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Precision and Accuracy of Cross-Sectional Area Measurements Used to Measure Coronary Endothelial Function with Spiral MRI

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Abstract

Purpose—Coronary endothelial function (CEF) reflects vascular health and conventional invasive CEF measures predict cardiovascular events. MRI can now noninvasively measure CEF by quantifying coronary artery cross-sectional area changes in response to isometric handgrip exercise, an endothelial-dependent stressor. Area changes (10 to 20% in healthy; 2 to –12% in impaired vessels) are only a few imaging voxels because of MRI's limited spatial resolution. Here, with numerical simulations and phantom studies, we test whether Fourier interpolation enables sub-pixel area measurement precision and determine the smallest detectable area change using spiral MRI.

Methods—In vivo coronary signal-to-noise ratio (SNR) with the currently used CEF protocol at 3T was measured in 7 subjects for subsequent in vitro work. Area measurements of circular vessels were simulated by varying partial volume, vessel diameter, voxel size, SNR, and Fourier interpolation factor. A phantom with precision-drilled holes (diameters 3–3.42mm) was imaged 10 times with the current CEF protocol (voxel size, $\Delta x=0.89\text{mm}$) and a high-resolution protocol ($\Delta x=0.6\text{mm}$) to determine precision, accuracy, and the smallest detectable area changes.

Results—In vivo coronary SNR ranged from 30 to 76. 8-fold Fourier interpolation improved area measurement precision by a factor 6.5 and 4.9 in the simulations and phantom scans, respectively.

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SUPPORTING INFORMATION

The results of the statistical analyses are reported in the online supporting information.

Supporting Information Figure S1: A) shows a large and a small circle resampled to a 32×32 matrix. B) shows the image in A) after 8-fold zero-filling (ZF), where the additional interpolated pixels reveal Gibbs ringing artifacts with locally increased signal intensities. The area measurements of the phantom scans acquired with the in-plane spatial resolution of the current standard MRI-CEF protocol ($\Delta x=0.89\text{mm}$) were repeated and the maximum signal of each vessel, S_{max} , as used in the FWHM algorithm was stored for ZF factors 1, 2, 4, and 8. The average change in S_{max} for ZF factors 2, 4 and 8 relative to no zero-filling (ZF 1) is shown in C), where S_{max} is increased by about 3%. In D) on the left, zero-filling leads to area underestimation (same as Figure 7B). Compared to the area of a 3mm-diameter vessel, the additional ZF-induced underestimation is 2.4%. In D) on the right, accuracy is not further reduced after zero-filling if FWHM segmentation is performed using the S_{max} determined from the image without zero-filling (ZF 1), confirming that the increased maximal signal intensity leads to the ZF-induced accuracy reduction.

The current CEF protocol can detect mean area changes of 4%-5% for SNR above 30, and 3%-3.5% for SNR above 40 with a higher-resolution protocol.

Conclusion—Current CEF spiral MRI with in vivo SNR allows detection of a 4%-5% area change and Fourier interpolation improves precision several-fold to sub-voxel dimensions.

Keywords

Coronary endothelial function; vasodilation; MRI; spiral; Fourier interpolation; cross-sectional area measurement

INTRODUCTION

The endothelium forms an interface between circulating blood elements in the vessel lumen and the vessel wall. Endothelial cells lining healthy coronary arteries normally secrete vasoactive, anti-thrombotic and anti-inflammatory molecules like nitric oxide (NO) and healthy arteries respond to endothelial-dependent stressors with vasodilation and increased blood flow (1). Impaired endothelial NO release, or endothelial dysfunction, is a marker for sub-clinical disease, an independent predictor of adverse cardiac events, and a potential target for medical interventions (2–7). Historically, coronary endothelial function (CEF) was measured with invasive cardiac catheterization where the magnitude of changes in arterial diameter in response to endothelial-dependent vasomotor interventions were assessed (2,8). Recently, spiral cine MRI was proposed to noninvasively measure CEF (9) wherein coronary cross-sectional areas are measured at baseline and during the endothelial dependent stressor, isometric handgrip exercise (10–12), and the exercise induced cross-sectional area change is a measure of CEF. The MRI-detected coronary artery responses to isometric handgrip exercise are NO-dependent, reproducible, and impaired in coronary artery disease (9,12,13).

The isometric handgrip exercise induced area change measured with MRI ranges from 10 to 20% in healthy coronary arteries, and exhibits reduced dilation or even a paradoxical constriction from 2 to –12% in impaired vessels (9,12–17). However, the cross-sectional area change is on the order of only a few imaging voxels because MRI's sensitivity and time constraints lead to a limited spatial resolution. The standard spiral cine MRI protocol used in those prior studies had an acquired in-plane voxel size of 0.89 mm, leading to a voxel area of 0.79 mm², which is 11% of the area of a 3-mm diameter vessel.

When studying atherosclerotic disease progression or testing whether medical or lifestyle interventions improve CEF, it is useful to know how small an area change can be detected with this new method. Recently, phantom studies showed that radial MRI is capable of distinguishing area changes of 3 to 4% on images with high (~50) signal-to-noise ratio (SNR), and area changes of 6 to 8% on images with low (~25-30) SNR for a 3-mm vessel. The same study showed that the dependence of the smallest detectable area change on the voxel size was negligible when keeping the acquisition time identical (18). This latter finding was not anticipated. Further, because Fourier interpolation (zero filling) is routinely used in MRI, and MR angiography specifically, to display images at higher than acquired resolutions (19,20), we hypothesize here that Fourier interpolation enables sub-pixel area measurement precision. Jiang et al. have shown in simulations that zero filling improves

vessel area measurement accuracy and precision, and predict a precision of less than 2% when at least 4 voxels are acquired across the diameter of a vessel (21). However, those simulations only varied the noise in the image but did not change the vessel location relative to the imaging grid, and hence the partial volume error remained the same for all simulations. Therefore, in this study, we performed numerical simulations to probe the impact of Fourier interpolation on area measurement precision including all possible partial volume contributions for the first time, and to understand the relative importance of image interpolation, acquisition voxel size, and SNR.

Additionally, because most MRI CEF studies to date have been performed with spiral (9,12–17) rather than radial MRI, the second goal of this work was to determine the precision and accuracy of coronary cross-sectional area measurements, and the smallest detectable area change using spiral MRI with the identical phantom as was used in (18).

Methods

In vivo SNR

To determine the SNR from in vivo data acquired with the current standard MRI-CEF protocol (9), the SNR at the level of the left anterior descending (LAD) and the right coronary artery (RCA) was measured in previously acquired 3T datasets (5 each). Datasets with minimal motion between two diastolic frames were selected from prior studies. Those human studies were approved by the Johns Hopkins School of Medicine Institutional Review Board and written consent was obtained from all 7 subjects. The images were acquired on a 3T clinical scanner (Achieva, Philips Healthcare, Best, the Netherlands) with a 32-channel cardiac phased array, and the data from the different coils were combined based on a sensitivity map to achieve uniform signal sensitivity leading to spatially varying noise, i.e. elevated noise in the center of the body at locations further away from the coil elements (22). Therefore, to determine SNR both noise and signal levels have to be measured at the level of the coronary arteries. To achieve this, the subtraction method described in the National Electrical Manufacturers Association standards was applied (23). In the subtraction method, signal and noise levels are determined from two images acquired with identical settings by either averaging or subtracting the two images, respectively. For cardiac cine imaging this requires two cardiac frames with minimal motion between them. Figure 1 shows an example of the RCA with two cardiac phases with minimal motion during mid-diastole and the resulting noise image after subtraction. The signal of the coronary artery, S_c , was determined by adding the absolute values of the two cardiac phases, dividing them by 2, and averaging the signal values of the voxels within the full width at half maximum (FWHM) segmentation of the coronary artery. The noise at the level of the coronary artery, N_c , was determined by the standard deviation of the real part of voxels in a 10×10 (of the original acquired matrix size) region of interest surrounding the artery after subtracting the complex data of the two cardiac phases, and dividing the standard deviation by the square root of 2. SNR was then calculated as S_c/N_c .

Numerical Simulations

The potential challenge of measuring the cross-sectional area of coronary arteries with limited spatial resolution is depicted in Figures 2A-C. When measuring the area of a theoretical vessel shown in Figure 2A using a FWHM algorithm in images acquired with a voxel size that is only a few times smaller than the diameter of that vessel, the resulting area depends on the voxel grid location relative to the vessel due to partial volume effects. Figures 2B and C show two extreme cases where the same vessel imaged with the same voxel size but shifted grid may result in an area of either 9 or 12 voxels, respectively, a difference of 33%. To study the effects of partial volume, area measurements were performed on simulated images for a full range of imaging grid locations. In addition to partial volume, vessel size, acquisition voxel size, Fourier interpolation factor, and SNR were also varied to better understand the relative importance of each.

Vessel area measurements were numerically simulated in MATLAB (Mathworks, Natick, MA). Digital high-resolution, circular phantoms with known areas were created with a resolution of 1 μm (Figure 2D). 26 vessel diameters from 2.5 to 5 mm in steps of 0.1 mm were simulated. Those simulated vessels were resampled in the image domain with imaging grids at acquired voxel sizes Δx from 0.4 to 1 mm in steps of 0.1 mm with the exception of 0.89 mm instead of 0.9 mm because this is the resolution of the current standard CEF-MRI protocol. For each of those combinations the imaging grid was shifted to 528 different locations to simulate a full range of partial volume effects. Those 528 grid locations were homogeneously distributed within a right isosceles triangle with 32 grid locations placed along each of the two equal sides. The equal sides of the triangle were half the length of the voxel size Δx , and one corner of the triangle coincided with the center of the vessel as shown in Figure 2E assuring all possible partial volume scenarios.

Each of those images sampled at the acquisition resolution were then Fourier interpolated and noise was added to achieve a range of SNR as shown in Figure 2F. For image interpolation, the acquired images were inverse Fourier transformed to k-space and zero-filled by factors 1, 2, 4, and 8, where factor 1 means no zeroes were added. Additionally, two filters were applied in k-space before transforming back to image domain via Fourier transform: First, to replicate the vendor reconstruction pipeline, a ringing filter was added to smooth the outer 20% of k-space with a Hanning window. Second, because signal decay during long spiral readouts leads to image blurring, T_2^* -decay along the 13 ms spiral readout was added based on the $T_2^* = 57$ ms of arterial blood (24). Back in the image domain, Rician noise was added to attain SNR ranging from 10 to 150 (10, 20, 30, 40, 50, 60, 80, 100, 150), where SNR was calculated from the mean simulated signal in the vessel divided by the standard deviation of the added noise, and multiplied by 0.655 to correct for the Rician noise distribution in magnitude images (25).

Overall more than 3.4 million images were created and the vessel area was determined in each of them with FWHM segmentation. The FWHM segmentation included all voxels with signal intensity greater or equal to half of the difference between the maximum signal within the vessel and the minimum signal in the entire image. The vessel area was then calculated by the multiplication of the number of voxels in the FWHM segmentation and the area of the interpolated voxel.

Simulated vessel area measurement precision was determined with the standard deviation over the 528 grid locations, and accuracy by the mean of the difference from the true value.

Phantom Measurements

In a last step, the simulations were validated with phantom measurements applying the in-plane spatial resolution of the current standard MRI-CEF protocol ($\Delta x = 0.89$ mm) and that of an additional protocol with improved spatial resolution $\Delta x = 0.6$ mm. The identical phantom as used in reference (18) with precision-drilled holes was placed in a container filled with gadolinium-doped (Gadavist, Bayer HealthCare Pharmaceuticals Inc.) water ($T_1 \sim 200$ ms). The holes in the phantom had 22 different diameters (3 to 3.42 mm in steps of 0.02 mm) and each size was repeated 5 times. The size of the drilled holes was previously validated with a touch trigger probe (Werth VideoCheck HA, Werth Messtechnik GmbH, Gießen, Germany) and yielded a standard deviation of 0.033 mm^2 and a nonsignificant bias of 0.005 mm^2 (18).

Spiral cine MRI with the two protocols were acquired orthogonal to the drilled holes. Both protocols were repeated 10 times, each acquisition rotated in plane by an additional 1° , maintaining orthogonality to the holes, to ensure different partial volume effects in each acquisition leading to 50 measurements for each hole size. The acquisition parameters were field of view = 220 mm, voxel size $\Delta x = 0.89$ mm, 20 spiral interleaves, 13 ms spiral readout duration, pulse repetition time (TR)/echo time (TE) of 18.3 ms/2.1 ms, 18s breath-hold for a simulated heart-rate of 70 beats per minute for the standard protocol, and $\Delta x = 0.6$ mm, 26 spiral interleaves, 18 ms readout, TR/TE = 23.8 ms/2.1 ms, 23 s breath-hold for the high-resolution protocol. Localized shimming of both the static and radio-frequency fields were performed based on acquired field maps (26,27).

Post-processing including coil phase removal, off-resonance deblurring, Fourier interpolation, FWHM segmentation, and SNR measurements were implemented in the graphical programming interface (GPI) (28): First, slowly varying phase was removed by multiplying the images with the normalized conjugate of a low resolution version of them, created with a 20%-Hanning window in k-space. Because in vivo measurements are performed on three diastolic frames with minimal coronary motion and averaged (9), three cardiac phases were similarly analyzed here; phases 28-30 of 42 and 18-20 of 32 for the standard and high-resolution protocols, respectively. The 110 holes were identified semi-automatically based on the user clicking on three holes in corners of the phantom. Off-resonance blurring was corrected automatically at the location of each hole separately based on the method proposed by Noll et al (29). The complex images were blurred based on the applied spiral readout trajectory to 33 different frequencies from -80 to 80 Hz. For each hole, the frequency minimizing the sum of the square root of the imaginary part of the voxels in a 4 mm radius was chosen to deblur the image. The deblurred images were zero filled by factors 1, 2, 4, and 8. Areas were determined based on FWHM segmentation as described in the *numerical simulations* section above, and the areas of the 3 cardiac phases were averaged. The center of mass voxel of the FWHM segmentation was used as a starting point for the SNR analysis. SNR was determined with the method described in the *in vivo*

SNR section above using the first two and the second two of the three cardiac phases used in the area analysis.

All of those post-processing steps were repeated for different SNR levels. Noise was added to generate data with lower SNR. To ensure the noise had the same spatial behavior, data from later cardiac phases were subtracted to create noise maps. Those noise maps were scaled and combined to ensure that each analyzed dataset had a different noise distribution.

To determine the smallest cross-sectional area change that is detectable, a statistical test based on the area under the curve (AUC) of the receiver operating characteristic curve (ROC) was used as proposed in (18). A nonparametric ROC curve was computed from the measured areas of two different diameters. The corresponding area under the ROC curve was computed for each combination of diameters. The change in cross-sectional area between the two diameters was considered statistically detectable if the AUC ≥ 0.95 . The smallest area difference that consistently passed this test was determined for every diameter. The smallest detectable area change, or limit of detection (LOD), was then defined as the mean of these smallest detectable area changes (18). The standard deviation of the smallest detectable area changes was also computed to quantify the variability.

Statistical Analysis

Statistical analyses were performed in Prism (version 7, GraphPad Software, Inc., La Jolla, CA) with $\alpha=0.05$ as the significant threshold. Area measurement precision and accuracy, and LOD data were paired for either the simulated or phantom vessel size. Data for the different vessel sizes were first tested for normality with the D'Agostino & Pearson normality test. If more than 75% of the datasets were normally distributed, they were further analyzed with a repeated measures one-way analysis of variance (ANOVA) and a follow-up Tukey multiple comparison test with Greenhouse-Geisser correction, otherwise, a non-parametric Friedman test was performed, followed up by Dunn's multiple comparison test. First, the simulated precision and accuracy results were tested among zero filling factors and acquisition voxel sizes for the highest SNR (150). Second, simulated precision and accuracy were tested among different SNR values and acquisition voxel sizes for the highest zero filling factor 8. And third, precision, accuracy, or LOD based on the phantom images were tested among zero filling factors and the two protocols for the highest SNR, and then among different SNR values and the two acquisition protocols for zero filling factor of 8. The statistical analyses are reported in the online supporting information.

RESULTS

In vivo SNR

To guide SNR used in simulations and phantom studies, we measured in vivo coronary SNR with the current standard MRI-CEF protocol in 7 subjects (3 women, 41 ± 13 years, 24 ± 3 kg/m² BMI) and found it to be 53 ± 19 (mean $\pm$ standard deviation). The SNR at the level of the RCA and LAD were 70 ± 6 ($n = 5$, ranging from 62 - 76) and 35 ± 8 ($n = 5$, 30 - 50), respectively.

Numerical Simulations - Effects of Partial Volume and Fourier Interpolation

Figure 2F shows examples of simulated vessel images with different zero-filling factors and added noise. To illustrate the effects of partial volume and image interpolation on vessel area measurements, Figure 3 shows simulated area measurements of a single 3-mm diameter vessel resampled with an acquisition voxel size of $\Delta x = 0.89$ mm for all 528 imaging grid locations without image interpolation in Figure 3A, and with Fourier interpolation factors 2, 4 and 8 in Figures 3B-D. The highest simulated SNR of 150 was chosen to remove any additional effects from noise. Without image interpolation (Figure 3A), the measured area varies up to 57% depending on the grid location leading to a wide precision of 8% relative to its mean. Fourier interpolation with zero filling factors 2, 4, and 8 effectively reduces this variation to 33%, 12%, and 8%, and hence improves precision to 6%, 2%, and 1%, respectively. At the same time, the accuracy is reduced from -15% to -22% as area underestimation is increased with Fourier interpolation, independent of the interpolation factor.

Numerical Simulations - Effects of Fourier Interpolation on Area Measurements

Figure 4 shows the impact of Fourier interpolation on vessel area measurements averaged over the different vessel sizes at a high SNR of 150. Area measurement precision improves with Fourier interpolation on average 2.5, 5.0, and 6.5-fold with zero filling factors 2, 4, and 8, respectively (Figure 4A). Reducing the voxel size from $\Delta x = 1.0$ mm to 0.4 mm improves the precision by a factor of 4.6 (with zero filling factor 8) which is less than one may expect based on the voxel area decreasing by a factor 6.25. Figure 4B shows that Fourier interpolation increases underestimation, and therefore reduces accuracy, of the area measurements by about 40% independent of zero filling factor ($\Delta x = 2$) and acquisition voxel size. Similar to precision, the accuracy is improved by a factor of 4.3 (with zero filling factor 8) when reducing the voxel size from 1 to 0.4 mm.

Numerical Simulations - Effects of SNR and Spatial Resolution on Area Measurements

The effects of SNR and spatial resolution on area measurements are shown in Figure 5 for 8-fold zero filled simulated images. Both precision and accuracy remain about constant for SNR at or above 60, and slowly worsen as SNR decreases independently of acquisition voxel size. The precision quickly deteriorates below an SNR of 20. Smaller acquisition voxel sizes improve both precision and accuracy if SNR is kept the same. In practice, however, SNR scales with the voxel size if the acquisition duration (breath-hold duration) remains equal. Thus, gray dotted lines were added to Figure 5A that indicate the SNR decrease proportional to the acquired voxel area. Following the gray dotted line starting at an SNR of about 60 for a voxel size of 0.89 mm, corresponding to the lowest SNR measured in vivo at the level of the RCA, the precision significantly improves down to a voxel size of 0.5 mm after which it starts to deteriorate as the SNR drops below 20. Following the gray dotted lines at lower SNR values of 53 and 30 for a voxel size of 0.89 mm, corresponding to the average in vivo SNR and the lowest SNR measured in the LAD, the precision decreases down to a voxel size of 0.6 mm and 0.7 mm, respectively, but those changes were not statistically significant.

Phantom Measurements

An example phantom analysis is shown in Figure 6. Panel A shows an image of the phantom acquired with the standard CEF-MRI protocol prior to Fourier interpolation. Figure 6B shows cropped images of all 110 holes arranged according to the layout of the phantom, after 8-fold Fourier interpolation and corrected for off-resonance blurring. The FWHM segmentation of those holes is shown in Figure 6C.

Similar to the simulation results, area measurement precision improves with Fourier interpolation in the phantom scans. Figure 7A shows that area measurement precision improves on average 3.0, 5.2, and 5.9-fold with zero filling factors 2, 4, and 8, respectively. Reducing the voxel size from $\Delta x = 0.89$ mm to 0.6 mm improves the precision by a factor of 1.3 (with zero filling factor 8) also less than expected based on 2.2 times smaller voxel area. Area measurement accuracy (Figure 7B) is reduced with Fourier interpolation by less than 20% independent of zero filling factor (≥ 2) and acquisition voxel size.

The average SNR for the 10 acquisitions and the 110 holes was 133 ± 16 (mean $\pm$ standard deviation) and 94 ± 10 for the standard and the high-resolution protocols, respectively. Different measured noise maps were added to those acquisitions leading to a range of SNR as low as 31 and 18 for the standard and the high-resolution protocols, respectively. Area measurement precision and accuracy are plotted vs. SNR for both the standard and high-resolution protocols in Figure 8. The phantom measurements show a similar behavior to that predicted by the numerical simulations. Both precision and accuracy remain constant for high SNR and start to degrade once the SNR drops below a certain threshold. That threshold is slightly higher in the phantom measurements. Precision starts to worsen below an SNR of 40 in the standard protocol, and below 30 in the high-resolution protocol.

The impact of Fourier interpolation on the smallest detectable area change, or LOD, is shown in Figure 9. LOD improves on average 2.5, 3.8, and 4.3-fold with zero filling factors 2, 4, and 8, respectively. Figure 10 shows the measured LOD over a range of SNR. The LOD is a 4% area change for SNR above 55, a 5% area change or better for SNR above 30 with the current standard protocol, and a 3%-3.5% area change for SNR above 40 with the high-resolution protocol.

DISCUSSION

This work demonstrates that Fourier interpolation enables sub-voxel precision for measurements of small vessel cross-sectional area. Numerical simulations and phantom measurements predict that both accuracy and precision depend primarily on the acquisition voxel size as long as the image SNR is above 20 and 30, respectively. MRI in combination with isometric handgrip exercise was previously shown to noninvasively and reproducibly measure nitric oxide-mediated CEF by assessing exercise-induced changes in coronary artery cross-sectional area (9). The standard spiral cine MRI protocol uses an acquired voxel size of 0.89 mm, leading to a voxel area that is 11% of the area of a 3-mm diameter vessel. Phantom measurements presented here show that the current CEF spiral MRI can detect area changes of 4% in most current situations and 5% even at the lowest SNR level measured for

the LAD. This could potentially be improved to 3%-3.5% with an acquired voxel size of 0.6 mm and sufficient SNR above 40.

Prior studies have shown isometric handgrip exercise induced mean coronary cross-sectional area changes from 10 to 20% in healthy vessels and reduced dilation or even a paradoxical constriction from 2 to -12% in diseased vessels (9,12-17), approximately a 20% absolute difference in area change on average between healthy and diseased vessels. The ability to measure one-fifth or a quarter of the difference between healthy and diseased enables the comparison of patient groups at earlier stages of atherosclerotic disease progression and the investigation of the impact of medical or lifestyle interventions on CEF where the improvement may only be a fraction of the difference measured between healthy and diseased vessels.

The results from the phantom measurements in combination with the coronary SNR measured in vivo predict that CEF-MRI measurements of the RCA detect smaller area changes compared to those of the LAD. The SNR at the LAD (35 on average and always > 30) was lower compared to that at the RCA (70 and > 62) likely because the LAD is located further away from the MRI receiver coils leading to a lower signal sensitivity. Phantom measurements showed that the current CEF-MRI protocol with an SNR above 60, such as at the RCA, detects area changes of 4%, compared to 5% for an SNR above 30 as measured at the LAD.

While Fourier interpolation up to a factor of 2 is routinely used in MRI, Zhu et al. previously argued that zero-filling should be performed until individual voxels become invisible in the zoomed image (19). Simulations by Jiang et al. predicted a precision of less than 2% (similar to what is reported here) for a similar acquisition resolutions but at even lower SNR of 5 (21). However, those simulations did not include variations in partial volume as caused by different vessel locations relative to the imaging grid as exemplified in Figures 2B and 2C. In this work, we test the impact of Fourier interpolation on area measurement precision of small vessels for the first time including a full range of partial volume effects. The above mentioned 4% area change of a vessel with a diameter of 3 mm corresponds to about a third of the acquired voxel area, indicating that with sufficient SNR, area changes of a third of an imaging voxel can be detected. Numerical simulations in this work show that Fourier interpolation improved area measurement precision by a factor of 6.5 compared to non-interpolated images, enabling sub-voxel precision. This is a surprisingly large improvement for a process that basically only adds zeroes but no additional information. The following two arguments are key to make sense of this. First, we showed that partial volume effects cause low area measurement precision in images without interpolation (Figures 2 and 3A). Second, even though this is not how we performed our numerical simulations, different partial volume effects – or a translation of the object relative to the imaging grid – can be generated by adding a linear phase to a single dataset in k-space based on the Fourier shift theorem (19). In other words, one could take an image without interpolation and keep measuring the area after adding different amounts of linear phase to shift the image to all the different partial volume positions, and eventually average out the partial volume effects. Fourier interpolation (zero filling) achieves this in a single step: the additional interpolated voxels correspond to voxels with shifted grids (or different partial volume). 8-fold zero filled

images, therefore, contain 64 different grid locations, and hence remove the risk of randomly picking a grid location that leads to an extreme area measurement, and thereby improves the area measurement precision as shown in the numerical simulations.

Furthermore, the numerical simulations predict that area measurement precision could be improved with smaller acquisition voxels, as long as a sufficient SNR above 20 is maintained. This was confirmed in the phantom acquisitions where both precision and limit of detection were improved with the high-resolution protocol compared to the standard protocol, albeit at a higher SNR threshold of 40. This appears to contradict the phantom measurements presented by Yerly et al. (18), where both area measurement precision and the limit of detection with radial MRI remained the same for different acquisition resolutions while keeping the acquisition duration identical. In contrast, their study showed that both precision and the smallest detectable area difference was highly dependent on SNR, and the authors discussed that the positive effect of having an improved resolution may be counterbalanced by a detrimental effect associated with lower SNR due to the reduced voxel size (18). The simulations presented here suggest that precision could be improved with higher spatial resolution even with a loss in SNR due to the smaller voxel sizes. This is shown in Figure 5A with dotted gray lines that connect the predicted precision for the different voxel sizes assuming the SNR scales with the acquired voxel area (the square of the voxel size $\propto x$) for measurements with identical breath-hold durations. Applying the same rule to the phantom results, where the high-resolution protocol outperforms the standard protocol as long as SNR is 40 or higher, the corresponding SNR at the larger voxel size of 0.89 mm would need to be 88 or above, slightly higher than the SNR of 70 measured here at the level of the RCA. Conversely, an SNR of 70 with $x = 0.89$ mm reduces to 32 at $x = 0.6$ mm, below 40, and leads to a measured limit of detection of 4%, the same as with the current standard protocol, which aligns with the results presented by Yerly et al. (18). The challenge remains to obtain a high-resolution protocol with sufficient SNR in vivo.

The high-resolution protocol tested in the phantom study fully sampled k-space leading to longer acquisition times and/or reduced temporal resolution compared to the standard protocol, a significant difference from the radial approach by Yerly et al. (18) where the same number of spokes were used leading to identical scan durations but higher k-space undersampling as the resolution was increased. Potential future modifications to the spiral trajectory such as variable density (30) or parallel imaging undersampling (31,32) allowing smaller voxel sizes while also shortening the breath-hold duration would require another phantom validation as the current study assumes fully sampled k-space.

Area measures were underestimated in both numerical simulations and phantom studies, and the underestimation was worse with Fourier interpolation. Hoogeveen et al. showed that the FWHM algorithm may underestimate area measurements (33). A potential reason why Fourier interpolation further reduces the measured area is that the FWHM-threshold would be raised if the maximum signal intensity in the vessel is higher compared to before interpolation. The maximum signal intensity after Fourier interpolation could be increased if Gibbs ringing is present and the additional interpolated pixels now resolve the Gibbs ringing (Supporting Information Figures S1 A and B). An increase in maximal signal intensity of about 3% with zero-filling was observed (Supporting Information Figure S1 C) in the

phantom acquisitions with voxel size $\Delta x = 0.89$ mm, along with the area underestimation. Moreover, if FWHM segmentation in the zero-filled images is performed with the maximum signal intensity measured in the image prior to zero-filling, the area is no further underestimated. However, for CEF-MRI, area measurement precision is arguably more important than accuracy because the change in coronary cross-sectional area is measured.

SNR measurements performed here used the subtraction method (23). This method determines spatially varying noise from the subtraction of two identical acquisitions. This approach performed well in the phantom acquisitions without motion between the different cardiac phases. Using the standard spiral protocol an SNR of 133 was measured, more than 2 times higher than with the radial protocol used in (18). Spiral MRI is expected to have higher SNR compared to radial MRI due to the radial oversampling of the center of k-space and because one spends more time sampling data each TR using long spiral readouts compared to the short radial spokes. In vivo, however, the noise generated from the subtraction of the two cardiac phases is likely to be contaminated with some artifactual signal due to remaining motion, as shown in the example in Figure 2, potentially leading to an increased measure of noise and, hence, an underestimation of the measured in vivo SNR.

CONCLUSION

In conclusion, both numerical simulations and phantom measurements showed that 8-fold Fourier interpolation enables sub-pixel area measurement precision. Area measurement precision and accuracy can be further improved with smaller acquisition voxels as long as the signal-to-noise ratio remains above 30. Importantly, the currently used CEF-MRI protocol (9,12–17) distinguishes area changes of 4%-5% at SNR levels achieved in vivo. Noninvasive CEF measures by MRI promise a window into predicting atherosclerotic progression and testing new interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The subtraction method (23) was used to measure SNR. A) and B) show two cardiac phases of an RCA with minimal motion during mid-diastole. C) shows the noise image obtained from subtracting the two images shown in A) and B). The noise intensity was scaled by a factor of 10 compared to anatomical images. For SNR, signal is determined from the mean of the vessel voxels segmented with a FWHM algorithm, and noise is given by the standard deviation of the intensity of the voxels within the white box at the level of the RCA. The noise image is imperfect because of residual motion and moving blood in the images, especially obvious at the level of the papillary muscle (white arrow). Hence, the measured SNR is most likely underestimated with this technique as the motion induced artifacts in the subtraction lead to overestimation of the noise.

Figure 2.

A) Shows a circular cross-section of a coronary artery, which typically has a diameter of 3-5mm. B-C) Because of the limited spatial resolution of MRI, the measured area using a full-width at half-maximum algorithm may depend on the location of the imaging grid relative to the vessel due to partial volume effects, in an extreme case here leading to a measured area of 9 voxels in B) and 12 voxels in C). We performed simulations to evaluate whether Fourier interpolation improves the partial volume induced variability. D) Digital phantoms with a pixel size of 1 μm (not shown to scale as the matrix size of a 3mm vessel is 3000×3000) were created for a range of vessel sizes. E) To simulate the full range of possible partial volume effects the imaging grid was shifted to 528 locations in a triangle half the size of the grid. F) The resampled images were then Fourier interpolated by factors 1, 2, 4, and 8, and noise was added to achieve a wide range of SNR.

Figure 3.

Simulated area measurements of a 3-mm diameter vessel with data acquired with an SNR of 150 and a voxel size $\Delta x = 0.89$ mm for 528 different imaging grid locations causing differences in area due to partial volume effects. A) Not interpolating the image leads to rather discrete area measures. B)-D) With Fourier interpolation applying zero-filling factors 2 (B), 4 (C), and 8 (D) the precision, as measured with the standard deviation of the area measures, is improved, while the accuracy, the difference of the mean of the measures to the true value, shows a larger underestimation independent of zero filling factor ($\propto \Delta x$). (The arrow in (A) spans 2 standard deviations and, hence, 2 times the defined precision.)

Figure 4.

The impact of Fourier interpolation on vessel area measurements performed with FWHM segmentation on simulated images: A) precision and B) accuracy averaged over vessel diameters from 2.5 to 5 mm plotted against the acquisition voxel sizes and for 4 different Fourier interpolation factors. Fourier interpolation up to zero filling factor 8 improves precision, but decreases accuracy (increases area underestimation) though the underestimation remains the same for zero filling factors of 2 and above. Relative to a 3 mm diameter vessel, a precision of 0.13 mm² ($x = 0.89$ mm, zero filling factor = 8) is 1.8%.

Figure 5.

A) Precision and B) accuracy of area measurements on 8-fold zero filled simulated images: Each data point is averaged over a range of vessel diameters from 2.5 to 5 mm and plotted over a range of different SNR levels and for simulated voxel sizes from 0.4 to 1 mm. The dotted gray lines indicate SNR decrease proportional to the acquired voxel area assuming equal scan duration.

Fig. 6.

A) Example image of the phantom with precision drilled holes acquired with the standard CEF-MRI protocol prior to Fourier interpolation. The only user interaction needed in the analysis is the selection of the 3 holes marked with blue and green circles. Dotted lines show origin of the zoomed inset. B) Composition of cropped images of the 110 holes arranged in the same pattern as in the phantom after off-resonance deblurring. C) The same holes as B) after FWHM segmentation.

Figure 7.

The impact of Fourier interpolation on vessel area measurements performed with FWHM segmentation on phantom images acquired with high-SNR spiral MRI: A) Precision and B) accuracy averaged over a range of vessel diameters from 3 to 3.42 mm for 4 different Fourier interpolation factors and for voxel sizes of 0.89 mm and 0.6 mm. Fourier interpolation improves precision markedly up to a zero filling factor 4, but slightly decreases accuracy (increases area underestimation) though the underestimation remains similar for zero filling factors of 2 and above. Relative to a 3-mm diameter vessel, a precision of 0.09 mm² ($x = 0.89$ mm, zero filling = 8) is 1.3% (bars are standard deviations).

Figure 8.

Measured A) precision and B) accuracy of area measurements averaged over a range of vessel diameters from 3 to 3.42 mm for a range of different SNR levels with data acquired with voxel sizes of 0.89 mm and 0.6 mm (bars are standard deviations).

Figure 9.

The impact of Fourier interpolation on the smallest detectable area change, or limit of detection (LOD). LOD was averaged over a range of vessel diameters from 3 to 3.42 mm and plotted for 4 different Fourier interpolation factors and for high-SNR spiral MRI with voxel sizes of 0.89 mm and 0.6 mm. Fourier interpolation improves LOD up to a zero filling factor of 4 (bars are standard deviations).

Figure 10.

Limit of detection, or the smallest detectable area change averaged over a range of vessel diameters from 3 to 3.42 mm for a range of different SNR levels with data acquired with voxel sizes of 0.89 mm and 0.6 mm (bars are standard deviations).