Noninvasive Coronary Vessel Wall and Plaque Imaging With Magnetic Resonance Imaging

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Background—Conventional x-ray angiography frequently underestimates the true burden of atherosclerosis. Although intravascular ultrasound allows for imaging of coronary plaque, this invasive technique is inappropriate for screening or serial examinations. We therefore sought to develop a noninvasive free-breathing MR technique for coronary vessel wall imaging. We hypothesized that such an approach would allow for in vivo imaging of coronary atherosclerosis.

Methods and Results—Ten subjects, including 5 healthy adult volunteers (aged 35±17 years, range 19 to 56 years) and 5 patients (aged 60±4 years, range 56 to 66 years) with x-ray–confirmed coronary artery disease (CAD), were studied with a T2-weighted, dual-inversion, fast spin-echo MR sequence. Multiple adjacent 5-mm cross-sectional images of the proximal right coronary artery were obtained with an in-plane resolution of 0.5×1.0 mm. A right hemidiaphragmatic navigator was used to facilitate free-breathing MR acquisition. Coronary vessel wall images were readily acquired in all subjects. Both coronary vessel wall thickness (1.5±0.2 versus 1.0±0.2 mm) and wall area (21.2±3.1 versus 13.7±4.2 mm²) were greater in patients with CAD (both \( P<0.02 \) versus healthy adults).

Conclusions—In vivo free-breathing coronary vessel wall and plaque imaging with MR has been successfully implemented in humans. Coronary wall thickness and wall area were significantly greater in patients with angiographic CAD. The presented technique may have potential applications in patients with known or suspected atherosclerotic CAD or for serial evaluation after pharmacological intervention. (Circulation. 2000;102:2582-2587.)

Key Words: vessels ■ plaque ■ magnetic resonance imaging ■ atherosclerosis

Conventional coronary angiography frequently underestimates the true burden of atherosclerosis. As reported by Glagov et al,¹ the initial response to endothelial injury and development of atherosclerosis is vessel enlargement, with relative preservation of lumen diameter. Subsequent plaque progression, with lumen-encroachment stenoses, is a later event. Invasive x-ray coronary angiography and bright-blood¹³ coronary magnetic resonance angiography (MRA) only allow for assessment of luminal vessel diameter and do not provide direct information regarding coronary vessel wall thickness or atherosclerotic plaque. Recent intravascular ultrasound (IVUS) studies¹⁴,¹⁵ have shown that lesion-site cross-sectional area, minimum lesion diameter, cross-sectional narrowing, and area stenosis are good predictors for subsequent acute cardiac events. However, this invasive technique is not appropriate for screening or serial examinations. Apart from plaque burden and luminal encroachment, plaque composition is a predictor of plaque vulnerability. Lipid-rich plaques with thin fibrous caps are often associated with acute coronary events, not only because of their greater vulnerability to rupture, but also because of enhanced thrombogenicity after rupture.⁶ A noninvasive technique that would allow for visualization of plaque area and luminal vessel area narrowing and that also allowed for characterization of the plaque constituents would therefore be of great interest.

Noninvasive MR coronary vessel wall and plaque imaging is particularly challenging owing to cardiac and respiratory motion, small coronary vessel wall thickness, and low contrast-to-noise ratios (CNRs) between the coronary vessel wall and the surrounding epicardial fat, coronary blood, and myocardium. Because bulk cardiac motion during the respiratory cycle may exceed a multiple of the coronary wall thickness, accurate respiratory motion compensation is critical for coronary vessel wall imaging and has been successfully applied for bright-blood coronary MRA.⁷ Because of intrinsic bulk cardiac motion, coronary artery imaging is best achieved during end systole or mid diastole, a short time period (<100 ms) of relative myocardial diastases.⁸⁹ T2-weighted black-blood fast spin-echo (TSE) techniques have been successfully applied for aortic⁹⁰ and carotid⁹¹ vessel wall imaging. However, signal from slow-flowing blood in the laminar boundary layer adjacent to the vessel wall may mimic vessel wall signal and cause an overestimation of wall thickness/area. This situation can be minimized by the use of...
a double-inversion prepulse (dual IR), which depends on blood exchange instead of spin dephasing. Because of the long T1 of blood and the need to image close to the zero crossing of its longitudinal magnetization, the resultant inversion delay only allows for diastolic image acquisition.

Recently, preliminary results of coronary MR plaque imaging with breathhold (BH) approaches have been reported.12-15 BH strategies, however, are often difficult to implement in patients, especially those with coronary artery or pulmonary disease. We sought to develop a noninvasive, free-breathing coronary vessel wall imaging approach using a dual IR TSE sequence and to compare coronary vessel wall and lumen area in healthy and diseased subjects. In this article, we discuss the given boundary conditions, present possible solutions, and show first in vivo results. We hypothesize that this technique might also have potential for noninvasive in vivo imaging of coronary plaque.

Methods

Subjects
Ten subjects, including 5 healthy adult subjects (aged 35±17 years, range 19 to 56 years) without history of coronary artery disease (CAD) and 5 patients (60±4 years, range 56 to 66 years) with x-ray–confirmed CAD, were examined in the supine position with a 5-element cardiac synergy coil for signal reception. For cardiac synchronization, 3 electrodes were placed on the left anterior hemithorax, and scans were triggered on the R wave of the ECG. All examinations were done during uncoached free breathing by use of a Philips Gyroscan NT MR system (Philips Medical Systems) equipped with PowerTrak 6000 gradients and an advanced cardiac software patch (CPR6). Written informed consent was obtained from all participants.

Imaging Sequence

Localization of the RCA
A rapid, ECG-triggered multislice, multistack, segmented gradient echo scan allowed for localization of the heart in 3 (transverse, coronal, and sagittal) orthogonal planes (TR=8 ms, TE=2 ms, shots=2, flip angle=30°, slice thickness=3 mm, field of view=180×180 mm, matrix=256×64). For subsequent planning of cross-sectional views of the right coronary artery (RCA) a fast, navigator-gated16 and -corrected17,18 transverse 3D turbo field echo (TFE)/echo planar imaging (EPI) scan19 that allowed for identification of the RCA was planned on a coronal view of the first scout scan. The navigator was placed on the dome of the right hemidiaphragm, and all subsequent scanning was performed with a 5-mm gating window and a constant superior-inferior correction factor (0.6).20 A 3-point plan-scan tool19 was used to prescribe an imaging plane along the major axis of the RCA. This plane was used in a subsequent 3D TFE/EPI scout scan21 of the RCA (Figure 1) that allowed for display of the RCA in-plane. Navigator parameters were maintained for all subsequent imaging sequences.

Coronary Vessel Wall Imaging

With a coronary scout scan that depicted the proximal RCA (Figure 1), a free-breathing 2D dual IR TSE scan was planned orthogonal to the proximal RCA. This imaging sequence can be divided into 4 sequence blocks (Figure 2).

Dual IR
Immediately after detection of the R wave of the ECG, a dual IR prepulse22,23 was applied. This consisted of a nonselective, followed by a slice-selective, 180° radiofrequency pulse. Slice thickness (12.5 mm) of the labeled slice was 2.5 times the thickness of the imaged slice. The TR-dependent inversion delay with respect to the TSE imaging sequence was given by the zero crossing time24 of the longitudinal magnetization of blood and allowed for middiastolic image acquisition, a time period of relative cardiac diastasis.6,9

MR Navigator
Shortly before the 2D TSE image acquisition block, a 2D selective real-time navigator was applied for respiratory gating and real-time slice-position correction.17,18 Total navigator duration for excitation and real-time correction was 35 ms.

TSE Image Acquisition
To suppress signal from epicardial fat, a frequency-selective small-bandwidth radiofrequency pulse (15 ms) was applied immediately

Figure 1. Double-oblique MR view of RCA (scout No. 3) that allowed planning the subsequent coronary vessel wall scan perpendicular to RCA. Image was acquired with navigator-gated and -corrected 3D TFE-EPI technique.21 RV indicates right ventricle; LV, left ventricle; Ao, aorta; and PA, pulmonary artery.

Figure 2. Schematic of navigator-gated and -corrected dual IR 2D TSE sequence. Dual IR prepulse, consisting of a nonselective followed by a slice-selective 180° radiofrequency pulse, is applied immediately after detection of R wave. 2D selective navigator for gating and slice-position correction precedes frequency-selective fat suppression prepulse (FAT SAT) and middiastolic 2D TSE imaging sequence. Inversion delay is adjusted to null magnetization of blood at time of 90° radiofrequency pulse of TSE imaging sequence.
before the imaging portion of the sequence. Middiastolic imaging was performed with a 2D T2-weighted TSE sequence with a linear profile order, echo train length of 7 to 9, echo spacing (ESP) of ~5.7 ms, and 5-mm slice thickness. The effective echo time (eTE) was set to 25 ms to maximize signal from the vessel wall (Appendix). The resulting acquisition window was 50 ms. A repetition time (TR) of 2 heartbeats and 4 signal averages were used. With a field of view of 260×208 mm and an image matrix of 512×204, in-plane spatial resolution was 0.5×1.0 mm. Phase-encoding direction was parallel to the chest wall to minimize respiratory motion artifacts.

SNR and CNR Measurements
We determined signal-to-noise ratio (SNR) of the RCA wall by manually segmenting the wall area and calculating the mean signal (S). Noise (N) was determined within a region of interest drawn in front of the chest wall. CNR \((S_{wall} - S_{I})/N\) was measured between vessel wall and epicardial fat \((S_{fat})\) and coronary blood \((S_{blood})\). The index I stands for fat and coronary blood, respectively.

Lumen and Vessel Wall Area Measurements
To minimize angulation errors due to the initial curvature of the RCA, we imaged ~2 to 3 cm distal to the origin in a relatively linear portion of the RCA. In patients with CAD, vessel wall scans were preferably performed proximal, within, and distal to the stenosis/occlusion. On magnified cross-sectional images of the RCA, the inner lumen and outer vessel borders were then manually segmented to determine lumen (inner area) and wall area (vessel area minus lumen). Average lumen diameter and wall thickness was calculated assuming a circular vessel shape.

\[ \text{Lumen diameter} = 2 \cdot \frac{\text{lumen area}}{\pi} \]

Wall thickness = \(\sqrt{\frac{\text{vessel area} - \text{lumen area}}{\pi}}\)

Statistics
Data analysis was performed by 2 blinded observers (W.Y.K., E.S.), and data are expressed as mean±SD. Continuous variables were compared with a 2-tailed unpaired Student’s t test, with significance as \(P<0.05\).

Results
The total examination time was ~20 minutes, with an average scanning time for each 2D slice of ~4.5 (90 bpm) to 6.8 (60 bpm) minutes (with navigator efficiency of 50%). In all subjects, the RCA wall was successfully visualized with definition from surrounding epicardial fat and coronary blood (Figure 3) with suppression of blood signal using the dual IR prepulse and middiastolic image acquisition. No artifacts from in-plane blood flow in the ventricles were observed.

Vessel Wall Thickness
Among healthy subjects, wall thickness (including adventitia) was 1.0±0.2 mm, with lumen diameter of 3.4±0.4 mm, wall area of 13.7±4.2 mm², and lumen area of 9.3±1.9 mm². Mean vessel wall thickness was higher in CAD patients (1.5±0.2 mm; \(P<0.004\) versus healthy subjects). Similarly, mean wall area was also increased (21.2±3.1 mm², \(P<0.02\)). There was also a trend toward a reduced lumen area in patients with CAD (7.0±2.3 versus 9.3±1.9 mm; \(P<0.14\)). All vessel wall and lumen measurements were done in the proximal RCA (30±7 mm, range 22 to 36 mm versus 29±4 mm, range 24 to 33 mm in patients with CAD; \(P=NS\)) and always proximal to the stenosis in patients with CAD.

Discussion
In this study, we demonstrate the ability to obtain in vivo free-breathing coronary MR vessel wall and plaque images in humans. Such an advance offers the potential opportunity to identify coronary atherosclerosis before the development of flow-limiting luminal stenoses.

Coronary Wall Images
MR estimates of coronary lumen diameter and lumen area compare favorably with historical IVUS data, but MR values...
overestimate historical IVUS coronary wall thickness and wall area. The MR overestimation may be explained by the lower in-plane (500×1000 versus 100×100 μm) and through-plane spatial resolution (5 versus 0.15 mm) compared with IVUS. This would lead to partial volume effects resulting in an overestimation of the true vessel wall area and thickness. Furthermore, residual respiratory or cardiac motion may cause image blurring, thereby leading to an overestimation of the true vessel wall area. Incomplete flow exchange of slow-flowing blood might mimic signal from the vessel wall, thereby causing an additional overestimation of the true vessel wall thickness, but this effect is expected to be small, because the dual IR prepulse was optimized for minimization of blood signal. Compared with MRI, IVUS vessel wall measurements do not include the adventitia, which might also contribute to the larger coronary vessel wall areas as measured by MRI.

Coronary wall thickness and wall area were significantly greater in patients with CAD than in healthy adult subjects. There was also a trend toward a reduced lumen area in patients with CAD. Although we suspect the wall thickening is due to atherosclerosis, we cannot fully exclude the impact of the age difference between the 2 groups. The positive correlation between x-ray–confirmed CAD and MR-based measurements of coronary wall thickness suggests that MR coronary vessel wall imaging is able to assess coronary vessel wall thickening in vivo. Additionally, MR vessel wall imaging allowed assessment of x-ray–confirmed occlusive CAD. The bright signal at the location of the suspected stenosis may be the result of slow-flowing blood or may be from a lumen-narrowing plaque and/or a plaque overlaid by a thrombus.

Signal-to-Noise Values
The relatively high SNR values of the MR RCA wall data demonstrate that there is a potential to further increase spatial resolution. 3D approaches might be another alternative to facilitate higher spatial resolution, but this remains to be explored. CNR measurements between the RCA wall and epicardial fat and coronary blood demonstrate the good...
delineation of the RCA wall from the surrounding tissues, primarily epicardial fat. Average signal of ventricular blood was similar to the noise level, demonstrating the desired impact of the dual IR prepulse.

**Dual IR Prepulse**
The use of a dual IR for black-blood imaging in the heart seems to be crucial to minimize signal from slow-flowing blood and artifacts from incomplete spin dephasing, as are often seen in conventional TSE techniques. However, longer echo times, which would increase spin dephasing and eventually lead to a complete nulling of the blood signal, are not suited for coronary vessel wall imaging because (1) measurements with long acquisition window durations (>100 ms) are prone to artifacts due to cardiac motion and (2) the optimal TE for wall imaging is 25 ms (Appendix). Additionally, incomplete spin dephasing due to slow-flowing blood in the boundary layer may mimic signal that is similar to the vessel wall, thus leading to an overestimation of the coronary wall thickness. Compared with a conventional TSE technique, black-blood properties of the dual IR prepulse only rely on blood exchange, which is expected to be sufficient within the relatively long inversion time period of ≈500 to 600 ms.

**Navigator**
The use of a 2D selective navigator for respiratory motion compensation allows removal of the constraints of a BH and thereby enables free-breathing coronary vessel wall imaging. Compared with BH techniques that rely on rapid image acquisition, navigator techniques allow for a broader range of echo trains and TE, thus providing greater flexibility in choosing the optimal contrast between vessel wall, lipsids, and epicardial fat. This flexibility can be used to optimize contrast for best vessel delineation or best differentiation between the different plaque constituents. The good delineation of the RCA wall (Figure 3), a structure of <1 mm, also demonstrates that navigator gating and real-time tracking in concert with a dual IR prepulse are effective. Because labeling with the dual IR prepulse is performed during end diastole and imaging is performed during mid diastole, matching of the labeled and imaged slice is not trivial. It can, however, be facilitated by increasing the slice thickness of the labeled slice to a multiple (2.5) of the thickness of the imaged slice.

**Cardiac Motion and Acquisition Window**
In addition to bulk motion related to respiration, bulk cardiac motion during the cardiac cycle adds another boundary condition to coronary vessel wall measurements. Imaging during mid diastole minimizes motion-related artifacts. As previously reported by our group,9 reduction of the acquisition window from 120 to 60 ms significantly improves the quality of coronary MRA. Based on this knowledge, we chose a relatively short acquisition window of 50 ms. With this acquisition window duration and a linear k-space acquisition scheme, an echo time of 25 ms was chosen according to our simulations as the optimal effective echo time (TE=T2/2) for maximal SNR of smooth muscle and maximal CNR between smooth muscle and epicardial fat (Appendix). As a beneficial side effect of the short acquisition window, the point-spread function could be kept small,26 which is essential for high-resolution vessel wall measurements. Compared with bright-blood techniques, TSE techniques have the advantage that they are relatively insensitive to complex or turbulent flow, thus allowing for artifact-free visualization even of diseased stenotic vessels.27 Furthermore, these techniques are especially well suited for the visualization of smaller vessels such as the coronary arteries, because the artifact level decreases with smaller vessel size.27

**Conclusions**
In vivo free-breathing coronary vessel wall and plaque imaging with MR has been successfully implemented in humans. Coronary wall thickness and wall area were significantly higher in patients with angiographic CAD, which suggests that MR vessel wall imaging can visualize atherosclerotic plaque in vivo. The presented technique might have potential applications in patients with known or suspected atherosclerotic CAD or for serial evaluation after pharmacological intervention.

**Appendix**
In a fast spin-echo sequence (TSE), the signal of a uniform voxel decays exponentially with the T2 relaxation time during the course of
the echo train and is directly proportional to the number of signal averages. Compared with a conventional spin-echo sequence, the echo time (TE) has to be modified by the eTE, which depends on the k-space acquisition scheme.\textsuperscript{26}

\begin{equation}
\text{SNR} \propto (1 - e^{-T_{\text{TE}}/T_1}) \cdot e^{-e\text{TE}/T_2} \cdot \text{NSA}
\end{equation}

Between subsequent shots, the signal recovers exponentially with the time constant (T1) and the repetition time (TRR; RR interval). Noise (N) is dependent on the receiver bandwidth (BW), the number of signal averages (NSA), the number of samples in readout direction, and the total number of phase-encoding steps N_x and N_z.

\begin{equation}
N_x \propto \frac{\text{BW} \cdot \text{NSA}}{N_y} \cdot N_z
\end{equation}

For a given echo train length, a given NSA, a constant repetition time (T_{\text{TR}}), and N_x/N_z phase-encoding steps, SNR is primarily dependent on eTE and ESP. The ESP is directly proportional to the number of samples (N_z) in readout direction and inversely proportional to the BW.

\begin{equation}
\text{SNR} \propto (1 - e^{-T_{\text{TE}}/T_1}) \cdot e^{-e\text{TE}/T_2} \cdot \sqrt{\text{NSA} \cdot N_y \cdot N_z \cdot \text{ESP}}
\end{equation}

with

\begin{equation}
\text{BW} \cdot \text{ESP} = \frac{\text{N}_x}{\text{TE}} \cdot \text{ETL} = \frac{\text{ETL}}{2} \cdot \text{ESP}
\end{equation}

For a linear k-space acquisition, the eTE can be written according to Equation 6. Optimization of SNR with respect to ESP yields an eTE that only depends on T2.

\begin{equation}
\max(\text{SNR}); \quad e\text{TE} = \frac{T_2}{2}
\end{equation}

Because the media consists primarily of smooth muscle cells (T1 = 600 ms,\textsuperscript{27} T2 = 50 ms\textsuperscript{11}), SNR was optimized with respect to eTE (Equation 6) and resulted in an eTE of 25 ms. The optimal contrast \([S1 - S2]/N\) between smooth muscle and epicardial fat (T1 = 270 ms, T2 = 100 ms) and smooth muscle and lipids (T1 = 500 ms, T2 = 30 ms\textsuperscript{13}) was determined numerically by plotting CNR with respect to eTE. Optimal contrast was found at an eTE of \(\approx 25\) ms for epicardial fat and 60 ms for lipids.

Additionally, the influence of T_{\text{TR}} on SNR was examined. There was a 21% gain in SNR between a T_{\text{TR}} of 1 and 2, but the gain of 4% between a T_{\text{TR}} of 2 and 3 heartbeats seems to be relatively small compared with the increase in measurement time.

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