The diagnostic performance of SPECT-MPI to predict functional significant coronary artery disease by fractional flow reserve derived from CCTA (FFR<sub>CT</sub>): sub-analysis from ACCURACY and VCT001 studies

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Abstract
Although single photon emission computed tomography-myocardial perfusion image (SPECT-MPI) and fractional flow reserve (FFR) derived from coronary computed tomographic angiography (CCTA) (FFR<sub>CT</sub>) have permitted functional assessment of coronary artery disease (CAD), the concordance between these modalities has not been well described. The aim of this study is to compare SPECT-MPI and anatomical stenosis by CCTA and invasive coronary angiography to FFR<sub>CT</sub> for assessing functional significance of CAD. We identified 62 patients with suspected CAD who underwent ≥64 slice coronary CTA and SPECT-MPI within 3 months. FFR<sub>CT</sub> was analyzed from CCTA data using the computational fluid dynamic techniques. The association between SPECT-MPI ischemia and FFR<sub>CT</sub> (≤0.80) was evaluated. Out of 62 patients, 186 vessels were evaluated. On a per-vessel analysis, accuracy, sensitivity and specificity of SPECT-MPI to predict FFR<sub>CT</sub> ≤ 0.80 was 74.2, 45.0 and 77.7%, respectively. The area under the curve (AUC) by receiver-operating characteristic curve analysis for SPECT-MPI demonstrated a modest performance for predicting FFR<sub>CT</sub> ≤ 0.80 (AUC 0.56). Among patients with suspected CAD who were assessed by non-invasive functional modalities, SPECT-MPI showed modest concordance with FFR<sub>CT</sub>.

Keywords
Single photon emission computed tomography-myocardial perfusion image · Fractional flow reserve · Coronary computed tomographic angiography · Ischemia

Introduction
Non-invasive imaging modalities such as single photon emission computed tomography-myocardial perfusion image (SPECT-MPI) and coronary computed tomographic angiography (CCTA) are established methods to identify patients who have coronary artery disease (CAD). An array of prior investigations has observed that SPECT-MPI failed to identify high risk coronary anatomy by invasive coronary angiography (ICA) [1, 2], or functional significance of CAD confirmed by invasive fractional flow reserve (FFR) [3]. The issue can be clinically problematic in identifying patients who have coronary artery disease (CAD). An array of prior investigations has observed that SPECT-MPI failed to identify high risk coronary anatomy by invasive coronary angiography (ICA) [1, 2], or functional significance of CAD confirmed by invasive fractional flow reserve (FFR) [3]. The issue can be clinically problematic in identifying patients who require ICA for the further evaluation of CAD [4]. In addition, this misclassification may subsequently lead to errors of omission or commission in guiding treatment decision-making.

CCTA has been utilized as a potentially more sensitive modality for identifying patients who have obstructive CAD compared to other non-invasive modalities [4, 5]. FFR derived from CT (FFR<sub>CT</sub>) can be calculated by a novel technology using fluid dynamics and its diagnostic accuracy has been recognized to be higher than other non-invasive modalities [6–9]. However, the concordance between FFR<sub>CT</sub> and standard non-invasive functional modalities has not been examined. The aim of the current study was to investigate for the first time the accuracy of SPECT-MPI versus FFR<sub>CT</sub>.
Methods

Study population

Among 370 patients with stable typical or atypical chest pain who were clinically referred for ICA and enrolled in prospective, multicenter studies of CCTA (n=230 for ACCURACY and n=77 for VCT001 study) [10, 11], we identified 94 patients (n=58 for ACCURACY and n=36 for VCT001 study) who underwent both CCTA and stress/rest SPECT-MPI with available data. Of those, we subsequently excluded 3 and 29 patients, due to an interval >180 days between CCTA and SPECT-MPI, and insufficient image quality for FFRCT, respectively. Thus, we identified 62 patients for the present study. All patients underwent CCTA and SPECT-MPI within 3 months of one another. Details regarding study population in ACCURACY and VCT001 studies were described in prior publications [10, 11]. Briefly, both studies were multicenter studies which were designed to investigate the diagnostic accuracy of 64-slice CCTA for detecting coronary artery stenosis compared with ICA among patients with suspected CAD. All subjects were >18 years old, had atypical or typical chest pain, were clinically being referred for non-emergent ICA, and underwent CCTA. Exclusion criteria were known iodinated contrast allergy, renal insufficiency, irregular or high heart rate, low blood pressure at rest (<100 mmHg), contraindication to premedication such as β-blocker, calcium-channel blocker or nitroglycerin, pregnancy, or known history of CAD. Each participating institution obtained Institutional Review Board approval.

CCTA image acquisition protocols and interpretation

All the details regarding the CCTA protocol were described previously [10, 11]. In brief, all participants underwent a 64-slice CT scan (Lightspeed VCT, General Electric Healthcare, Milwaukee, Wisconsin). The following scanning parameters were used: retrospective electrocardiogram-gated study with dose modulation during systolic and end-systolic phases, collimation 64×0.625 mm, tube voltage 120 kV, tube current 350–780 mA. Immediately before scanning, sublingual nitroglycerin or nitroglycerin spray 0.4 mg was administrated. Pre-scan oral and/or intravenous beta-blocker was administered to reach target heart rate <65 beats/min (bpm).

CCTA image analysis for FFRCT

FFRCT was independently analyzed from CCTA data using the computational fluid dynamic techniques at HeartFlow, Inc. (FFRCT v1.4, Redwood City, California, USA), with blinding to the SPECT-MPI findings. The anatomy, physiology and fluid dynamics were used for the calculation of FFRCT [12]. Blood flow in coronary arteries was calculated from anatomical models of coronary artery and left ventricular mass derived from CCTA images. Information including cardiac output, aortic pressure and microcirculatory resistance were used for calculation of coronary physiology. In order to compute FFRCT with computational fluid dynamics, these anatomical and physiological models were assessed.

SPECT-MPI image acquisition and interpretation

After Thallous Chloride TI 201 (n=1) or Tc99m Sestamibi (n=61) were injected intravenously at rest, SPECT imaging was initiated and performed in 10–60 min. The patients then underwent treadmill exercise stress or pharmacologic stress using adenosine (n=12), persantine (n=4) or dobutamine (n=1). After exercise or 30–60 min after pharmacologic stress, gated SPECT imaging was initiated. SPECT image data were reconstructed in short axis, vertical long-axis, and horizontal long-axis planes, and visual interpretation was performed. Attenuation correction was applied when needed.

Statistical analysis

Continuous variables are expressed as the mean±SD in the descriptive statistics. Receiver-operating characteristics (ROC) curve analysis was used to assess the diagnostic performance of SPECT-MPI in predicting FFRCT ≤ 0.80, at per-vessel and per-patient bases. The area under the ROC curves (AUC) was compared between these variables by regression models. A p value of <0.05 was set as the significance level. All statistical calculations were performed using SAS (Version 9.3, SAS Inc., Cary, NC) for Windows.

Results

Mean age of the study population was 55.1±8.4 years old and 51.6% were male. Overall, 54.2% of patients were obese with BMI > 30 (kg/m²). In the ACCURACY study, prevalence of history of hypertension, hyperlipidemia and diabetes were 54.0, 81.1 and 21.6%, respectively. In VCT001 study, mean value of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides were 185.9±43.1, 107.1±32.8, 47.9±11.4 and 150.5±74.7 mg/dl, respectively. The mean of systolic and diastolic blood pressures was 129.9±15.1 and 79±8.7 mmHg, respectively (Table 1).

Mean interval between CCTA and SPECT-MPI was 12 days. Exercise and pharmacologic stress SPECT-MPI protocols were performed in 45 and 17 patients, respectively.
Among patients undergoing exercise SPECT-MPI, mean exercise duration and METS were 9.3 min and 9.9, respectively. Only two patients did not achieve the 85% threshold of percent of maximum predicted heart rate (%MPHR), achieving 49 and 81% MPHR, respectively. The patient with 49% MPHR exercised 10 min with 11.9 METS, and the patient with 81% MPHR exercised for 30 min. No serious complications were reported during stress testing in any patient.

Overall, 15 patients (24.2%) and 20 vessels had functionally significant CAD by FFR\textsubscript{CT}. Of 20 vessels, 11, 3, and 6 vessels had FFR\textsubscript{CT} < 0.8 in left anterior descending artery, left circumflex and right coronary artery, respectively. On a per-vessel analysis, accuracy, sensitivity and specificity for the identification of stenosis >50% by ICA were 90.3, 56.3 and 93.5% for FFR\textsubscript{CT} and 72.0, 31.3 and 75.6% for SPECT-MPI, respectively. Regarding the concordance between FFR\textsubscript{CT} and SPECT-MPI, accuracy, sensitivity and specificity for the identification of FFR\textsubscript{CT} ≤ 0.8 were 74.2, 45 and 77.7% for SPECT-MPI (Table 2). The area under the curve (AUC) by ROC curve analysis for SPECT-MPI demonstrated a modest performance for predicting FFR\textsubscript{CT} ≤ 0.80 on a per-vessel analysis (AUC 0.56). On a per-patient analysis, the AUC by ROC for SPECT-MPI similarly demonstrated a modest performance for predicting FFR\textsubscript{CT} ≤ 0.80 (AUC 0.54) (Fig. 1).

Findings from the current study and prior studies examining diagnostic accuracy of SPECT-MPI compared to invasive FFR are summarized in Table 1. Accuracy, sensitivity and specificity from our study are comparable with those from previous studies [3, 13–18].

### Table 1: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>ACCURACY (n = 37)</th>
<th>VCT001 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.0 ± 9.1</td>
<td>54.0 ± 7.4</td>
</tr>
<tr>
<td>Male gender</td>
<td>51.4%</td>
<td>52.0%</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>34.3 ± 6.5</td>
<td>33.5 ± 6.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>54.0%</td>
<td>–</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>81.1%</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21.6%</td>
<td>–</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>–</td>
<td>129.9 ± 15.1</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>–</td>
<td>79 ± 8.7</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mg/dl)</td>
<td>–</td>
<td>185.9 ± 43.1</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mg/dl)</td>
<td>–</td>
<td>107.1 ± 32.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>–</td>
<td>47.9 ± 11.4</td>
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</tbody>
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### Discussion

The current study is the first to investigate the concordance between FFR\textsubscript{CT} and SPECT-MPI among patients with stable chest pain and suspected CAD. The relationship between FFR\textsubscript{CT} and SPECT-MPI in the current study was similar with that between invasive FFR and SPECT-MPI as demonstrated by prior studies.

### Table 2: The concordance between SPECT-MPI and invasive FFR or FFR\textsubscript{CT}

<table>
<thead>
<tr>
<th>Number of vessels/patients</th>
<th>ACCURACY/VCT001</th>
<th>ACCURACY</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>186 vessels in 62 patients</td>
<td>74.2 (vs. FFR\textsubscript{CT})</td>
<td>45.0</td>
<td>77.7</td>
<td>19.6</td>
<td>92.1</td>
<td></td>
</tr>
<tr>
<td>212 vessels in 84 patients</td>
<td>– (vs. FFR)</td>
<td>80</td>
<td>91</td>
<td>84</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>58 vessels in 58 patients</td>
<td>– (vs. FFR)</td>
<td>85 (quantitative)</td>
<td>84</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>201 vessels in 67 patients</td>
<td>67.2 (vs. FFR)</td>
<td>47.5</td>
<td>80.2</td>
<td>61.3</td>
<td>69.8</td>
<td></td>
</tr>
<tr>
<td>216 vessels in 72 patients</td>
<td>84 (vs. OCA/FFR)</td>
<td>62</td>
<td>90</td>
<td>62</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>88 vessels in 36 patients</td>
<td>69.3 (vs. FFR)</td>
<td>59.3</td>
<td>85.3</td>
<td>88.5</td>
<td>58.9</td>
<td></td>
</tr>
<tr>
<td>50 patients with 50–75% stenosis</td>
<td>– (vs. FFR)</td>
<td>70</td>
<td>93</td>
<td>78</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>161 vessels in 127 patients</td>
<td>75 (vs. FFR)</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
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</table>

A recent prospective multicenter trial revealed that CCTA stenosis was a better method than non-invasive functional testing for detecting significant CAD [defined as ≥70% stenosis or invasive fractional flow reserve (FFR) ≤0.80 if intermediate stenosis with 30–70% in any main three coronary arteries, or ≥50% stenosis by ICA in the left main] [5]. The current study demonstrated similar results that SPECT was only modestly concordant with FFRCT. Of interest, the findings of our study are comparable with prior investigations in terms of the comparative relationship between SPECT-MPI and invasive FFR. We demonstrated modest concordance between the two non-invasive functional tests (Table 2). In the current study, the diagnostic accuracy of SPECT-MPI for the identification of FFRCT<0.80 was modest with 74.1%, which is in line with that of these studies for the identification of abnormal invasive FFR, ranging between 67.2 and 84% [3, 15, 16, 18]. Similarly, SPECT-MPI was likely to demonstrate lower sensitivity for predicting ischemia by invasive FFR, which is also concordant with our results. The reason of the low sensitivity of SPECT-MPI for the identification of abnormal FFRCT that is observed in the current study may be similar to that found between SPECT-MPI and invasive FFR in previous studies, such as balanced ischemia. Ragosta and colleagues observed that patients with FFR<0.75 but no perfusion abnormality on SPECT were likely to have 3-vessel disease compared to patients with ischemia by both of SPECT and FFR [16]. Similarly, in 67 patients undergoing SPECT and ICA with invasive FFR, 58% of patients with 2- or 3-vessel disease showed discordance between SPECT and invasive FFR findings [3]. In the current study, while not reaching the threshold, the three patients with a FFRCT ≤ 0.8 who did not show ischemia on SPECT were likely to have FFRCT close to the cut-off of ischemia in the other vessels. While data on invasive FFR were absent in the current study, this interesting similarity between our findings and previous reports indicates modest diagnostic yield of SPECT for functional significance as demonstrated by current clinical investigations and suggests that FFRCT may be a more practical modality for identification of significant ischemia in a setting where CCTA is abnormal. Such high diagnostic accuracy may in turn potentially influence physicians’ choices for invasive evaluation, reducing downstream tests such as ICA. Indeed, the recent multicenter PLATFORM study revealed that the strategy of CCTA, and then FFRCT for stenosis >30%, reduced unnecessary ICA by 61% [19]. Subsequently, Nørgaard and associates have confirmed this result in a study of 1248 real-world patients and similarly demonstrated cancelation of 69% of ICA by FFRCT use [20]. Importantly, no adverse cardiovascular events were observed after a conservative strategy based on CCTA or FFRCT strategy were applied in these studies. These findings suggest safety and feasibility of FFRCT and highlight its integral role in real-world clinical practice to manage patients with suspected CAD.

The National Cardiovascular Data Registry (NCDR) examined contemporary patterns of invasive FFR among patients undergoing PCI and demonstrated a low penetration of invasive FFR use with only 6% before PCI [21]. Angiography-guided PCI has been common in clinical practice, although FFR-guided PCI is established for the determination of lesions that will benefit from revascularization on the basis of the relative risk reduction of cardiovascular events [22]. The utility and reliability of non-invasive tests for the evaluation of CAD should play a more important role in aiding physicians for guiding therapeutic decisions. However, in a recent large observational study, rates of revascularization were not always comparable with the results of functional stress tests [23]. By contrast, in conjunction with the previous 3 multicenter trials showing high diagnostic accuracy of FFRCT for the identification of functional significance of CAD [6–8], the recent RIPCORD study supplied further evidence for FFRCT for therapeutic decision-making. In this study, Curzen and associates demonstrated that the FFRCT findings adding to CCTA stenosis alone aid in managing patients with stable chest pain and enhance the utility of FFRCT use in clinical practice [24]. Importantly, the clinical management plan was altered in 46% of patients after FFRCT, and no patient required more data for therapeutic decision-making after taking into account FFRCT results. These findings confirm the concept that FFRCT can provide reliable results for physicians in their design of a therapeutic plan and likely explain the high rate in successful ICA cancelation after FFRCT use in the aforementioned real-world study [20].
Given the limited data to suggest the utility of SPECT-MPI for guiding revascularization [25, 26], non-invasive test results alone may not be suitable for this purpose [27]. Similarly, the limitations of guiding treatment strategy for revascularization by anatomical stenosis on CCTA alone have also been reported [28]. Studies of the added value of FFR$_{CT}$ use in conjunction with anatomical information of CAD by CCTA through longer-term follow up must be undertaken, and an array of recent accumulated evidence and future investigations should continue to confer a key role of FFR$_{CT}$ in clinical practice for diagnosis, therapeutic decision-making, appropriateness of revascularization and risk assessment among patients with suspected CAD.

There are several limitations to be addressed in the current study. Our study included a small sample size from two prospective multicenter studies and retrospectively analyzed the concordance of SPECT-MPI with FFR$_{CT}$. Although patients who were clinically referred for non-invasive tests and ICA were enrolled in these studies, results in a real-world context remain limited. Quantitative assessment for SPECT-MPI may be useful to identify ischemia, however, we do not have quantitative assessment of SPECT as well as invasive FFR which may provide more details on ischemia. Of importance, however, we report for the first time the relative limitations of using SPECT-MPI to diagnose vessel-specific ischemia as compared to FFR$_{CT}$. The prevalence of abnormal FFR$_{CT}$ is also limited in the current study, which may be a reason for the low positive predictive value of SPECT-MPI. Due to this low prevalence of abnormal FFR$_{CT}$, we also could not perform sub-analyses per vessels and pharmacological or exercise stress. Larger prospective studies which extend our results are needed. FFR$_{CT}$ with CCTA may provide a better decision making pathway for the identification of patients who would benefit from invasive coronary angiography. However, the diagnostic pathway after CCTA in patients with inconclusive results has not been validated to date. It might be of interest to investigate the cardiac events between SPECT-MPI and FFR$_{CT}$; however, we do not have the information of outcome data in the current study.

Conclusion

In the current study of two functional non-invasive tests, FFR$_{CT}$ showed only modest concordance with SPECT-MPI. These results are comparable with those from prior studies comparing SPECT-MPI and invasive FFR.

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Compliance with ethical standards

Conflict of interest Unrestricted money as grant support to institution to do independent research from HeartFlow. The other authors have no conflict of interest.

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