Performance of computed tomography-derived fractional flow reserve using reduced-order modelling and static computed tomography stress myocardial perfusion imaging for detection of haemodynamically significant coronary stenosis

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Aims
To compare the diagnostic performance of a reduced-order computed tomography-derived fractional flow reserve (CT-FFR) technique derived from luminal deformation and static CT stress myocardial perfusion (CTP).

Methods and results
Forty-six patients (84 vessels) with suspected coronary artery disease from a single institution planned for elective coronary angiography prospectively underwent research indicated invasive fractional flow reserve (FFR) and 320-detector CT coronary angiography (CTA) and static CTP. Analyses were performed in separate blinded core laboratories for CT-FFR and CTP. CT-FFR was derived using a reduced-order model with dedicated software on a standard desktop computer. CTP was assessed visually and quantitatively by transmural perfusion ratio (TPR). Invasive FFR was significant in 33% (28/84) of vessels. Overall per-vessel sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for CT-FFR were 81%, 84%, 71%, 90%, and 83%, respectively, those of visual CTP were 54%, 92%, 79%, 77%, and 78%, respectively, and TPR were 64%, 48%, 42%, 70%, and 54%, respectively. Per-vessel receiver operator curve analysis demonstrated a significantly larger area under the curve (AUC) for CT-FFR (0.89) with that for visual CTP (0.72; \( P < 0.016 \)), TPR (0.55; \( P < 0.0001 \)), and CTA (0.76; \( P = 0.04 \)). The addition of CT-FFR to CTA provided superior improvement in performance (AUC 0.93; \( P < 0.0001 \)) compared with CTA alone, a combination of CTA with visual CTP (AUC 0.82; \( P = 0.007 \)) and CTA with TPR (AUC 0.78; \( P = 0.0006 \)).

Conclusion
Based on this selected cohort of patients, a reduced-order CT-FFR technique is superior to visual and quantitative assessed static CTP in detecting haemodynamically significant coronary stenosis as assessed by invasive FFR.

Keywords
computed tomography • fractional flow reserve • imaging • ischaemia • myocardial perfusion
Introduction

In stable coronary artery disease, clinical outcomes and the need for revascularization is dependent on the presence and total burden of ischaemia.\textsuperscript{1–3} Traditional non-invasive functional imaging accurately detect the presence or absence of ischaemia on a per-patient or per-territory basis, but lacks the spatial resolution to identify lesion-specific ischaemia.\textsuperscript{3} Fractional flow reserve (FFR) is the invasive reference standard for lesion-specific ischaemia, and is defined as the difference in pressure proximal and distal to a stenosis under maximal hyperaemia.\textsuperscript{4} Its use in guiding revascularization is associated with improved clinical outcomes and a reduction in healthcare costs.\textsuperscript{5,6}

Coronary computed tomographic angiography (CTA) is a well-established non-invasive test for the detection of anatomical stenoses,\textsuperscript{7} with a high sensitivity and negative predictive value (NPV) but limited specificity for identifying functional significance.\textsuperscript{8} Therefore, in the presence of identified disease, patients are often managed with further stress testing in an attempt to determine functional significance.\textsuperscript{9}

Given this limitation of CTA, there are two emerging techniques that provide the ability to assess both anatomy and estimate function from a cardiac CT. CT stress myocardial perfusion (CTP) is based on the principle of a direct relationship between the degree of contrast in the myocardium and myocardial blood flow.\textsuperscript{10} It requires an acquisition at rest and then repeated during pharmacological stress, and is therefore, associated with side-effects of hyperaemia, increased radiation, and contrast media exposure.\textsuperscript{11}

Computed tomography-derived fractional flow reserve (CT-FFR) is a technique that applies computational fluid dynamics to determine lesion specific ischaemia from a single resting CTA.\textsuperscript{12} Its diagnostic performance has been compared with invasive FFR using techniques that require external off-site image processing operating on a parallel supercomputer and more recently, performed onsite using a standard workstation.\textsuperscript{13–17} We have previously described a reduced-order CT-FFR technique that is derived from the structural deformation of the coronary lumen and aorta. It can be performed at point of care using a standard desktop computer with analysis in under 30 min. Its accuracy compared to FFR is high with an area under the curve (AUC) of 0.88.\textsuperscript{18}

Comparison of a workstation-based CT-FFR technique based on luminal deformation with the performance of static CTP is not known. Therefore, the primary aim of this study was to compare the per-vessel diagnostic performance of CT-FFR and static CTP using FFR as reference standard.

Methods

Study design

Patients from a single institution with suspected coronary artery disease planned for elective coronary angiography prospectively underwent research indicated invasive FFR and 320-detector CTA and static CTP. Exclusion criteria included age <40 years, atrial fibrillation, renal insufficiency (estimated glomerular filtration rate <30 ml/min/1.73 m\textsuperscript{2}), severe bronchoplastic airway disease, non-diagnostic CTA image quality, possible pregnancy or breastfeeding, and iodine contrast anaphylaxis. Screened patients were included in the study upon providing consent to undergo a research-indicated CTA and CTP in addition to an invasive FFR in at least one major epicardial artery >2 mm diameter with a visually assessed stenosis between 10% and 90% during invasive coronary angiography (ICA). Only vessels with invasive FFR measurements were included, with no assumptions made for normal or occluded vessels not assessed with invasive FFR. The study was approved by the institutional human research ethics committee, and all participants gave written informed consent.

CT imaging protocol

Patients underwent cardiac CT assessment using a 320-row detector CT scanner (Aquilion One Vision; Toshiba Medical Systems Corp., Otawara, Japan). The CT acquisition protocol has been previously described\textsuperscript{11} and consists of a calcium score scan and a resting CTA followed by a stress perfusion CTA 20 min later. All patients received sublingual nitroglycerine and beta-blockers were administered to achieve a pre-scan heart rate of <60 b.p.m. Scanning was triggered in the arterial phase using automated contrast bolus tracking with the region of interest placed in the descending aorta, and automatically triggered at 300 Hounsfield units. Scanning parameters were: detector collimation 320 × 0.5 mm; tube current 300–500 mA [depending on body mass index (BMI)]; tube voltage 120 kV if BMI >25 and 100 kV if BMI <25; temporal resolution 135 ms; 75 mL of contrast were used in both rest and stress CTP. Prospective ECG (AW: Please spell out ECG if necessary,) gating with a broadened acquisition window 70–99% of the R–R interval was used for both resting and stress CTA acquisitions to facilitate CT-FFR analysis and CTP interpretation. The stress perfusion scan was performed 20 min after resting CTA with intravenous adenosine infusion (140 μg/kg/min for 3 min).

CTA analysis

Stenosis severity on CTA was interpreted using a dedicated workstation (Vitrea Fx 6, Vital Images, MN, USA) in accordance with the 18 coronary segment model\textsuperscript{19} by two experienced CT angiographers at a CTA core laboratory (The Heart Centre, Rigshospitalet, Denmark), blinded to the results of ICA and FFR, with disagreement resolved by consensus. Each coronary segment >2 mm in diameter was visually assessed for percent luminal stenosis and a vessel was considered significantly diseased if there was >1 segment which is non-evaluable or showed >50% luminal stenosis.

CTP image analysis

Assessment of CTP images was performed using both rest and stress images in a core laboratory blinded to FFR result (The Heart Centre, Rigshospitalet, Denmark). Datasets were reconstructed every 3% of the R–R interval with a FC03 reconstruction kernel, which incorporated a beam hardening correction algorithm. The phase with the least cardiac motion was selected using a short axis multiplanar reconstruction series with 3–5 mm slices. CTP was assessed visually and quantitatively by the transmural perfusion ratio (TPR).

Visual assessment of myocardial perfusion was determined by either one of two experienced independent readers (J.J.L. 8 years, M.H.S. 5 years) according to the American Heart Association 17 segment myocardial segment model\textsuperscript{20} with disagreement resolved by consensus. First, each myocardial segment was specifically matched to its subtending major epicardial artery and branches as determined by its course on CTA. Then each segment on stress CTP was scored either on the presence or absence of a hypotenuation perfusion defect. The presence of artefacts such as motion, beam hardening, and cone beam defects on each myocardial segment were recorded.

Quantitative assessment with TPR was calculated at rest and during adenosine stress using the same series of images chosen for visual interpretation. Images were displayed in the cardiac short axis, and an
automated border detection algorithm applied to define the three myocardial layers (subendocardium, mid-myocardium, and subepicardium). The mean attenuation density in each layer was calculated. The TPR of a segment was defined as the ratio of the mean subendocardial attenuation density to the mean attenuation density of the combined subepicardial layers of all segments in the same cross-sectional part of the left ventricle. The segment with the lowest TPR was chosen to represent perfusion for each major vessel.

CT-FFR analysis

The CT-FFR analysis was performed by experienced post-processing engineers at the Toshiba Medical Systems Corp core laboratory, blinded to the results of invasive FFR, using a standard desktop computer (Xeon E5-2620, 6 core 2 processor, Intel, Mountain View, CA, USA) and dedicated software (Toshiba Medical Systems Corp). 3D models of the coronary tree were constructed from CT slice data. Vessel centreline and luminal contours were automatically processed. Manual adjustments were performed as required. Four diastolic phases between 70 and 99% of the R-R interval (70%, 80%, 90%, and 99%) were reconstructed for use in the CT-FFR analysis. The physiological principles used to derive analysis conditions have been previously described in detail. CT-FFR is calculated in three key steps; firstly pressure and flow are estimated at the inlet and outlet by assessing changes in in the luminal volume and shape across diastole. The microvascular resistance is then assumed as constant based on the assumption that the CTA acquisition in late diastole occurs in a period of the cardiac cycle in which resistance is lowest and most stable, therefore, pressure becomes proportional to flow. Finally, the 3D coronary vessel model is reduced to a 1D model and the equations of fluid dynamics are applied to this reduced-order model using a standard desktop computer. CT-FFR is then determined across each luminal cross-section.

The clinical site provided the Toshiba core laboratory with the distance measured from the vessel ostium to the pressure sensor of the FFR wire for each interrogated vessel, in order to directly match the FFR result with the CT-FFR estimate. CT-FFR values were calculated from the derived pressures along the entire length of the vessel until a diameter of 1.8 mm was reached.

ICA and FFR

ICA and FFR was performed as per standard practice. Quantitative coronary angiography was performed using a semi-automated edge detection system (Xcelera Cath R3.2, Philips, Amsterdam, Netherlands). Invasive FFR was performed in at least one vessel of diameter ≥2 mm and visual stenosis between 10% and 90% chosen at the discretion of the operator, blinded to the CT findings. FFR was recorded in the distal coronary artery following intracoronary glyceroltrinitrate (100 mcg) and steady-state hyperaemia achieved with administration of intravenous adenosine at 140 μg/kg/min. The pressure sensor was then pulled back into the tip of the guiding catheter and only runs with ≤0.05 drift were accepted for analysis. An FFR value of ≤0.8 was chosen to define functionally significant stenosis.

Endpoints

The primary endpoint was the per-vessel diagnostic performance of CT-FFR, visually assessed CTP and TPR as assessed by the area under the receiver operating characteristic curve at identifying haemodynamically significant stenosis using invasive FFR ≤0.8 as reference standard. Secondary endpoints included the incremental per-vessel diagnostic value of adding CT-FFR or CTP to CTA as assessed by AUC and integrated discrimination improvement (IDI) index. Additional secondary endpoints include per-patient diagnostic performance as assessed by AUC and per-patient and per-vessel diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and NPV.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range (IQR) according to their distribution. Categorical variables are provided as frequencies (%). Patient identity was included as a cluster variable to account for likely within-individual correlations, given that evaluation of multiple arteries was performed for each individual. AUC comparisons were performed using the approach of DeLong et al. and treating CT-FFR and TPR as continuous variables. The optimal TPR threshold (<0.94) for detecting FFR defined haemodynamically significant stenosis was calculated using the Youden index. The incremental diagnostic value of adding CT-FFR or CTP to CTA was assessed by AUC using a binary logistic regression model. Furthermore, the IDI index was also used to determine whether CT-FFR and CTP improved vessel classification as haemodynamically significant, compared with CTA alone. An IDI index that is significantly greater than zero is taken to demonstrate the incremental value of the studied technique when added to CTA. Inter-observer reproducibility for CT-FFR, visually assessed CTP and TPR was assessed using the kappa statistic value by treating all modalities as dichotomised variables. Bland–Altman analysis was also performed for CT-FFR and TPR to assess inter-observer reproducibility. The correlation between CT-FFR and invasive FFR values was determined with a Pearson correlation coefficient. Statistical analysis was performed using SPSS version 24. A P-value <0.05 was considered statistically significant.

Results

Patient population

Forty-six patients (mean age 61.7 ± 10.0 years, 71.6% male) were prospectively enrolled into the study. The patient enrolment flowchart is illustrated in Figure 1. Baseline patient and vessel characteristics are listed in Tables 1 and 2. CT-scan parameters are listed in Table 3. Eighty-four vessels were included, CT-FFR was feasible in 98% of vessels with two vessels excluded due to being too small for analysis. CTP analysis was feasible in 93%, with six vessels excluded due to motion artefact. There were an additional two vessels excluded due to missing stress CTA data.

Eighty-four included vessels were interrogated by FFR, of which 28 (33.3%) had an FFR ≤0.8. The per-vessel diagnostic performance of CTA, CT-FFR, visually assessed CTP, and TPR is summarized in Table 4. An example is shown in Figure 2.

Comparison of diagnostic performance

The primary endpoint of per-vessel AUC for CT-FFR was 0.89 which was superior to visually assessed CTP (0.72, P=0.016), TPR (0.55, P<0.0001), and CTA (0.76, P=0.04) using an FFR threshold of <0.8 (Figure 3). Visually assessed CTP demonstrated a superior per-vessel AUC compared with TPR (P=0.029). The secondary endpoint of per-patient AUC also demonstrated diagnostic superiority of CT-FFR with an AUC of 0.88 compared with visually assessed CTP (0.70, P=0.024), TPR (0.61, P=0.004), and CTA (0.66, P=0.005).

CTA

CTA assessment was feasible in all included vessels. The mean radiation exposure for the resting CTA acquisition was 4.9 ± 2.2 mSV.
with a mean contrast volume of 75 mL. The per-vessel diagnostic accuracy of CTA alone was 73% with a sensitivity of 86% and specificity of 66%. The PPV was 56% and NPV 90%.

**CT-FFR**

The mean time for automatic lumen segmentation including manual adjustments to the centreline and contour was 14.41 ± 5.42 min. The average computational time for CT-FFR was 10.47 ± 2.06 min. Therefore, the average per-patient time required for CT-FFR analysis was 25.28 ± 6.15 min. CT-FFR demonstrated a modest and statistically significant correlation with invasive FFR (Pearson R = 0.56, \( P < 0.0001 \)) (Figure 4). On Bland–Altman analysis (Figure 4) there was a moderate and significant agreement between FFR and CT-FFR with a difference of 0.063 ± 0.135 (\( P = 0.001; 95\% \) CI: -0.201 to 0.325). Both graphs demonstrate that the correlation and agreement was best in non-ischaemic vessels with reduced precision in vessels with functionally significant disease. CT-FFR had a per-vessel diagnostic accuracy of 83% for FFR-significant stenosis. The per-vessel sensitivity was 81% and specificity 84%. The PPV was 71% and NPV 90%. CT-FFR reduced the number of false positive vessels on CTA by reclassifying 53% as true negative.

**CTP**

Visually assessed CTP had a per-vessel diagnostic accuracy of 64% for identifying functionally significant stenosis. The sensitivity was 54% and specificity 92%. The PPV was 79% and NPV 77%. Among the 13 false negative vessels in CTP, 84.5% were in major epicardial vessels with the majority in the left anterior descending (LAD) artery (77%). The range of FFR among the false negative vessels was 0.65–0.80 with a mean and IQR of 0.76 and 0.75–0.80, respectively. In patients with an appropriately identified perfusion defect on visually assessed CTP \( (n = 15) \), the mean FFR was 0.71 with an IQR of 0.65–0.77. CTP assessed quantitatively by TPR had a per-vessel diagnostic accuracy of 54%, sensitivity of 64%, and specificity of 68%. The PPV was 42% and NPV 70%. Stress CTP was associated with an additional mean radiation exposure of 6 ± 4 mSv and a contrast volume of 75 mL.

**Per-vessel incremental diagnostic value of CT-FFR or CTP added to CTA**

The addition of visually assessed CTP to CTA demonstrated a significant increase in diagnostic performance with an AUC of 0.82 compared with CTA alone \( (P = 0.02) \). No significant increase in diagnostic performance was demonstrated with the addition of TPR to CTA.
with an AUC of 0.78 (P = 0.49). The addition of CT-FFR to CTA demonstrated a significant increase in AUC to 0.93 compared with CTA alone (P < 0.0001), a combination of CTA with visually assessed CTP (P = 0.007) and CTA with TPR (P = 0.0006) (Figure 5). There was no significant diagnostic value in combining CTA, CT-FFR, and visually assessed CTP (AUC = 0.94) in comparison to the combination of CTA and CT-FFR (P = 0.37). The IDI index for CT-FFR was 0.262 (P < 0.01) and higher than visually assessed CTP at 0.099 (P < 0.01).

**Per-patient analysis**

The diagnostic accuracy of CTA alone was 65% with a sensitivity of 86% and specificity of 46%. The PPV was 59% and NPV 79%. Compared with CTA, CT-FFR demonstrated higher diagnostic accuracy at 78%, a specificity of 75%, PPV 75%, and NPV of 82% with a sensitivity of 82%. Visually assessed CTP demonstrated a diagnostic accuracy of 69% with a specificity of 80% and positive predictive value of 76%. Sensitivity of CTP was 59% and NPV 64%. CTP assessed by TPR demonstrated a diagnostic accuracy of 55% with a sensitivity of 68% and specificity at 40%. The PPV was 56% and NPV 53.

**Table 2**  
**Vessel characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n = 46), vessels (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium score (Agatston Units), median (IQR)</td>
<td>330.5 (95.3–1043)</td>
</tr>
<tr>
<td>Vessel</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>45.2% (38/84)</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>23.8% (20/84)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>15.5% (13/84)</td>
</tr>
<tr>
<td>Diagonal branch</td>
<td>3.6% (3/84)</td>
</tr>
<tr>
<td>Obtuse marginal branch</td>
<td>7.1% (6/84)</td>
</tr>
<tr>
<td>PDA or PLV branch</td>
<td>4.8% (4/84)</td>
</tr>
<tr>
<td>Vessels with QCA maximal stenosis &gt;50%</td>
<td>32% (27/84)</td>
</tr>
<tr>
<td>Vessels with ICA visual stenosis &gt;50%</td>
<td>54% (45/84)</td>
</tr>
<tr>
<td>Patients with CTA maximum stenosis &gt;50%</td>
<td>69.6% (32/46)</td>
</tr>
<tr>
<td>Vessels with CTA maximum stenosis &gt;50%</td>
<td>51.2% (43/84)</td>
</tr>
<tr>
<td>Patients with CT-FFR ≤0.80</td>
<td>52.2% (24/46)</td>
</tr>
<tr>
<td>Vessels with CT-FFR ≤0.80</td>
<td>37.8% (31/82)</td>
</tr>
<tr>
<td>Patients with CT perfusion defect by visual assessment</td>
<td>40.5% (17/42)</td>
</tr>
<tr>
<td>Vessels with CT perfusion defect by visual assessment</td>
<td>25.0% (19/76)</td>
</tr>
<tr>
<td>Patients with CT perfusion defect by TPR (≤0.94)</td>
<td>64.3% (27/42)</td>
</tr>
<tr>
<td>Vessels with CT perfusion defect by TPR (≤0.94)</td>
<td>56.7% (43/76)</td>
</tr>
<tr>
<td>Patients with FFR ≤0.80</td>
<td>47.8% (22/46)</td>
</tr>
<tr>
<td>Vessels with FFR ≤0.80</td>
<td>33.3% (28/84)</td>
</tr>
<tr>
<td>Patients with FFR ≤0.80 in &gt;1 vessel</td>
<td>10.9% (5/46)</td>
</tr>
</tbody>
</table>

QCA, quantitative coronary angiography.

**Reproducibility**

In 15 randomly selected patients, including 30 vessels the inter-observer variability of CT-FFR was moderate at (k = 0.54, P < 0.01), modest for visually assessed CTP (k = 0.435, P = 0.02), and good for TPR (k = 0.677, P < 0.001). Bland–Altman analysis for CT-FFR demonstrated a significant mean inter-observer difference of 0.054 (P = 0.035, 95% limits of agreement: 0.003–0.10) and for TPR a mean inter-observer difference of -0.017 (P = 0.18, 95% limits of agreement: -0.14 to 0.10).

**Discussion**

In this prospective study, we demonstrated that in patients with suspected coronary artery disease, a reduced-order CT-FFR technique can identify lesion specific ischaemia with high accuracy compared with FFR; and is superior to CTA and static CTP assessed visually and quantitatively, in a per-vessel and per-patient analysis. When compared with CTP, CT-FFR had superior incremental diagnostic value when added to CTA for identifying functionally significant stenosis as assessed by FFR. Importantly, the benefit of CT-FFR was delivered using a standard desktop computer from a single widened acquisition CTA, without the need for additional medications and with reduced contrast and radiation exposure compared with CTP.

The computation of CT-FFR is performed using a reduced-order model and hence can be performed rapidly in less than 30 min using a standard desktop computer. Our study demonstrated a similarly high-diagnostic accuracy for CT-FFR as reported in the recently published validation paper for this technique. These results are also comparable to 3D fluid model based CT-FFR and other workstation-based techniques. The higher diagnostic performance of CT-FFR as compared with CTA was predominantly driven by an improvement in the specificity and positive predictive value, with a substantial 53% reduction in false positive findings.

**Table 3**  
**CT-scan characteristics**

<table>
<thead>
<tr>
<th>Patients (n = 46)</th>
<th>CTA</th>
<th>CTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b.p.m.)*</td>
<td>53.4 ± 6.4</td>
<td>66.5 ± 9.7</td>
</tr>
<tr>
<td>Nitrites administered</td>
<td>100 (46/46)</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>78.2% (36/46)</td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>37.0% (17/46)</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker dose (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral metoprolol</td>
<td>58.2 ± 46.0</td>
<td></td>
</tr>
<tr>
<td>Intravenous metoprolol</td>
<td>4.0 ± 6.3</td>
<td></td>
</tr>
<tr>
<td>Tube voltage (kV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>43.5% (20/46)</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>56.5% (26/46)</td>
<td></td>
</tr>
<tr>
<td>Single beat acquisition</td>
<td>100% (46/46)</td>
<td></td>
</tr>
<tr>
<td>Radiation exposure (mSv), mean ± SD</td>
<td>4.9 ± 2.1</td>
<td>5.5 ± 3.5</td>
</tr>
</tbody>
</table>

*At time of CT acquisition.
Figure 2  Coronary artery disease with positive CT-FFR and CTP. Forty-two-year-old man with increasing exertional chest pains and suspected coronary artery disease. CTA demonstrated moderate to severe stenosis (x) in the proximal LAD artery with further moderate disease in the mid-vessel (y) (A). Invasive coronary angiography (B) demonstrated moderate 40–50% stenosis in the proximal (x) and mid-segment (y) of the LAD. Invasive FFR was functionally significant at 0.75 in the distal vessel. CT-FFR (C) was functionally significant at 0.77 in the distal vessel. Visually assessed CTP identified perfusion defects in the anterior wall indicating LAD territory ischaemia (D). Transmural perfusion polar plot (E, F) demonstrating TPR values and abnormal perfusion in anterior wall. Orange colour indicates TPR values <0.94 and blue colour indicates TPR values >0.99. CT-FFR, CT-derived fractional flow reserve; CTA, CT coronary angiogram; CTP, CT stress myocardial perfusion imaging; FFR, fractional flow reserve; LAD, left anterior descending; TPR, transmural perfusion ratio.
Two studies have recently been published comparing the diagnostic performance of a workstation-based CT-FFR technique against CTP, with invasive FFR as the reference standard.\textsuperscript{14,15} The CT-FFR techniques described utilize boundary conditions which estimate coronary blood flow based on allometric scaling laws and the relationship between coronary artery diameter and myocardial mass subtended,\textsuperscript{14} with simulation of adenosine induced hyperaemia. In contrast, CT-FFR in this study was derived by assessing changes in the volume and shape of the coronary lumen and aorta across diastole.

Yang et al.\textsuperscript{15} described in a prospective cohort of 72 suspected CAD patients, undergoing elective invasive angiography and invasive FFR, a high and comparable diagnostic accuracy for both CT-FFR (AUC 0.89) and visually assessed static CTP (AUC 0.89). In a similar group of patients, Coenen et al.\textsuperscript{14} demonstrated an equivalent diagnostic performance with an AUC of 0.78 in both CT-FFR and quantitatively assessed CTP. Similar to the results in our study, both studies demonstrated an incremental diagnostic value for the combination of CT-FFR or CTP with CTA.

The results in our study demonstrated a lower diagnostic accuracy for CTP, driven by a significantly lower sensitivity and NPV than that which has been reported in previous FFR correlated CTP studies as described in a recent meta-analysis.\textsuperscript{27} These results were consistent on both a per-vessel and per-patient analysis. Compared with visually assessed CTP, TPR was more reproducible and consistent with recently published FFR correlated studies, its diagnostic performance was inferior to visually assessed CTP.\textsuperscript{11,28} There are several potential explanations for the low sensitivity of CTP demonstrated in this study. A frequently encountered cause of false negatives is cone beam artefact involving the right coronary artery, however, the most

<table>
<thead>
<tr>
<th>Per vessel</th>
<th>CTA (&gt;50%) (n = 84)</th>
<th>CT-FFR (&lt;0.8) (n = 82)</th>
<th>Visual CTP (n = 76)</th>
<th>TPR (&lt;0.94) (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>24</td>
<td>22</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>True negative</td>
<td>37</td>
<td>46</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>False positive</td>
<td>19</td>
<td>9</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>False negative</td>
<td>4</td>
<td>5</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>% Accuracy</td>
<td>73</td>
<td>83</td>
<td>78</td>
<td>54</td>
</tr>
<tr>
<td>% Sensitivity</td>
<td>86 (67–96)</td>
<td>81 (62–94)</td>
<td>54 (34–72)</td>
<td>64 (44–81)</td>
</tr>
<tr>
<td>% Specificity</td>
<td>66 (52–78)</td>
<td>84 (71–92)</td>
<td>92 (80–98)</td>
<td>48 (33–63)</td>
</tr>
<tr>
<td>% PPV</td>
<td>56 (46–65)</td>
<td>71 (57–82)</td>
<td>79 (58–91)</td>
<td>42 (27–58)</td>
</tr>
<tr>
<td>% NPV</td>
<td>90 (79–96)</td>
<td>90 (80–95)</td>
<td>77 (69–84)</td>
<td>70 (51–84)</td>
</tr>
<tr>
<td>AUC\textsuperscript{a}</td>
<td>0.76</td>
<td>0.89</td>
<td>0.72</td>
<td>0.55</td>
</tr>
</tbody>
</table>

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; TPR, transmural perfusion ratio.
\textsuperscript{a}AUC comparison: CT-FFR vs. CTA (\textit{P} = 0.04), CT-FFR vs. visual CTP (\textit{P} = 0.016), and CT-FFR vs. TPR (\textit{P} < 0.001).
The commonly associated vessel in our false negative cohort was the LAD. The majority of false negatives occurred in the FFR ‘ischaemic grey zone’ of 0.75–0.80, suggesting that static CTP may have reduced performance in detecting borderline ischaemic lesions. Visual interpretation of CTP is also subjective with a modest inter-observer reproducibility demonstrated in our cohort (kappa = 0.435). The sensitivity of CTP may potentially have been affected by delayed contrast enhancement as 96% of patients had their CTP performed 20 min after CTA. CT-FFR techniques depend on the accurate visualization and contouring of the coronary lumen. Societal guidelines emphasize the administration of beta-blockers and nitrates to enhance image quality by reducing motion and maximising luminal diameter and have been demonstrated to improve diagnostic performance of both CTA and CT-FFR. In contrast, these agents can potentially mask ischaemia in stress perfusion studies, and therefore, may have contributed to the low sensitivity demonstrated our results. In addition, 32% of false negatives were associated with a perfusion defect in the adjacent epicardial territory, therefore, it is possible that in some cases there was misclassification of the subtending major epicardial artery to the corresponding myocardial segment. Finally, the performance of CTP may have potentially been disadvantaged by using FFR as reference. CTP assesses ischaemia by considering both epicardial stenosis and microvascular dysfunction rather than lesion specific ischaemia alone, which raises the possibility that the performance of CTP may improve by comparison to invasive coronary flow reserve rather than FFR.

Yang et al. demonstrated the utility of CTP in heavily calcified vessels, with a higher positive predictive value and specificity compared with a workstation-based CT-FFR technique. Given the sample size, we did not assess the diagnostic performance of this CT-FFR technique across different spectrums of coronary calcification severity, however, the high-diagnostic performance of CT-FFR was still observed in a cohort with a median per-patient Agatston score of 330.5 (95.3–1043).

Although the diagnostic performance of CT-FFR (AUC 0.89) in this study further supports the feasibility of reduced-order modelling in simulating invasive physiology, its clinical utility remains undefined. To accurately assess its diagnostic performance, the location of CT-FFR measurement was carefully matched to that of invasive FFR assessment, however, as a stand-alone clinical tool, the location at which CT-FFR is measured in the absence of an invasive reference point is unclear. The majority of clinical utility studies using established CT-FFR techniques have thus far applied the most distal value.
in guiding clinical decisions. This strategy potentially overestimates the severity of CT-FFR, reducing its specificity, and is in contrast to invasive FFR guidelines which recommend measurements 20–30 mm distal to a stenosis. The moderate agreement between FFR and CT-FFR values (mean difference 0.063 ± 0.135) and the inter-observer variability of CT-FFR (0.054 ± 0.023) in this study demonstrate the potential for misclassification for CT-FFR values around the 0.80 cut-off and highlight the importance of avoiding a dichotomous approach to clinical interpretation of CT-FFR. This is further illustrated in a recent review in which intermediate range CT-FFR values (0.70–0.80) were associated with the lowest diagnostic accuracy (46%) compared with invasive FFR. Accordingly, the concept of a CT-FFR grey zone for values between 0.75 and 0.80 has been proposed, in which clinical decisions should be supported by additional information such as symptoms, myocardium at-risk, trans-murality, and the presence of focal vs. diffuse disease. Further investigation into the optimal strategy for interpreting CT-FFR is needed prior to its use as a diagnostic tool in broader clinical practice.

The main strength of this prospective study was the use of blinded core laboratories for CTA, CT-FFR, and CTP analysis. There were also inherent limitations associated with a single-centre study and small sample size. There is a potential for selection bias as recruited patients were awaiting elective coronary angiography, reflecting a higher pre-test probability of coronary artery disease. Similar to previously published studies, not every vessel for included patients was interrogated with invasive FFR, additionally our criteria of including vessels with minimal disease may potentially overestimate the specificity of CT-FFR and CTP. There were also several lesion subsets not investigated, such as the accuracy of CT-FFR in patients with previous coronary stents and all scans were performed using a 320-detector CT, hence the feasibility of this CT-FFR technique with narrow detector CT is not known. Furthermore, CT-FFR was assessed as a mimic of invasive FFR and hence interpreted as a continuous variable. This potentially may have affected the comparison of diagnostic performance against visually assessed CTP which was analysed as a dichotomous variable. Our study compared static CTP using a 320-detector single source CT with CT-FFR, therefore the results cannot be conferred to other CTP techniques including dynamic perfusion and dual energy CTP. Using a resting invasive reference standard such as the instantaneous wave-free ratio may better reflect the microvascular assumptions made in CT-FFR and therefore result in improved diagnostic accuracy and correlation to invasive measurements.

### Conclusion

In this selected prospective cohort of patients, a reduced-order CT-FFR technique was superior to visually and quantitative-ly assessed static CTP in detecting haemodynamically significant coronary stenosis as evaluated by invasive FFR. Larger prospective studies in an intermediate risk population will be required to further assess the real-world feasibility of this CT-FFR technique.

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### Conflict of interest: B.S.K. has been an invited speaker at symposi-ums sponsored by St Jude, Pfizer, Bristol-Myers Squibb, and Lilly. S.K.S. has been an invited speaker at a Toshiba sponsored meeting. K.F.K. has received institutional unrestricted research grants form Toshiba Medical Corporation and has been an invited speaker at symposi-ums sponsored by Toshiba Medical Corporation, T.S. and Y.F. are employees of Toshiba Medical Systems, Japan, J.H.-J. is an employee of Toshiba Medical Australia and New Zealand. All other authors have reported they have no relationships relevant to contents of this art-icle to disclose. This research is investigator initiated and not spon-sored by any CT vendor. Toshiba Medical Japan acted as the core-lab
for CT-FFR assessment but had no input in the study design, data analysis, or interpretation of results.

References