis in a single major extramural coronary artery potentially amenable by interventional treatment were eligible. Exclusion criteria were the presence of other more severe coronary lesions, stable angina, acute coronary syndrome, severe LV hypertrophy and lack of patient consent as well as contraindications to DSE or to the application of transpulmonary ultrasound contrast agents. In patients characterized as above, ad hoc coronary intervention is usually deferred at our institutions, because neither stenosis severity on visual assessment nor clinical symptomatology convincingly justifies immediate coronary revascularization. Instead, the functional significance of the lesions is assessed by invasive coronary pressure measurement during a second cardiac catheterization after DSE has been performed as an additional aid for decision making. Beta-blockers are as a rule withheld for at least 36 h prior to DSE. For the purpose of the present investigation, echocardiographic images were acquired at rest and at peak stress each time before and after bolus application into an antecubital vein of either Sonovue® (Bracco Diagnostics Inc., Princeton, NJ, USA; 0.5–1 mL) or Optison® (Amersham, USA, 0.3–0.5 mL). Thus, native and contrast imaging were performed within one examination. To avoid shadowing or swirling artefacts the timing of image acquisition was individually optimized and an intermediate or low mechanical index (0.17–0.4) was applied.

Dobutamine stress echocardiography

Data acquisition

DSE was performed using Vingmed System V or VII electronic sector scanners (GE Vingmed Ultrasound, Horten, Norway) and a standard dobutamine protocol with progressive doses from 5 to 40 μg/kg/min. Atropine 0.25 mg was additionally administered if the calculated peak heart rate was not achieved with dobutamine alone. Harmonic imaging was applied throughout all phases of the stress protocol with a transmit/receive frequency of 1.7/3.4 MHz. End points for dobutamine infusion were: 85% of maximal heart rate reached, systolic blood pressure increase to >240 mmHg or decrease to <100 mmHg, development or deterioration of wall-motion abnormalities (VMAs), severe chest pain, severe arrhythmia or other intolerable side effects. Cineloops of the apical 4-, 2- and 3-chamber-views as well as the parasternal long- and short-axis views were recorded digitally and on S-VHS videotape throughout each phase of the test.

Data reading

Two experienced observers blinded to the location of the stenosis and the FFR results interpreted the LV wall motion during an offline analysis, with DSE images displayed in a synchronized quad screen format (showing rest, medium, and peak stress recovery). Thus, as in clinical practice, an individual segment was evaluated against the background information of three other images. The reader was aware of the contrast modality used (native vs. contrast enhanced), but was unaware of the segmental analysis of the matching pair. The standard LV 16-segment model as recommended by the American Society of Echocardiography was applied. Accordingly, segments 1, 2, 7, 8, 12, 13–16 were defined as left anterior descending (LAD) artery perfusion territory, segments 3, 4, 9, 10 as right circumflex (RCX) artery perfusion territory, and segments 5, 6, 11 as right coronary artery (RCA) perfusion territory.10 Segments were evaluated regarding wall thickening and radial movement of the LV endocardium, which was classified semiquantitatively on a four-point scale as normo-, hypo-, a- or dyskinetic. EBD was defined as inadequate, if the image quality did not allow the assessment of wall motion within the specified segment. Segments with inadequate EBD were classified as ‘non-interpretable’. In case of disagreement, consensus was sought and achieved in every instance in a second joint session of both observers.

Coronary angiography and fractional flow reserve

All patients underwent repeat cardiac catheterization including determination of FFR within 3 weeks of DSE. At least two orthogonal views were obtained and the projection showing the most severe narrowing was used for assessment. Quantitative coronary analysis (QCA) was carried out offline by a computer-based edge-detection method (QCA, Pie Medical, Rotterdam, The Netherlands). FFR was determined using a sensor-tipped 0.014 in. angioplasty guide wire...
Data analysis

Data were entered into a dedicated database (Filemaker-Pro5, Filemaker Inc., USA). For data analysis, the SPSS software package (version 15.0.1 SPSS, Chicago, IL, USA) and SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) were used. Groups were compared using the t-test for unpaired samples after testing for equality of variances by Levene’s test. Categorical variables were compared using Fisher’s exact test. Comparison of numeric (QCA measurement) and binary data (EBD) was carried out using the student t-test or the McNemar test, as indicated. Multiple segments per perfusion territory were considered and, during resting and stress echocardiography, each segment was evaluated several times using different modalities. To account for this, generalized estimation equations methods were applied, allowing for appropriate consideration of subject- and within-subject-effects.

Differences regarding the diagnostic potential of native vs. contrast-enhanced DSE were estimated by receiver operating characteristics (ROC) curve analyses using the approach of Liu and Wu. Differences in the areas under the ROC curves with their 95% confidence intervals (CI) were estimated taking into account the correlation of data sets as they were based on the same cases. The 95% CI for diagnostic test characteristics were calculated according to the approach of Zhou and co-workers. All statistical tests were two-sided and a P-value of <0.05 was considered statistically significant.

Results

Clinical data

Of 266 patients undergoing diagnostic coronary angiography, 78 revealed a suitable angiogram. Five patients refused to participate in the study, 73 gave their informed consent and entered the study. One patient had to be excluded due to missing FFR data or incomplete digital recording of DSE images. Hence, 70 patients with complete data sets were included in the study. Table 1 details the demographic and clinical characteristics of this cohort. Mean age was 65 ± 10 years, 64% were males and 44% had a previous myocardial infarction. No serious adverse effects occurred during native or contrast-enhanced DSE, cardiac catheterization, coronary angiography or determination of the FFR.

Dobutamine stress echocardiography

During DSE, mean heart rate was 73 ± 17 min⁻¹ at rest and 133 ± 19 min⁻¹ during peak stress. Systolic (diastolic) blood pressure increased from 135 ± 20 (73 ± 16) to 153 ± 30 (60 ± 13) mmHg, respectively. EBD was assessed in a total of 4480 LV segments. Figure 1 shows percentages of adequately delineated LV segments corresponding to the perfusion territories of the three major extramural coronary arteries for both imaging modalities at rest and at peak stress, respectively. For the perfusion territory of the RCA, native imaging facilitated interpretation of >96% of the segments. Here, contrast application provided no additional benefit. By contrast, in the perfusion territories of the RCX and LAD artery, contrast-enhanced imaging improved EBD substantially. At rest, the percentages of interpretable segments increased from 84.6 to 98.6% (RCX; P = 0.007) and from 82.4 to 98.1% (LAD; P = 0.004), and from 82.2 to 97.8% (RCX; P < 0.001) and from 85.9 to 97.1% (LAD; P = 0.010) during peak stress.

Coronary angiography and fractional flow reserve

The target lesion identified by conventional coronary angiography was in most cases located in the LAD (34 patients, 48.6%) followed by the RCX (20 patients, 28.6%) and the RCA (16 patients, 22.9%). QCA in the 70 patients revealed a mean diameter reduction in the target lesion of 56.7 ± 10%. Diameter reductions as assessed by QCA were comparable in patients with pathological (57.7 ± 10.4%) and those with a normal FFR (56.1 ± 9.8%), and also in patient subgroups with normal vs. abnormal results during native (60.6 ± 10.4 vs. 54.6 ± 9.2%) as well as during contrast enhanced (58.9 ± 9.8 vs. 54.5 ± 10.1%) DSE (Figure 2). FFR was abnormal in 29 patients (41%). During DSE, WMA indicative of stress-induced myocardial ischaemia were observed in 25 patients (36%) during native and in 35 patients (50%) during contrast-enhanced imaging. An overview over the results of all tests and methods is provided in Figure 3.

Figure 4 relates the results of native and contrast-enhanced DSE to the FFR values. Stress-induced WMA during native DSE suggesting a haemodynamically significant coronary lesion was present in 25 cases; however, compared with FFR as the reference standard, only 14 cases were true positives.

Of 45 normal DSE results 30 were true negatives according to the corresponding FFR values. Thus, the sensitivity, specificity, and accuracy (%; with 95% CI) of native DSE amounted to 48% (CI 40–57%), 73% (CI 67–77%) and 62% (CI 56–69%), respectively. Contrast DSE resulted in 24 out of 35 true positives and 30 out of 35 true negatives. The corresponding values for sensitivity, specificity, and accuracy were 83% (CI 76–91%), 73% (CI 68–77%) and 77% (CI 71–82%), respectively. As an example, Figure 5 shows cross-sections of a DSE study illustrating that during native imaging wall motion may appear normal, whereas contrast application reveals a stress-induced WMA. In the entire cohort, DSE studies with true positive or true negative results showed a somewhat better echocardiographic image quality compared with DSE studies with false positive or false negative results. The number of non-interpretable segments [median (25–75th percentile)] during native and contrast-enhanced imaging decreased from 2 (1–3) to 0 (0–0) at rest and from 1 (0–3) to 0 (0–0) at peak stress (both P < 0.001), supporting the concept that the quality of EBD is one possible determinant of the diagnostic yield of DSE. With contrast application, the number of false negative test results decreased from 33 (CI 28–37%) to 14% (CI 9–19%). Consistently, the area under ROC curve increased from 0.57 (CI 0.42–0.71) for native DSE imaging to 0.78 (CI 0.65–0.88) for contrast-enhanced imaging (P = 0.039).
Table 1  Patient demographic and clinical characteristics

<table>
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<tr>
<th></th>
<th>All</th>
<th>FFR &gt; 0.75</th>
<th>FFR ≤ 0.75</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>Number of patients</td>
<td>70</td>
<td>41</td>
<td>29</td>
<td></td>
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<tr>
<td>Female, n (%)</td>
<td>25 (35.7)</td>
<td>15 (36.6)</td>
<td>10 (34.5)</td>
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<td>Male, n (%)</td>
<td>45 (64.3)</td>
<td>26 (63.4)</td>
<td>19 (65.5)</td>
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<td>Age (years)</td>
<td>65 ± 10</td>
<td>65 ± 9</td>
<td>64 ± 10</td>
<td>0.58</td>
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<tr>
<td>Comorbidities</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (20.0)</td>
<td>2 (4.9)</td>
<td>12 (41.4)</td>
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<td>Arterial hypertension, n (%)</td>
<td>53 (75.7)</td>
<td>31 (75.6)</td>
<td>22 (75.9)</td>
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<td>Hyperlipidaemia, n (%)</td>
<td>55 (78.6)</td>
<td>31 (75.6)</td>
<td>24 (82.8)</td>
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<tr>
<td>Previous smokers, n (%)</td>
<td>19 (27.1)</td>
<td>12 (29.3)</td>
<td>7 (24.1)</td>
<td>0.42</td>
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<tr>
<td>Current smokers, n (%)</td>
<td>9 (12.9)</td>
<td>4 (9.8)</td>
<td>5 (17.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>Familial disposition, n (%)</td>
<td>32 (45.7)</td>
<td>18 (43.9)</td>
<td>14 (48.3)</td>
<td>0.45</td>
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<tr>
<td>Weight (kg)</td>
<td>76 ± 14</td>
<td>75 ± 16</td>
<td>78 ± 13</td>
<td>0.30</td>
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<td>Antianginal therapy</td>
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<td>Betablockers, n (%)</td>
<td>50 (71.4)</td>
<td>31 (75.6)</td>
<td>19 (65.5)</td>
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<tr>
<td>Nitrates, n (%)</td>
<td>34 (48.6)</td>
<td>25 (61.0)</td>
<td>9 (31.0)</td>
<td>0.01</td>
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<tr>
<td>Calcium channel blockers, n (%)</td>
<td>14 (20.0)</td>
<td>8 (19.5)</td>
<td>6 (20.7)</td>
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<tr>
<td>Target lesion</td>
<td></td>
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<td>LAD, n (%)</td>
<td>34 (48.6)</td>
<td>20 (48.8)</td>
<td>14 (48.3)</td>
<td>0.58</td>
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<tr>
<td>RCX, n (%)</td>
<td>20 (28.6)</td>
<td>13 (31.7)</td>
<td>7 (24.1)</td>
<td>0.34</td>
</tr>
<tr>
<td>RCA, n (%)</td>
<td>16 (22.9)</td>
<td>8 (19.5)</td>
<td>8 (27.6)</td>
<td>0.31</td>
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<tr>
<td>DSE</td>
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<tr>
<td>Heart rate at rest (min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>73 ± 17</td>
<td>73 ± 17</td>
<td>73 ± 16</td>
<td>0.97</td>
</tr>
<tr>
<td>Heart rate at peak stress (min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>133 ± 19</td>
<td>130 ± 22</td>
<td>135 ± 14</td>
<td>0.23</td>
</tr>
<tr>
<td>Systolic blood pressure at rest (mmHg)</td>
<td>135 ± 20</td>
<td>137 ± 20</td>
<td>132 ± 20</td>
<td>0.28</td>
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<tr>
<td>Diastolic blood pressure at rest (mmHg)</td>
<td>73 ± 16</td>
<td>73 ± 10</td>
<td>73 ± 22</td>
<td>0.96</td>
</tr>
<tr>
<td>Systolic blood pressure at peak stress (mmHg)</td>
<td>153 ± 30</td>
<td>157 ± 31</td>
<td>148 ± 29</td>
<td>0.21</td>
</tr>
<tr>
<td>Diastolic blood pressure at peak stress (mmHg)</td>
<td>60 ± 13</td>
<td>60 ± 12</td>
<td>60 ± 14</td>
<td>0.88</td>
</tr>
<tr>
<td>Maximum dobutamine dose (µg/kg/min)</td>
<td>29 ± 10</td>
<td>28 ± 9</td>
<td>31 ± 10</td>
<td>0.20</td>
</tr>
</tbody>
</table>

FFR, myocardial fractional flow reserve; DSE, dobutamine stress echocardiogram.
<sup>a</sup>-test for unpaired samples/χ<sup>2</sup>-quadrat Fisher exact test; metric values are mean ± SD.

Discussion

This clinical study investigated the use of contrast enhancement for improved EBD during DSE in patients with intermediate coronary artery stenoses. Myocardial FFR was used as a quantitative reference standard for assessment of the functional significance of these coronary lesions. The study shows that the interpretability and diagnostic yield of DSE are improved by the use of a transpulmonary contrast agent.

Dobutamine stress echocardiography

Despite recent concern about the safety of ultrasound contrast agents in patients with CAD, we encountered no adverse effect in the course of this study in patients with stable angina.

Impaired image quality limits the diagnostic value of DSE. Using magnetic resonance imaging, a comparative study<sup>13</sup> demonstrated that both sensitivity and specificity of DSE were significantly lower in patients with unsatisfactory echocardiographic visibility of the LV (62 vs. 85%, and 54 vs. 86%, respectively). Contrast enhancement of the LV cavity with second-generation transpulmonary contrast agents has repeatedly been shown to improve EBD and, thus, assessability of LV wall thickening and motion.<sup>14–18</sup>

The findings of the present DSE study are consistent with these observations both at rest and peak stress. EBD improved best in the RCX and LAD perfusion territories (apical, lateral, and anterior region of the LV), whereas native harmonic imaging alone yielded already satisfactory image quality in the basal segments without further improvement in EBD after contrast application. The current study is the first to investigate the diagnostic potential of contrast-enhanced imaging during DSE in consecutive patients with angiographically intermediate stenoses irrespective of the quality of native echocardiographic imaging, using FFR values as the reference standard. FFR reliably identifies functionally significant stenoses by accounting for both antegrade and collateral flow contributions to maximum myocardial perfusion.<sup>9,19</sup> It is not surprising that in the present study group the diagnostic...
Figure 1 Percentage of interpretable left ventricular segments according to perfusion territories of the major coronary arteries during different imaging modalities.

Figure 2 Diameter reduction as assessed by QCA in patients with pathological fractional flow reserve (FFR) and FFR within the normal range, native, and contrast-enhanced dobutamine stress echocardiography (DSE).
yield of native DSE compared with FFR was lower than previously reported. In clinical practice, some of these patients might *a priori* not have been considered for diagnostic DSE due to insufficient native image quality.

In addition, diagnosis and assessment of the functional significance of intermediate stenoses is particularly challenging, irrespective of the diagnostic methods used. Even invasive coronary angiography using QCA has a disappointingly low accuracy. Our results clearly indicate, that independent of the native echocardiographic image quality the diagnostic yield of DSE may be substantially improved by the use of a second-generation transpulmonary contrast agent. In five patients of our cohort, an FFR value ≤0.75 indicated the haemodynamic significance of the stenosis, but neither native nor contrast-enhanced DSE showed a WMA suggestive of stress-induced ischaemia. Possibly, this denotes a principal limitation of semiquantitative visual assessment of WMA: more subtle abnormalities of regional myocardial systolic function may not be detectable by eye-balling.

Recently, we demonstrated in a smaller group of patients with intermediate coronary lesions that quantitative assessment of the change in strain rate during DSE represents an attractive alternative method for the detection of subclinical stress-induced ischaemia with a sensitivity of 89% and specificity 86% derived from ROC curves. However, this method also depends on echocardiographic image quality and may not be applicable in all patients in whom a high quality contrast-enhanced DSE study is feasible. Intravenous myocardial contrast echocardiography is another recently developed technique that has shown that the sensitivity and specificity of qualitative assessment of myocardial perfusion in patients with acute and chronic ischaemic heart disease are comparable with other techniques such as cardiac scintigraphy. Unfortunately its routine use is less feasible due to the need for a continuous contrast infusion.

The mean vessel diameter in patients in whom DSE failed to show ischaemia was 54.3% for native and 51.5% for contrast-enhanced DSE, both non-significantly different from the overall mean vessel diameter.

Eleven patients showed stress-induced WMA despite an FFR within the normal range. As almost half of our cohort had suffered from previous myocardial infarction and many patients had undergone revascularization procedures prior to inclusion into the study, we speculate that myocardial damage may have caused...
stress-induced WMA. Further investigation of such patients using myocardial strain rate imaging at rest and during DSE may help to clarify this finding in future studies.

Clinical implications
A significant and clinically relevant increase of sensitivity and accuracy of DSE was found applying a second-generation contrast agent to patients with intermediate stenoses. The results prove for the first time that the improvement of image quality leads to a higher diagnostic value of DSE. The number of false negative test results decreased by a remarkable 19%. This means, that 19% of the study patients would not be referred to further diagnostic testing and angioplasty because of a false DSE result. In clinical routine, a screening test for CAD should exhibit a high sensitivity rather than a high specificity. It appears to be more reasonable performing heart catheterization in a person with non-significant CAD than missing a significant stenosis in another. On the other hand, the prevalence of coronary artery stenosis in an arbitrary population of asymptomatic men aged 60 years is 20%. It is, hence, not unlikely that any coronary lesion found at angiography is coincidental and PCI (percutaneous coronary intervention) is performed unnecessarily in that case. Because the number of elderly patients presenting with CAD is rapidly growing, it is important to develop reliable means to recognize the haemodynamic relevance of a stenosis. Adding contrast application to the protocol appears to substantially improve the clinical utility of a non-invasive, widely available and robust technique such as DSE, which will be of increasing clinical importance especially in the difficult patient with an intermediate stenosis.

Limitations
The study comprised patients with intermediate stenoses, i.e. a selected subgroup of those patients undergoing routine DSE in clinical routine. By study design, we are unable to conclude with confidence that our finding of the added diagnostic value using contrast enhancement may also apply to consecutive patients seen in clinical practice. However, because the intermediate stenosis is the most challenging lesion in terms of DSE diagnostics, and because we deliberately did not exclude patients with poor image quality at the baseline scan, we consider it likely that our results may be generalizable to a broader range of patients with suspected CAD. We used FFR as the reference standard. Besides its excellent validation in patients with one-vessel disease and absence of small vessel disease, the utility of FFR in more complex patient groups with multi- or small vessel disease or with hypertrophic heart disease is currently being discussed. Further, data underscoring the diagnostic value of FFR in unselected patients with multiple comorbidities are growing rapidly. Our sample size was relatively small. Nonetheless, the differences in diagnostic data were pronounced and statistically consistent. Further examinations should be carried out to confirm these results in a larger patient group with broader inclusion criteria. Future studies should contribute to investigate, whether these data are also applicable to patients with unknown coronary status screened for CAD.

Conclusion
In patients with intermediate coronary stenoses contrast enhancement significantly improves the interpretability and diagnostic utility of DSE.

Conflict of interest: none declared.

References


