In Vivo Measurement of Pulsewave Velocity in Small Vessels Using Intravascular MR

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A one-dimensional intravascular MR (IVMR) technique for the measurement of pulsewave velocity in a single cardiac cycle is presented. The technique was used to measure pulsewave velocity in vivo in the intact rabbit model, where its sensitivity to different hemodynamic states was demonstrated using a pharmacological intervention with phenylephrine and nitroprusside. IVMR measurements of pulsewave velocity were found to increase with mean arterial pressure, as expected. Further, IVMR-based pulsewave velocity estimates were in agreement with those measured by pressure catheters and direct distensibility measurement. Because of their rapidity and highly localized nature, these measurements of vessel elasticity may complement the high-resolution vascular imaging information gained in an IVMR examination. This could allow assessment of atherosclerotic plaques and facilitate immediate treatment decisions. Magn Reson Med 45:53–60, 2001. © 2001 Wiley-Liss, Inc.

Key words: pulsewave velocity; intravascular MR; in vivo rabbit model

Atherosclerosis is an underlying factor in most cardiovascular disease. In addition to thickening of arterial walls, a variety of lesions characterize this disease process, from nonprotruding fatty streaks to more complex lesions or plaques consisting of lipid, smooth muscle cells, collagen fibers, and calcification (1). Along with these structural changes, however, plaque formation also leads to changes in the mechanical properties of the vessel wall (2), progressively altering these properties with changes in plaque composition (3). Further, although the disease of atherosclerosis is chronic in nature, frequently its clinical manifestations are acute, in the form of plaque rupture that leads to the formation of thrombus and heart attack or stroke. This plaque disruption is caused by plaque deformation and stress at vulnerable sites of the plaque’s fibrous cap, but the mechanisms of this process are controversial and still under investigation (4).

There is much interest in the in vivo imaging of atherosclerotic plaque to determine its composition and thus its propensity to rupture. Imaging alone, however, may not be sufficient to assess the mechanical properties of the plaque tissue, since factors other than its composition and macroscopic structure are involved. Localized elasticity information could be a beneficial complement to the structural information gained from imaging. For example, local measurements of vessel distensibility may aid in the diagnosis of early-stage atherosclerosis or, in the case of existing plaques, may provide insight into plaque stability.

It has been shown in vitro that MR microimaging can identify and quantify atherosclerotic lesions (5–8). However, the diversity of MR is useful for the assessment of all aspects of atherosclerosis. For example, spectroscopic evaluation can assess lipid content (9,10) and phase contrast techniques can be used to study the hemodynamic effects of atherosclerotic lesions (11). Finally, as a result of the development of several MR techniques for in vivo measurement of vessel compliance (12) and pulsewave velocity (13–16), the mechanical properties of the vascular wall can be interrogated as well.

When applying these techniques to smaller vessels and atherosclerotic lesions, especially those deeper in the body, decreasing voxel size leads to inadequate signal-to-noise ratio (SNR) in the region of interest. MR catheter probes can be placed inside the vessel, juxtaposing the RF coil to the arterial wall being interrogated, and thus provide the necessary SNR (17–19). The development of these probes has given birth to the new field of intravascular MR (IVMR) and the potential to assess and treat vascular disease under MR guidance (20).

In this article, we present an in vivo intravascular MR technique for the measurement of pulsewave velocity in a single heartbeat. This measurement can be inserted easily into a real-time intravascular MR exam and may be useful in the evaluation of the mechanical properties of small deep vessels such as the coronary and cerebral arteries. The sensitivity of this technique over the range of human pulsewave velocities is demonstrated in an in vivo rabbit model.

MATERIALS AND METHODS

MR Catheter Antenna

The RF coil used in this study was a 4 Fr catheter antenna designed by researchers in our group (17). The catheter, shown schematically in Fig. 1, is essentially a thin coaxial cable with the inner conductor extended beyond the shield a length of approximately 10 cm, about a quarter wavelength at 64 MHz in blood. With this design, all tuning and matching circuitry can be placed outside the body without losing performance.

Signal Localization With the Catheter Antenna

The catheter antenna was introduced into the rabbit abdominal aorta via the femoral artery and used to both
transmit and receive the MR signal. The excitation profile of the catheter antenna, like its sensitivity profile, is proportional to the inverse of the distance from the coil axis. Exploiting the confined nature of this excitation profile, the blood vessel lumen was selectively excited when non-selective RF pulses were applied (21,22), as shown in Fig. 2. The primary benefit is that nonselective RF pulses can be very short in duration, reducing the minimum TE and TR in the pulse sequence.

When no spatial encoding is applied normal to the catheter axis, the received signal is the projection of the entire vessel lumen on the catheter axis. The phase profile of the catheter antenna is inhomogeneous, as shown in Fig. 3, which would result in signal reduction when transmitting with an external coil due to phase cancellation between spins on opposite sides of the catheter. By transmitting with the catheter, this inhomogeneous phase is encoded on the blood during excitation and the effect of the catheter’s spatially dependent phase profile is negated.

The excitation diameter can be increased by increasing the transmitted power. Nonselective “hard RF pulses” are sufficient for small vessels such as the rabbit aorta. When larger diameters are required, however, simply increasing the transmitted power results in very large tip angles near the catheter, subsequent artifacts, and signal loss. Instead, in these situations the BIR-4 adiabatic pulse can be applied, as it produces a uniform tip angle over a broad range of power levels (23). A discussion of the application of the BIR-4 pulse to the large diameter case appears in the Appendix.

Single Heartbeat Arterial Pulsewave Velocity Acquisition

Velocity data for the estimation of pulsewave velocity in the rabbit aorta was collected using a rapid flow-encoded 1D gradient echo pulse sequence, shown in Fig. 4. This
sequence employs a fractional echo to reduce TE and TR and was implemented on a 1.5 T Signa Echospeed scanner (GE Medical Systems, Milwaukee WI), with a maximum gradient strength of 22 mT/m and a slew rate of 120 T/m/s. Triggered by the QRS complex of the ECG, a series of 120 gradient echoes is acquired with the readout direction oriented collinear to the abdominal aorta of the rabbit and concurrently with the catheter antenna. Using a dead-period minimization technique (24,25), velocity encoding is applied along the readout axis in the first dead-period between the RF pulse and the readout gradient. A crusher gradient during the second dead-period following readout spoils the remaining transverse magnetization. The TE and TR are typically 2 and 3.4 ms, respectively, for this sequence. The exact values used for each study are given in the Results section.

Pulsewave velocity measurements depend on the time course of the velocity waveform, not the actual velocity values. For this reason, it is only necessary to gather data at a single velocity encoding strength. It is necessary to correct for field inhomogeneity-related phase, but this can be accomplished using data from one time-point, usually an echo early in the acquisition, as a phase reference. This allows acquisition of all the data necessary for pulsewave velocity estimation in a single cardiac cycle.

Once the raw data is acquired, it is immediately transferred to a Sparc Ultra 60 workstation (SUN Microsystems, Mountainview CA) running MATLAB (Mathworks, Natick MA) for reconstruction and display. Fractional echo sampling is employed in this sequence which reduces the first half of each echo by 25%. These missing points are first replaced by zero-padding. The data is then reconstructed by applying a 1D-Fourier transform to each of the gradient echoes. Phase difference reconstruction is applied using an early time-point as a phase reference, resulting in an image of velocity as a function of position along the vessel and time, as shown in Fig. 5. Because the velocity is normalized to the peak velocity in this image, the noise level is apparent in areas of lower MR signal. From the velocity data, the pulsewave velocity is estimated using a matched filtering technique (26), in which the temporal location of the onset of flow, at each position along the vessel, is found by minimizing the mean square error between a prespecified template and the leading edge of the waveform in the temporal direction. The template consists of a horizontal segment joined to a linear ramp segment. The horizontal segment represents $\frac{2}{3}$ of the template and its amplitude varied with the mean of the data points in the region covered by the segment. The slope of the ramp section is held constant for the entire analysis. An example of this template positioned at the onset of flow is shown in Fig. 6.

The template matching procedure results in a set of temporal–spatial pairs reflecting estimates of the onset of flow at each position along the vessel. The slope of the regression line through this is an estimate of pulsewave velocity in the respective section of the vessel. The 95% confidence interval for this slope is calculated as well as the standard error of the fit. These are used as a measure of data quality.

In Vivo MR Pulsewave Velocity Measurements in the Rabbit Aorta

A series of experiments was performed in the anesthetized rabbit model. A surgical plane of anesthesia was maintained by a periodic bolus of pentobarbital I.V. for the...
duration of each experiment. The catheter antenna was introduced into the abdominal aorta of a 4–5 kg New Zealand White rabbit as described above. In addition, a 2 Fr catheter-tip pressure transducer (Millar Instruments, Houston, TX) was introduced into the right carotid artery. This catheter was advanced into the aortic arch and was used to monitor blood pressure in the aorta during the experiment. The experiments were performed in accordance with the guidelines of the Johns Hopkins Animal Care and Use Committee.

The hemodynamic state of the animal was altered during each study using pharmacological intervention. Phenylephrine dosages in the range of 16–39 µg/kg/min were used to create a hypertensive state and increased smooth muscle tone in the rabbit aorta. Nitroprusside, a vasodilator, was used in dosages between 6.7–13.4 µg/kg/min to induce a hypotensive state and increase vessel distensibility. These drugs were continuously administered I.V. via the ear vein.

Several intravascular pulsewave velocity (IVPWV) acquisitions were made in the rabbit aorta with no drug administered, under phenylephrine, and under nitroprusside. After the start of each intervention the animal was allowed to reach a steady state, as determined by a stabilization in blood pressure. In addition, the animal was allowed to reach normal blood pressure levels between interventions. An IVPWV acquisition consisted of 120 flow-encoded gradient echoes. The first moment in the interventions. An IVPWV acquisition consisted of 120 flow-encoded gradient echoes. The first moment in the interventions. An IVPWV acquisition consisted of 120 flow-encoded gradient echoes. The first moment in the interventions. An IVPWV acquisition consisted of 120 flow-encoded gradient echoes. The first moment in the interventions. An IVPWV acquisition consisted of 120 flow-encoded gradient echoes. The first moment in the interventions. An IVPWV acquisition consisted of 120 flow-encoded gradient echoes. The first moment in the interventions. An IVPWV acquisition consisted of 120 flow-encoded gradient echoes.

The pulsewave velocity was estimated from each of these acquisitions using the matched filtering technique. A segment of the vessel, beginning near the catheter tip, was analyzed using a seven-sample ramp template that was two thirds baseline and one third ramp. The slope of this ramp was set to the average upslope of the data and was kept constant for all the datasets in the study. The analysis procedure was automated. The user first selected the region of interest (ROI) containing the onset of flow, then executed the fitting algorithm. The algorithm first calculated a global fit over the selected ROI at the resolution of the data. Because of noise and motion artifacts, the global fit at some positions along the vessel may be drawn toward a location other than the foot of the flow waveform. For this reason, the global fit was monitored and, if necessary, interactively modified by the user. This was followed by a subpixel fit covering a range ±2 samples from the global fit.

Independent Validation of Aortic Pulsewave Velocity

To verify the validity of MR pulsewave velocity measurements, two additional measures of vessel distensibility were used in the third study. First, a direct measure of aortic distensibility was made by measuring the ratio of fractional change in cross-sectional diameter to pulse pressure. Pulsewave velocity, \(c\), can be derived from this direct distensibility measurement using the relationship:

\[
c = \sqrt{\frac{1}{\rho D}}, \text{ where } D \text{ is distensibility and } \rho \text{ is the density of blood.}
\]

Second, the pressure catheter was placed in the same region of the vessel over which MR pulsewave velocity measurements were made and pressure-based pulsewave velocity data were acquired. These latter measurements should be equivalent to those measured with MR.

Direct Distensibility Measurement

A set of cardiac-gated, multiphase, partial k-space, fast gradient echo images of the aortic cross-section were acquired in the area in which pulsewave velocity measurements were made. The catheter antenna was used in the receive mode for this acquisition. Imaging parameters were 7 cm field of view, 3 mm slice thickness, 256 × 160 matrix, TR/TE = 10/1.5 ms, and 2 views per phase, yielding a temporal resolution of 20 ms. There were 20 phases acquired through the cardiac cycle. The luminal cross-sectional area of the vessel was calculated as a function of time, from manually drawn contours, using Scion Image (Scion Corp., Frederick, MD), and compared to the pressure arterial pressure waveform.

Pressure-Based Pulsewave Velocity

The micromanometer-based technique is generally the “gold standard” for the direct measurement of pulsewave velocity. In the third study, under normal conditions, the imaging antenna was replaced with the pressure catheter previously positioned in the carotid. The tip of the pressure catheter was introduced to the same location as the tip of the imaging antenna. The pressure waveform and the ECG were then acquired simultaneously for 20 sec and sampled at 2 kHz using LabView (National Instruments, Austin, TX). The acquisition was repeated after withdrawing the catheter 3 and 6 cm from its initial location. Using the ECG as a time reference, all the pressure waveforms in each location were averaged. The pulsewave velocity was then calculated using the previously described template-matching technique from the three temporal spatial pairs.

RESULTS

Localization of Signal to the Abdominal Aorta

The composite of an image acquired with the body coil and one acquired with the catheter antenna is shown in Fig. 2. The bright area down the center of the image is the aorta. It is segmented from the image due to the high signal around the catheter antenna. It is this property of the catheter during transmission and reception of RF that is used to localize the signal to the aortic lumen in this experiment.

Pulsewave Velocity Changes Under Pharmacological Intervention

At the beginning of each study the FOV and velocity encoding strength were manipulated to optimize the data quality. The resulting MR acquisition parameters and the analysis parameters used are shown in Table 1.

The measured pulsewave velocity throughout the time course of the study is plotted in Fig. 7 for one animal (Study 1 in Table 1). This study included two hypertensive states (IIa&b) and two hypotensive states (IVa&b), which
are indicated in the synchronized pressure tracings on the lower portion of the figure. The phenylephrine intervention in this study was paused for animal maintenance purposes. The increase in baseline pressure upon resumption suggests that the newer drip rate was higher, and we therefore denote this as a separate dosage. A normal baseline (I) and control (V) state were measured before and after the pharmacological intervention, respectively.

For each intervention, the mean ± 1 SD of the pulsewave velocity measurements are denoted on the graph. The response to the two pharmacological agents is well demonstrated in Fig. 7, as is the strong correlation between blood pressure and intravascular MR-based pulsewave velocity. The relationship between the mean blood pressure and the single heartbeat IVMR pulsewave velocity measurements is shown directly in Fig. 8. Pulsewave velocity data from the three studies are plotted here vs. mean pressure, which was calculated from 3 sec of arterial pressure data acquired immediately after the conclusion of each 500 ms MR acquisition. The regression line in this graph is given by \( y = 3.5x - 28.5 \) with \( R^2 = 0.56 \).

**Independent Validation of Aortic PWV**

During the third study, analysis of the ECG-gated, cross-sectional images resulted in systolic and diastolic cross-sectional areas \( A_s = 75.2 ± 0.4 \times 10^{-3} \text{ cm}^2 \) and \( A_d = 65.8 ± 0.3 \times 10^{-3} \text{ cm}^2 \), respectively. The corresponding pulse pressure, \( \Delta P \), was \( 18.8 ± 0.4 \text{ mmHg} \). Using these values, the local vessel distensibility, \( D \), was calculated via the relationship,

\[
D = \frac{A_s - A_d}{A_d \Delta P}.
\]  

A distensibility of \( 57.1 \mu \text{m} \cdot \text{s}^2/\text{kg} \) was measured for this segment of the vessel. Via the relationship, \( c = \frac{1}{\sqrt{\rho D}} \), assuming a blood density, \( \rho = 1.057 ± 0.007 \text{ g/cm}^3 \), the corresponding pulsewave velocity for this distensibility measurement is \( 407.0 ± 22.9 \text{ cm/sec} \). This value is in good agreement with the normotensive intravascular MR pulsewave velocities, \( 481.7 ± 81.2 \text{ cm/sec} \), measured in the third study.

Calculation of the pulsewave velocity from catheter-based pressure waveforms at different locations along the vessel, under normotensive conditions, yielded a value of \( 484.0 ± 35.7 \text{ cm/sec} \), again in good agreement with the MR-derived measurements.

**DISCUSSION**

We have developed an intravascular MR pulsewave velocity technique as a direct solution to two problems of small vessel distensibility measurement: acquisition speed and SNR. If vessel elasticity measurement is to be interjected into a real-time intravascular MRI treatment, it is important that the necessary acquisition time be negligible with respect to the larger examination. Pulsewave velocity measurements present a challenge in this context because they require high time resolution. When the minimum sequence TR is insufficient, this can be accomplished with time-interleaving techniques (13), but the probability of respiratory motion in the multicycle acquisition is high. Reducing sequence TR allows motion artifact-free acquisition in one or two heartbeats.
The 1D-MR PWV technique requires localization of the MR signal to the vessel lumen. Selective excitation pulses capable of accomplishing this in smaller vessels are prohibitively long in terms of the TR necessary to adequately sample the arterial flow waveform. The use of the intrinsic excitation profile around the catheter antenna in these experiments allowed effective signal localization using very short 248 μs RF pulses. The resulting 3.4 ms TR was therefore limited by the gradient performance and not the excitation. When coupled with a catheter tracking algorithm, the use of oblique optimized flow encoding gradient waveforms (24) ensure that the minimum TR will be used regardless of the catheter antenna location or orientation.

The amplitude of the velocity signal may vary as a function of position along the vessel since the catheter samples a different region of the flow profile as it snakes through the vessel. In addition, vessel wall motion occurs in the radial direction during the cardiac cycle. The radial pressure gradient, however, is very small (27). Therefore, features in the time course of the velocity waveform, such as the onset of flow or waveform foot, occur simultaneously across the vessel cross section and do not create timing errors in the phase image. Further, phase errors due to eddy currents are reduced by using a later frame prior to the onset of flow, as opposed to the first frame, as the phase reference.

The necessity of intravascular coils in providing sufficient SNR for the imaging of deep small vessels is well documented (28). This is especially true in this application due to the lack of averaging in the single cardiac cycle acquisition and the small region of interest. The local nature of these measurements is a real strength. Atherosclerosis causes a localized as well as generalized increase in arterial wall stiffness (29). A technique capable of detecting local changes in vascular elasticity has the potential to help assess the vulnerability of a plaque to rupture.

The minimum theoretical limit for spatial localization of these PWV measurements can be calculated by using an expression for the estimation error of the 1D PWV measurement (26). By solving this relationship for the vessel length over which the measurement is made, given the waveforms seen in these experiments, it can be shown that PWV measurements with a spatial resolution of 8.4 mm are possible with a measurement error less than 10%. For this calculation, an SNR of 45 and temporal sampling period of 3.4 ms was assumed, as well as a Venc value equal to the maximum velocity in the vessel. By sliding an analysis window of this size over the spatial data range, pulsewave velocity as a function of position in the vessel can be calculated at the spatial resolution of the acquisition, albeit smoothed by the sliding window.

The experimental results presented above show the efficacy of the IVMR pulsewave velocity technique. In this study we analyzed the pulsewave velocity variation between successive acquisitions which were typically 10–20 sec apart. In most of the interventions presented, the pulsewave velocity changed as expected. There was, however, more variability in the measurements than can be explained by measurement noise alone (26). Vessel distensibility is a function of a variety of factors. The passive effects of mean arterial pressure are due both to vessel geometry and the changing contribution of different components in the arterial wall to its elasticity. This is shown very clearly by the pulsewave velocity vs. pressure relationships recorded in Fig. 8. During the administration of phenylephrine, however, an active component to this system, such as the baroreceptor reflex in the intact animal, can skew this result. At mild levels of hypertension (+20–30 mmHg), this system can be very effective, and can potentially add variation to pulsewave velocity measurements acquired on such a short time-scale. In the rabbit there is a close relationship between the length of time the animal is hypertensive and a reduction in baroreceptor sensitivity (30). Further, the dosage of phenylephrine used in the first study was quite high by normal administration guidelines. This undoubtedly was a factor in the larger measurement variance demonstrated in IIa and Ib of Fig. 7. Nitroprusside, on the other hand, acts via NO, causing a local relaxation of the vessel wall. Vessel elasticity would be expected to remain more stable under this local action, as demonstrated in the above studies.

CONCLUSION

With the rapid development of IVMR devices and techniques, MR may soon play a part in the diagnosis and treatment of vascular disease. High-resolution images of the vascular wall, an area where IVMR has shown great promise, is only a small fraction of the information IVMR is capable of providing. Our goal in this article was to introduce a new application for IVMR that takes advantage of the intrinsic properties of the catheter probe. We have demonstrated that, because of these unique properties, without other special MR hardware, single heartbeat IVMR-based PWV measurements are not only possible but are also sensitive to localized changes in arterial elasticity in the intact in vivo rabbit model. Because these measurements can be acquired rapidly, they can be easily included as part of a larger IVMR procedure, allowing near real-time samples of elasticity in a small region of vessel or plaque,
without placing time constraints on other portions of the examination.

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**APPENDIX: LARGE DIAMETER EXCITATION USING THE CATHETER COIL**

The effectiveness of the adiabatic BIR-4 pulse in the large diameter situation is demonstrated by implementing the pulse in both a cardiac-gated SPGR pulse sequence (25) and an enhanced 3D fast gradient echo pulse sequence (GE Medical Systems). The 3D sequence allows easy interrogation of the catheter excitation profile with nonselective RF pulses. Imaging was performed on a 1.5 T GE Horizon Echospeed system using the 4 Fr catheter antenna described above.

Coronal 3D FGRE images of a homogeneous water phantom were acquired with the catheter in-plane. The slice thickness was 1 mm and the FOV was 8 × 4 cm, with TR = 10.8 ms, and TE = 3.4 ms. Images were acquired at several values of transmitter power using both the “hard” RF pulses and the BIR-4 pulses. For the BIR-4 pulse, the tip angle was set at 20° and \( D_{\text{v,max}}/2 \pi = 71.6 \text{ kHz} \). Two of these images demonstrating excitations of 1.2 cm in diameter produced with the 1 ms “hard” pulse and the 1 ms BIR-4 pulse are shown in Fig. 9. Profiles through the catheter tip, at the level of the white line, show the recovery of signal near the catheter when the BIR-4 pulse is used.

Bloch equation simulations of the BIR-4 show that, at low power, below the adiabatic threshold, off-resonance effects may cause the tip angle to increase as power decreases, as shown in Fig. 10, potentially degrading the profile of the excitation. At lower tip angles, such as those used in fast imaging, excitations become more sensitive to these effects. Shortening the duration of the pulse, on the other hand, reduces the off-resonance sensitivity. When using the 1 ms BIR-4 pulses, off-resonance effects were negligible, while at pulse widths over 4 ms, insufficient shimming caused irregularities in the excitation profile at different positions along the catheter. In addition to reducing off-resonance effects, the shorter pulses also allowed the use of shorter TR values.

**REFERENCES**


