Cardiovascular magnetic resonance profiling of coronary atherosclerosis: vessel wall remodelling and related myocardial blood flow alterations

Cosima Jahnke1*, Robert Manka2,3, Sebastian Kozerke3, Bernhard Schnackenburg4, Rolf Gebker2, Nikolaus Marx1, and Ingo Paetsch1

1Department of Cardiology, University Hospital RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany; 2Department of Cardiology, German Heart Institute Berlin, Berlin, Germany; 3Institute for Biomedical Engineering, University and ETH Zurich, Zurich, Switzerland; and 4Philips Clinical Science, Hamburg, Germany

Received 4 May 2014; accepted after revision 4 July 2014; online publish-ahead-of-print 7 August 2014

Published on behalf of the European Society of Cardiology. All rights reserved.

* Corresponding author. Tel: +49 241 80 89301; Fax: +49 241 80 82545, E-mail: cjahnke@alice.de

Aims
To determine the association between coronary vessel wall morphology and haemodynamic consequences to the myocardium using a combined cardiovascular magnetic resonance (CMR) imaging protocol. Non-invasive CMR profiling of coronary atherosclerotic wall changes and related myocardial blood flow impairment has not been established yet.

Methods and results
Sixty-three patients (45 men, 61.5 ± 10.7 years) with suspected or known coronary artery disease underwent 3.0 Tesla CMR imaging. The combined CMR protocol consisted of the following imaging modules at rest: 3D vessel wall imaging and flow measurement of the proximal right coronary artery (RCA), myocardial T2*, and first-pass perfusion imaging. During adenosine stress coronary flow, T2* and first-pass perfusion imaging were repeated. Coronary X-ray angiography classified patient groups: (i) all-smooth (n = 19); (ii) luminal irregular (diameter reduction < 30%; n = 35); and (iii) stenosed RCA (diameter reduction ≥ 50%; n = 9). The ratio of CMR-derived vessel wall area-to-lumen area significantly increased stepwise for the comparison of all-smooth vs. luminal irregular vs. stenosed RCA (1.9 ± 0.6 vs. 2.6 ± 0.6 vs. 3.6 ± 0.9, P < 0.01). Epicardial coronary flow reserve exhibited a stepwise significant decrease (3.4 ± 0.5 vs. 2.9 ± 0.7 vs. 1.7 ± 0.3, P < 0.01). On the myocardial level, stress-induced percentage gain of T2* values (ΔT2*) was significantly decreased between groups (29.2 ± 10.6 vs. 9.0 ± 9.8 vs. 2.2 ± 11.8%, P < 0.01) while perfusion reserve index decreased in the presence of stenosed RCA only (2.2 ± 0.6 vs. 2.0 ± 0.4 vs. 1.3 ± 0.3, P = ns and P < 0.01, respectively).

Conclusion
The proposed comprehensive CMR imaging protocol provided a non-invasive approach for direct assessment of coronary vessel wall remodelling and resultant pathophysiological consequences on the level of epicardial coronary and myocardial blood flow in patients.

Keywords
Magnetic resonance imaging • Coronary atherosclerosis • Vessel wall imaging • Coronary flow reserve • Myocardial blood flow • Myocardial oxygenation

Introduction
Coronary atherosclerosis has a long asymptomatic phase and only the later stages of disease progression, in particular segmental narrowing and significant luminal stenosis, can reliably be assessed by coronary angiography. Knowingly however, atherosclerosis represents primarily a disease of the arterial wall, whereas an angiogram is an image of the lumen. Consequently, mere assessment of coronary lumen integrity is of limited value for the detection of subclinical coronary artery disease (CAD), since at the early stages of coronary atherosclerosis the lumen is usually preserved due to outward arterial remodelling. Intravascular ultrasound is considered a well-established imaging technique for the detection of vessel wall remodelling and allows for the characterization of plaque composition. Nevertheless, the imaging method constitutes an invasive procedure and is thus, less suitable as a routine screening method or for serial assessments necessary to monitor atherosclerotic disease progression.

Cardiovascular magnetic resonance (CMR) imaging has been introduced for the assessment of coronary vessel wall remodelling while benefiting from its non-invasive and radiation-free nature.
The relationship of atherosclerotic vessel wall remodelling preceding the development of significant stenosis and its functional consequences on coronary blood flow and the myocardium are still not fully understood. Several modules of CMR imaging have been separately established mainly aiming at the detection of haemodynamically significant coronary stenosis: first-pass contrast-enhanced perfusion\(^7,8\) and blood-oxygen level-dependent imaging\(^9-11\) as well as CMR measurement of coronary blood flow\(^12-14\).

Advantageously, CMR imaging offers the unique possibility to combine various imaging components for morphological and functional assessment of the coronary arteries and the underlying myocardium. Hence, the current study sought to implement a comprehensive CMR imaging protocol in patients in order to elucidate the relationship of atherosclerotic coronary arterial disease and its functional consequences. Conceptually and in a model-like fashion, the study was designed to establish a one-to-one association between right coronary vessel wall changes and subsequent myocardial blood flow impairment; thus, we restricted functional quantitative measurements of myocardial blood flow to the basal inferior/inferoseptal myocardium, which is almost exclusively supplied via the right coronary artery (RCA).

### Methods

#### Patient population

The study was approved by the Charité Institutional Review Board. Sixty-five patients (46 men, 19 women; mean age: 61.7 ± 10.8 years; range: 37–80 years) referred to clinically indicated invasive coronary angiography for evaluation of chest pain or dyspnoea were prospectively enrolled after written informed consent was obtained; all participants underwent invasive testing irrespective of the results of prior CMR imaging. Patients with suspected or known CAD were included. Patients were not considered for study inclusion if they had typical contraindications for CMR imaging or the administration of adenosine, prior coronary artery bypass grafting, prior percutaneous revascularization of the RCA or an underlying condition that could impair microcirculatory vasoreactivity such as previous myocardial infarction, dilated/hypertrophic cardiomyopathy, moderate-to-severe valvular heart disease or severe hypertension. All patients were instructed to withdraw any antianginal medication and to refrain from cigarette smoking, tea, or coffee intake for at least 24 h prior to the study.

#### CMR imaging protocol

For CMR imaging, a 3.0 Tesla MR scanner system was used (Philips Achieva, Best, The Netherlands) equipped with a Quasar Dual gradient system (40 mT/m; 200 mT/m/ms) based on Philips software release 2.6.3. A 32-element cardiac synergy coil was employed for signal reception and cardiac synchronization was performed with a vector-ECG. First, standard cine sequences for the assessment of left-ventricular function were acquired. Secondly, a fast-gradient-echo multi-echo sequence for \(T2^*\) imaging was performed in short-axis geometry. Thirdly, 3D coronary vessel wall imaging of the proximal RCA was done followed by fourth, phase-velocity encoded measurement of right coronary arterial flow.

Subsequently, adenosine infusion (140 µg/kg/min; 6 min total infusion duration) was started and the identical sequence of \(T2^*\) imaging was repeated after 3 min of adenosine infusion. In addition, stress first-pass perfusion imaging was performed in the identical short-axis geometry (intravenous bolus application of 0.025 mmol/kg of gadolinium-DTPA, Magnevist\(^{30}\), Schering, Berlin, Germany; injection rate 4.0 mL/s followed by a 20 mL saline flush). Finally, during stress, a repeat scan of phase-velocity encoded right coronary flow was done (Figure 1).

After termination of adenosine infusion and a 10 min equilibration period, rest first-pass perfusion imaging was carried out with the identical contrast injection scheme. Then, a contrast agent bolus of 0.15 mmol/kg of gadolinium-DTPA was administered and after 10 min delayed enhancement images were acquired.

#### CMR imaging technique

##### Cine imaging

For cine imaging, balanced steady-state free precession sequences were used with retrospective gating (repetition time, 3.3 ms; echo time, 1.6 ms; flip angle, 40\(^\circ\); 30 phases per cardiac cycle; spatial resolution, 1.3 × 1.3 × 8.0 mm\(^3\)) during repetitive end-expiratory breath-holds (6–8 s). Cine images were acquired in three short-axis (apical, mid, and basal short-axis view) and three long-axis geometries (4-, 2-, and 3-chamber view) according to standard definitions.

##### \(T2^*\) imaging

\(T2^*\) imaging was carried out in identical basal short-axis geometry of the left ventricle using an electrocardiogram-triggered, spoiled segmented gradient-echo sequence with six echo times (first echo at 2.7 ms; echo spacing, 1.7 ms; repetition time, 13 ms; flip angle, 35\(^\circ\); spatial resolution, 1.2 × 1.2 × 8.0 mm\(^3\)). Image data acquisition was restricted to end-diastole in order to minimize cardiac motion related artefacts. A black-

---

Figure 1: Time course of CMR measurements during adenosine stress.
blood dual inversion pre-pulse allowed for nullifying the signal from flowing blood in the left-ventricular cavity.

**Coronary vessel wall imaging**
For coronary vessel wall imaging, a 3D dual inversion-recovery segmented k-space gradient-echo (turbo field echo) imaging sequence with a fat suppression pre-pulse was employed (repetition time, 10.0 ms; echo time, 2.9 ms; flip angle, 30°; spatial resolution, 0.4 × 0.4 × 2.0 mm³; eight slices; total scan duration, 186 heartbeats). Acquisition duration per heartbeat was individually adapted (maximum 90 ms) to the diastolic rest period of the RCA as previously described. Respiratory motion was corrected by navigator-gating and -correcting (gating window, 7.1 ms; echo time, 2.1 ms; flip angle, 30°; spatial resolution, 0.7 × 0.7 × 0.9 mm³). The geometry of the 3D coronary vessel wall scan was planned perpendicular to the course of the proximal RCA. In order to minimize angulation errors resulting from the initial RCA curvature the imaging stack was positioned ~2–3 cm away from the origin in a straight portion of the RCA.

**Coronary flow imaging**
Phase-velocity encoded coronary flow measurements were carried out perpendicular to the blood flow direction in the identical cross-sectional geometry as used for coronary vessel wall imaging. For quantitative flow imaging, a 2D segmented k-space gradient-echo (turbo field echo) sequence was acquired during breath-holding (repetition time, 7.0 ms; echo time, 3.4 ms; flip angle, 20°; spatial resolution, 0.5 × 0.5 × 4.0 mm³; temporal resolution, 18 frames/heartbeat; sensitivity-encoding, 3.0; total scan duration, 20 heartbeats; velocity encoding: 100 cm/s at rest and 150 cm/s during stress).

**First-pass perfusion imaging**
Dynamic contrast-enhanced first-pass perfusion imaging was planned ensuring coverage of previously acquired basal short-axis geometry. A saturation-prepared single-shot spoiled gradient echo sequence was employed (repetition time, 2.8 ms; echo time, 0.9 ms; flip angle, 18°; spatial resolution, 1.5 × 1.5 × 8.0 mm³), with one saturation pre-pulse per slice before data readout (pre-pulse delay, 95 ms). All three short-axis geometries were acquired at every heartbeat (acquisition duration, 165 ms/slice) throughout 60 consecutive cardiac cycles during contrast agent bolus passage.

**Delayed enhancement imaging**
Scar imaging was done in short-axis orientation with full left-ventricular coverage using a 3D inversion-prepared spoiled-gradient echo sequence (repetition time, 3.6 ms; echo time, 1.8 ms; flip angle, 15°; spatial resolution, 0.8 × 0.8 × 5.0 mm³). The inversion recovery pre-pulse delay was individually determined from a preparatory Look-Locker sequence and adjusted accordingly (range, 190–250 ms).

**CMR image analysis**

**T2⁺ imaging**
T2⁺ data sets were evaluated in the basal inferior/inferoseptal myocardium as defined by the standardized 16-segment model. The time constant of the signal intensity decay over all echoes was derived and T2⁺ values were provided at rest and during stress. In addition, the relative change of T2⁺ values (ΔT2⁺) was calculated by subtracting T2⁺ values during stress and at rest divided by rest values and given in percent. Due to its almost exclusive supply by the RCA in >90%, the basal inferior/inferoseptal region served as the myocardial reference segment to ensure a one-to-one association between measurements of right coronary vessel wall changes and myocardial blood flow impairment.

**Coronary vessel wall imaging**
From the 3D vessel wall scan, cross-sections of the RCA were identified and magnified four-fold for further analysis: the inner lumen and outer vessel borders were manually segmented and averaged from at least three serial cross-sectional images to determine coronary lumen area and vessel wall area. In order to reference the individual wall thickening to luminal size, a respective index was determined as the ratio of wall area-to-lumen area (WATLA). Finally, mean vessel wall thickness was calculated as previously published.

**Coronary flow imaging**
The paired magnitude images and velocity maps were displayed and flow calculations were performed at rest and during adenosine stress. The vessel border was traced manually on the magnitude image of each frame and copied to the velocity map. Coronary flow velocity (cm/s) was determined for each frame with the maximum value constituting peak flow velocity. The ratio of peak flow velocity during stress to peak flow velocity at rest defined coronary flow velocity reserve (CFVR). Coronary blood flow volume (mL/min) was calculated by summing coronary flow per frame over the cardiac cycle and multiplying by the mean heart rate during the measurement. The ratio of coronary flow volume during stress to coronary flow volume at rest defined coronary flow reserve (CFR).

**First-pass perfusion imaging**
First-pass perfusion images at rest and during stress were analysed semi-quantitatively: endo- and epicardial contours were traced manually and corrected for breathing-related motion. Signal intensity-time curves were constructed in the basal inferior/inferoseptal myocardium. For baseline correction, mean signal intensity before contrast agent application was subtracted from all post-contrast data and myocardial perfusion reserve index (MPRI) was calculated.

**Delayed enhancement imaging**
Delayed enhancement images were visually analysed with regard to the presence or absence of myocardial scar per myocardial segment.

**X-ray coronary angiography**
All patients underwent invasive coronary X-ray angiography in standard Judkins technique within 48 h after the CMR examination. The procedure was done according to angiographic guidelines using a simultaneous biplane, multidirectional, and isocentric X-ray system. Quantitative coronary angiography (Philips Inturis CardioVue, QCA V3.3, Pie Medical Imaging) was performed off-line. Three patient groups were defined by vessel morphology according to the severity of angiographic CAD: (i) all-smooth coronary arteries (‘smooth’), (ii) lumen irregularities but no focal stenosis of 30% or greater of the RCA (‘irregular’), and (iii) significant stenosis (≥50% luminal diameter reduction) of the RCA (‘stenosed’). In order to further refine angiographic CAD grading, patients of Group 2 were additionally subdivided in patients with mere lumen irregularities of RCA and LCA (irregular + LCA < 30%) and patients with lumen irregularities of the RCA only but significant stenosis of the LCA (irregular + LCA ≥ 50%).
Statistical analysis

Statistical analysis was performed using SPSS software package release 17.0.0 (Chicago, IL, USA). All tests were two-tailed; *P < 0.05 was considered statistically significant. Kolmogorov–Smirnov testing ensured the normality of the distributions. Error bars were plotted for the patient groups to visualize 95% confidence intervals of the measured parameters. Differences between groups were determined by One-Way ANOVA in-cluding post-hoc testing for pairwise multiple comparisons (Tukey’s HSD method) or Fisher’s exact test as appropriate. Receiver-operating characteristic (ROC) curves were constructed for CMR-derived WATLA index for the prediction of invasively defined lumen irregularities and significant stenosis, respectively, and the area-under-the-curves were calculated.

Results

Patient characteristics

Two patients had to be excluded from further analysis because of incomplete CMR data acquisition: one patient suffered from severe dyspnoea during adenosine perfusion and failed to perform adequate breath-holding and one patient had improper ECG-gating. The remaining 63 patients completed the CMR examination and invasive X-ray angiography and formed the final study population. Their clinical characteristics are summarized in Table 1.

Table 1  Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>All (n = 63)</th>
<th>All-smooth (n = 19)</th>
<th>Irregular (n = 35)</th>
<th>Stenosed (n = 9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>18/45</td>
<td>7/12</td>
<td>10/25</td>
<td>1/8</td>
<td>0.399</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.5 ± 10.7</td>
<td>56.6 ± 10.0</td>
<td>64.0 ± 9.4</td>
<td>62.0 ± 14.6</td>
<td>0.053</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 ± 3.4</td>
<td>25.0 ± 2.7</td>
<td>27.3 ± 3.1</td>
<td>28.0 ± 4.5</td>
<td>0.026</td>
</tr>
<tr>
<td>Historical information, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (79.4)</td>
<td>12 (63.2)</td>
<td>31 (88.6)</td>
<td>7 (77.8)</td>
<td>0.078</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (7.9)</td>
<td>2 (10.5)</td>
<td>3 (8.6)</td>
<td>0 (0.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hyperlipoproteinaemia</td>
<td>39 (61.9)</td>
<td>5 (26.3)</td>
<td>29 (82.9)</td>
<td>5 (55.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of smoking</td>
<td>19 (30.2)</td>
<td>8 (42.1)</td>
<td>8 (22.9)</td>
<td>3 (33.3)</td>
<td>0.324</td>
</tr>
<tr>
<td>CAD in family</td>
<td>14 (22.2)</td>
<td>4 (21.1)</td>
<td>8 (22.9)</td>
<td>2 (22.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Left-ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58.5 ± 6.9</td>
<td>58.5 ± 5.8</td>
<td>59.7 ± 5.6</td>
<td>54.1 ± 11.2</td>
<td>0.095</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>143.7 ± 50.4</td>
<td>146.4 ± 68.9</td>
<td>140.7 ± 33.3</td>
<td>149.2 ± 64.9</td>
<td>0.872</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>62.8 ± 27.7</td>
<td>65.8 ± 35.2</td>
<td>57.3 ± 18.3</td>
<td>77.7 ± 36.5</td>
<td>0.122</td>
</tr>
</tbody>
</table>

BMI, body mass index; CAD, coronary artery disease; LVEF, left-ventricular ejection fraction; LVEDV, left-ventricular end-diastolic volume; LVESV, left-ventricular end-systolic volume.

Coronary vessel wall imaging

Both, vessel wall thickness and vessel wall area were significantly increased in patients with lumen irregularities when compared with patients with all-smooth coronary arteries (*P < 0.01). However, no further increase of vessel wall thickness or vessel wall area was observed in the presence of a significant RCA stenosis (*P = 0.53 and *P = 0.93, respectively; Figure 4A and Table 2). Lumen area was similar in all patients with a slight increase in patients with lumen irregularities (Table 2). Hence, the WATLA index showed a stepwise significant increase for the comparison of smooth with irregular (*P = 0.002) and with stenosed RCA (*P < 0.001; Figure 4B).

ROC analysis was performed in order to determine the WATLA cut-off value for identifying invasively defined significant RCA stenosis and lumen irregularities, respectively (Figure 5): a cut-off value of WATLA = 3.0 and WATLA = 2.05, respectively, yielded the highest diagnostic values with a sensitivity/speciﬁcity of 77.8/85.2 and 86.4/73.7%, respectively.

Coronary flow imaging

CFR was significantly decreased in coronary arteries with lumen irregularities when compared with all-smooth coronary arteries (*P = 0.008) with a further decrease in significantly stenosed coronary arteries (*P < 0.001; see Table 2 and Figure 6B). In contrast, CFVR was similar in smooth and irregular RCA (*P = 0.31) signiﬁcantly dropping in stenosed RCA only (*P = 0.003; Figure 6B).

T2* imaging

At rest, T2* measurements in basal inferior/inferoseptal myocardium supplied by smooth or irregular RCA resulted in values of ~30 ms
However, myocardium supplied by stenosed RCA exhibited significantly reduced T2* values already at rest \((P = 0.009; \text{Table 2, Figure 6A})\).

Adenosine stress T2* values were highest in myocardium supplied by smooth RCA while being significantly reduced in segments supplied by irregular RCA and further decreasing in the presence of stenosed RCA \((P = 0.009; \text{Table 2, Figure 6A})\).

Adenosine-induced percentage gain of T2* values \((\Delta T2^*)\) was considerably different between groups with all-smooth coronary arteries yielding the highest \(\Delta T2^*\) \((29.2 \pm 10.6\%\) and significantly reduced \(\Delta T2^*\) in patients with irregular RCA \((9.0 \pm 9.8\%)\). In the presence of stenosed RCA, the adenosine-induced gain of myocardial T2* values was close to zero \((2.2 \pm 11.8\%; \text{Figure 6C})\).

### First-pass perfusion imaging

MPRI measurements in basal inferior/inferoseptal myocardium supplied by smooth or irregular RCA resulted in values > 2.0 with only marginally decreased MPRI in patients with irregular RCA \((P = 0.15)\). In contrast, myocardium supplied by stenosed RCA revealed a significantly reduced MPRI \((P < 0.01; \text{Table 2, Figure 6D})\).

### Delayed enhancement imaging

Importantly, none of the patients showed any scar tissue in the reference region of the myocardium being supplied by the RCA. However, delayed enhancement imaging revealed two patients with as yet unknown myocardial scar tissue, both patients showing subendocardial scar with a transmurality \(\leq 50\%\) in the anterior and anteroseptal segments, respectively.

### Subgroup analysis

Patients with irregular RCA were angiographically subclassified in those without and with a significant stenosis of the LCA territory with the latter possibly indicating a more advanced atherosclerotic disease state. In this subgroup analysis, WATLA index significantly increased with advanced disease state \((2.2 \pm 0.4 \text{ vs. } 2.7 \pm 0.6; P = 0.005; \text{Figure 7})\) while CFR and CFVR were slightly—though not significantly—decreased \((3.1 \pm 0.7 \text{ vs. } 2.8 \pm 0.7; P = 0.20 \text{ and } 2.2 \pm 0.5 \text{ vs. } 2.0 \pm 0.6; P = 0.28, \text{respectively})\). Furthermore, T2* values of basal inferior/inferoseptal myocardium were significantly reduced at rest \((30.8 \pm 4.3 \text{ vs. } 28.3 \pm 1.9; P = 0.02)\) and during adenosine stress \((34.7 \pm 5.1 \text{ vs. } 30.3 \pm 2.9; P = 0.003)\) while MPRI did not differ \((2.0 \pm 0.3 \text{ vs. } 2.0 \pm 0.4; P = 0.86)\).

### Discussion

The present study introduced a combined CMR imaging protocol to gain deeper insight into the pathophysiological relationship of atherosclerotic changes of the coronary arterial vessel wall and its consequences on coronary blood flow and microcirculation on the myocardial level. The major findings were as follows: (i) the suggested comprehensive CMR protocol was performed with a high success rate in consecutive cardiac patients; (ii) invasively determined lumen irregularities up to significant luminal narrowing were gradually...
reflected by CMR-derived thickening of the coronary vessel wall; (iii) the CMR-derived WATLA index showed the capability to separate patients with all-smooth coronary arteries from patients with coronary lumen irregularities and with significant coronary stenosis, respectively; (iv) the presence of a significant RCA stenosis led to reduced coronary flow volume and velocity reserve as well as a reduced MPRI and T2* values within the underlying myocardial segment; and (v) in the presence of mere lumen irregularities CFVR and myocardial perfusion reserve were primarily maintained while CFR and the stress-induced gain in T2* values were already diminished.

For the diagnosis of patients with coronary artery disease, CMR imaging offers the unique possibility to combine morphological and functional imaging of the coronary arteries and the myocardium.

Figure 3: CMR and X-ray angiographic imaging exemplifying the subgroup classification of patients with RCA lumen irregularities. Left: 3D CMR vessel wall imaging overview with the inlays depicting the zoomed cross-sectional RCA. Middle: invasive X-ray angiography of the RCA. Right: invasive X-ray angiography of the LCA. (A) Lumen irregularities of RCA and LCA; mean CMR vessel wall thickness was near normal. (B) Lumen irregularities of RCA and significant stenosis of LCA (LAD, white arrow); mean CMR vessel wall thickness was increased. (C) Lumen irregularities of RCA and significant stenosis of LCA (LCx, white arrow); positive outward remodelling of the RCA with significantly increased mean CMR vessel wall thickness.
Coronary luminal narrowing supplying coronary artery. To ensure the one-to-one association of myocardium and the RCA and the underlying basal inferior/inferoseptal myocardial imaging procedure was tightly focused on a reference segment of artery. Atherosclerotic vessel wall alterations, coronary arterial flow, and protocol to further elucidate the pathophysiological relationships of such a model-like CMR protocol in cardiac patients, the microcirculation on the myocardial level. To realize the implementa-

tion of such a model-like CMR protocol in cardiac patients, the present study introduced a comprehensive CMR imaging studies indicated that early stages of atherosclerosis can be prevented or modulated using medical therapy. Consequently, imaging techniques depicting coronary arterial wall remodelling came progressively into focus: non-invasive and radiation-free CMR vessel wall imaging showed great potential for the assessment of coronary arterial wall remodelling preceding the appearance of obstructive coronary disease. Positive arterial remodelling in early atherosclerosis consists of an increase in plaque area accompanied by an increase in total coronary artery cross-sectional area with the result of initially maintaining or even increasing lumen area. Consistent with these histopathological observations, the present study showed that the distinct increase in coronary vessel wall area in patients with lumen irregularities came along with a marginally increased lumen area. These results further corroborated the findings of Miao et al. reporting the capability of CMR vessel wall imaging to reliably depict alterations of coronary lumen and vessel wall thickness in the early stages of atherosclerosis. Calculating the WATLA index within the indicator segment of the RCA allowed for differentiation of patients with all-smooth coronary arteries (WATLA < 2.0) from those with lumen irregularities (WATLA 2.0–3.0) or significant stenosis (WATLA > 3.0). Though positive coronary arterial remodelling can be detected and quantified by CMR imaging, its pathophysiological consequences on coronary blood flow and myocardial microcirculation have not been explored in detail yet.

The current data showed that patients with angiographic lumen irregularities/CMR-derived vessel wall thickening already experienced measurable changes in coronary blood flow and myocardial oxygenation. CMR measurements of coronary arterial flow reserve in patients have been reported to be accurate, reliable, and reproducible and correlated well with invasive flow measurements. In our study, mean CFR in patients with all-smooth RCA was 3.4 ± 0.5 which is in the range of previously reported values. In a study by Hundley et al., CMR measurements of CFR provided high diagnostic accuracy for the identification of coronary stenosis > 70% and in the current study patients with significant RCA stenosis exhibited a

Hence, the present study introduced a comprehensive CMR imaging protocol to further elucidate the pathophysiological relationships of atherosclerotic vessel wall alterations, coronary arterial flow, and microcirculation on the myocardial level. To realize the implementation of such a model-like CMR protocol in cardiac patients, the imaging procedure was tightly focused on a reference segment of the RCA and the underlying basal inferior/inferoseptal myocardial region to ensure the one-to-one association of myocardium and supplying coronary artery.

Current non-invasive imaging mainly aims at the identification of coronary luminal narrowing > 50 or >70%, respectively, which is usually considered clinically relevant CAD. However, prior
**Figure 5:** ROC analysis to determine the cut-off value for WATLA index being predictive of the presence or absence of RCA stenosis (A) or lumen irregularities (B), respectively. Cut-off values of WATLA = 3.0 and WATLA = 2.0 showed the highest discriminatory power, respectively; area indicates area-under-the-curve.

**Figure 6:** Error-bar-charts of CMR-derived myocardial and coronary flow measurements. Mean values and corresponding 95% confidence intervals are provided for the three angiographic RCA classifications. (A) T2* values at rest and during adenosine stress, (B) CFR and CFVR, (C) Stress-induced percentage gain of T2* values (ΔT2*), and (D) MPRI as determined by first-pass perfusion imaging. Differences between groups were statistically significant (ANOVA).
significantly reduced mean CFR (1.7 ± 0.3) either. Notably, patients with mere lumen irregularities demonstrated an already reduced CFR; this observation is likely to result from coronary arterial flow reflecting alterations at both, the epicardial and the microcirculatory level.

$T_2^*$ measurements reflecting the blood oxygenation status of myocardium led to similar findings. In healthy volunteers, pharmacological vasodilation increased myocardial oxygen supply thereby exceeding demand. Consequently, during vasodilator stress, an increased oxygen saturation occurred within the myocardium with a subsequent decrease of deoxyhaemoglobin resulting in a higher signal on corresponding $T_2^*$ images. In case of a significantly stenosed supplying coronary artery, the capillary bed is already dilated at rest and, thus, further vasodilation during pharmacological provocation is limited resulting in an unvarying signal behaviour on $T_2^*$ images at rest and during stress. Hence, the stress-induced $T_2^*$ gain was 29% in myocardium supplied by all-smooth RCA but nearly nullified (2%) in myocardium supplied by a significantly stenosed RCA.

In remote myocardial segments of patients with obstructive CAD, other investigators already reported a reduced stress-provocable $T_2^*$ increase. When comparing luminal irregular with all-smooth RCA patient groups in our study, the dependent myocardium demonstrated a distinctly reduced $T_2^*$ gain (9 vs. 29%). This finding most likely reflected the already abnormal response of the microvasculature and suggested that RCA wall thickening may serve as an indicator of coexisting microvascular dysfunction.

Evaluation of first-pass perfusion imaging resulted in comparable MPRI values in myocardium supplied by all-smooth or luminal irregular RCA, whereas stenosed RCA led to reduced MPRI values. Overall, MPRI results were consistent with previous 3.0 Tesla CMR perfusion study data. Similarly, we found a significantly decreased CFVR in stenosed RCA only as has been previously reported for the identification of coronary lumen narrowing > 50%.

Conceptually, the present study was designed to identify functional parameters of myocardial blood supply being associated with early-to-late atherosclerotic alterations of CMR-characterized RCA vessel wall and the proposed model-like approach ensured the clear association between the supplying coronary artery (RCA) and the dependent myocardium (basal inferior/inferoseptal region). In particular, $T_2^*$ and CFR measurements proved sensitive to classify atherosclerotic disease stages gradually (Figure 7). For the initial purpose of the study, conventional invasive X-ray angiography had been chosen as the ‘classifier’ for CAD disease stages, though the value of the conventional angiogram (‘luminogram’) is inherently

---

**Figure 7:** Error-bar-charts of subgroup analysis according to the angiographic RCA/LCA classification. Mean values and corresponding 95% confidence intervals of myocardial and coronary flow CMR measurements are provided: (A) Stress-induced percentage gain of $T_2^*$ values ($\Delta T_2^*$), (B) MPRI, (C) Ratio of CMR wall area-to-lumen area (WATLA index of RCA), and (D) CFR. Differences between groups were statistically significant (ANOVA).
limited. Our results encourage further studies comparing the findings of intravascular ultrasound or optical coherence tomography with CMR-derived measurements in order to research the association between, e.g. coronary plaque composition and the resultant myocardial response in more detail. Furthermore, such data may help to separate the significance of concomitant epicardial CAD from impaired microvascular reactivity seen in other cardiac disorders like hypertensive, hypertrophic, or valvular heart disease. Perspectivev, combined functional and morphological CMR profiling of coronary atherosclerotic disease states carries the potential to guide medical therapy with regard to optimized cardiovascular risk reduction or to assist in pharmacological research, e.g. when testing cardiovascular drugs aimed at amelioration of microvascular dysfunction.

Study limitations
The current study represents an in vivo human validation of pathophysiological concepts with its investigative, model-like nature inherently implicating some limitations: though our primary goal was to associate CMR-based assessment of coronary remodelling with functional myocardial parameters, the lack of an invasive standard of reference with regard to coronary vessel wall alterations and the accompanying haemodynamical consequences (e.g. intravascular ultrasound and fractional flow reserve measurements, respectively) warrants further validation work. The limited number of patients in different subgroups (in particular those with significant RCA stenosis) did not allow to determine the relative incremental diagnostic value of different functional CMR measurements.

Knowningly, T2* measurements in the inferolateral myocardium may be influenced by susceptibility artefacts arising from the heart–air/lung tissue interface while T2* signal in the septal region is rather robust. Since we targeted the inferior-septal region representing the RCA supply territory, the influence of susceptibility can be considered minor in the present analysis.

Time constraints of an extensive, combined CMR protocol mandated to perform targeted imaging of the RCA supply territory only; in addition, extensive and in-depth functional characterization of one coronary arterial territory was deemed pivotal in order to elucidate the underlying pathophysiological interrelationships. Perspectivev, a triple vessel imaging approach with correlation to the functional status of the entire myocardium can be considered the ultimate goal.

Conclusion
The present patient study introduced a comprehensive single-session CMR imaging protocol for direct visualization of coronary arterial vessel wall remodelling and the assessment of related pathophysiological consequences regarding coronary arterial and myocardial blood flow. Combined CMR profiling of coronary vessel wall alteration and functional impact on dependent myocardium may contribute to further deepen the insights into atherosclerosis and its response to various therapies.

Supplementary data
Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

Conflict of interest: B.S. is an employee of Philips Clinical Science, all other authors reported no potential conflict of interest.

References
A 21-year-old male patient with newly diagnosed acute myeloid leukaemia was referred for cardiomyopathy assessment using cardiovascular magnetic resonance (CMR). The patient had recently undertaken doxorubicin treatment and routine cardiac assessment revealed incidental findings of T-wave inversion on electrocardiogram (Panel A) and an echocardiographic suspicion of left ventricular (LV) thrombus.

Short-axis CMR cine showed borderline normal global and regional LV systolic function (see Supplementary data online, Video S1). Short-axis $T_2^*$-weighted spin-echo images demonstrated areas of subtle signal increase (arrows) in the inferolateral (Panel C) and anterior/anterolateral (Panels D and E) walls with associated late gadolinium enhancement (arrowheads) on post-contrast $T_1$-weighted inversion-recovery images (Panels I–K), suggestive of an ongoing inflammatory process. A short-axis mid-LV septal pre-contrast $T_1$ map was obtained using a modified Look-Locker inversion-recovery sequence. $T_1$ values were increased (measured $T_1$ value: 1057 ms and normal value: <1000 ms), indicative of myocardial involvement. The presence of an apical LV thrombus (curved arrow) was confirmed, as noted on early enhancement short- and long-axis (Panels H and L, respectively) and late enhancement short-axis (Panel K) post-contrast images. Given the clinical context, a chemotherapy-related cardiomyopathy was diagnosed. Doxorubicin was suspended and anticoagulation was initiated.

With the use of robust tools for macroscopic and interstitial myocardial tissue characterization, CMR can detect early changes in subclinical cardiotoxicity and potentially predict overt heart failure. CMR could become a useful screening tool during initial stages of chemotherapy treatment for identifying patients at higher risk of chemotherapy-related cardiomyopathy and provide efficient guidance of patient management.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.