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A study of Quantification of Aortic Compliance in Mice using Radial Acquisition Phase Contrast MRI

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DOCTOR of PHILOSOPHY in the department of Physics of the college of Art and Science

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Abstract:

Spatiotemporal changes in blood flow velocity measured using Phase contrast Magnetic Resonance Imaging (MRI) can be used to quantify Pulse Wave Velocity (PWV) and Wall Shear Stress (WSS), well known indices of vessel compliance. A study was conducted to measure the PWV in the aortic arch in young healthy children using conventional phase contrast MRI and a post processing algorithm that automatically track the peak velocity in phase contrast images. It is shown that the PWV calculated using peak velocity-time data has less variability compared to that using mean velocity and flow.

Conventional MR data acquisition techniques lack both the spatial and temporal resolution needed to accurately calculate PWV and WSS in *in vivo* studies using transgenic animal models of arterial diseases. Radial k-space acquisition can improve both spatial and temporal resolution. A major part of this thesis was devoted to developing technology for Radial Phase Contrast Magnetic Resonance (RPCMR) cine imaging on a 7 Tesla Animal scanner. A pulse sequence with asymmetric radial k-space acquisition was designed and implemented. Software developed to reconstruct the RPCMR images include gridding, density compensation and centering of k-Space that corrects the image ghosting introduced by hardware response time. Image processing software was developed to automatically segment the vessel lumen and correct for phase offset due to eddy currents. Finally, *in vivo* and *ex vivo* aortic compliance measurements were conducted in a well-established mouse model for atherosclerosis: Apolipoprotein E-knockout (ApoE-KO). Using RPCMR technique, a significantly higher PWV value as well as a higher average WSS was detected among 9 months old ApoE-KO mice compare to in wild type mice. A follow up *ex-vivo* test of tissue elasticity confirmed the impaired distensibility of aortic arteries among ApoE-KO mice.
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## Contents:

Chapter 1 Introduction

1.1 Basic Concept of MRI

1.1.1 Spin in an external magnetic field

1.1.2 Spin-Lattice relaxation

1.1.3 Spin–Spin relaxation

1.1.4 Bloch Equation

1.2 MR sequences

1.2.5 Spatial Encoding

1.2.5.1 Slice Selection

1.2.5.2 Phase Encoding and Frequency Encoding

1.2.6 Typical MR Sequences

1.2.6.1 Spin Echo Sequence

1.2.6.2 Gradient Echo Sequence

1.2.6.3 Cine Sequence

1.2.7 T₁, T₂, T₂* and Proton Density weighted Sequence

1.3 MR Applications

2.1 Introduction

Chapter 2 The Arterial Structure and Function
2.1.1 The structure of the arterial wall ................................................................. 20
2.1.2 Mechanics of the large artery vascular wall ............................................... 21
2.2 Atherosclerosis ............................................................................................ 22
  2.2.1 Introduction ................................................................................................ 22
  2.2.2 The pathophysiological changes during atherosclerosis ......................... 23
    2.2.2.1 Endothelial function ............................................................................. 23
    2.2.2.2 Wall Shear Stress .............................................................................. 24
    2.2.2.3 Role of endothelial shear stress in endothelial gene expression .......... 25
    2.2.2.4 Role of low endothelial shear stress in the pathophysiology of
             atherosclerosis ...................................................................................... 25
  2.3 Arterial wall stiffening ................................................................................ 26
    2.3.1 The pathophysiological mechanism of arterial wall stiffening ............... 27
    2.3.2 Methods for measurement of arterial stiffness ....................................... 28
    2.3.3 Pulse pressure ....................................................................................... 28
    2.3.4 The measurement of pulse wave velocity .............................................. 29

Chapter 3 MRI in Arterial Disease diagnostic and Its Advantages ...................... 31
  3.1 MRI of Vascular Function .......................................................................... 31
  3.2 The measurement of PWV using Ultrasound .............................................. 32
  3.3 The measurement of PWV using MRI ....................................................... 34
    3.3.1 The measurement of PWV using MRI .................................................. 34
    3.3.2 Method 1, measure the PWV by the variation of the vessel cross-section area
                  34
    3.3.3 Method 2, 1-dimensional projection velocity method ............................ 35
Chapter 1 Introduction

Impaired arterial compliance characterized by raised pulse wave velocity (PWV) [1], low wall shear stress (WSS-the drag force of blood on the vessel wall) and oscillations in shear stress [2, 3] are early markers of atherosclerotic disease. With the increased use of small animal models to study the natural progression as well as the effects of therapeutic interventions in cardiovascular diseases, it is important to develop non-invasive techniques to measure vascular function in small animals. Although a number of studies have been performed in the past, very little effort has been devoted to methodological developments. Greve et al [4] combined cine flow images acquired from standard (rectilinear k-space acquisition) phase contrast (PC) magnetic resonance imaging with computational fluid dynamics to derive WSS in the mouse aorta. Hartley et al [5] used noninvasive Doppler ultrasound to measure aortic PWV in 13 month old Apolipoprotein E-knockout (ApoE KO) and wild-type (WT) mice. Wang et al measured the same with invasive techniques [6]. In both cases increased PWV was observed in the atherosclerotic ApoE KO mice. Considering that the R-R interval in mice is only about 120ms and that the mouse aorta is about 3cm in length, temporal resolution achieved with standard PC techniques is not sufficient to detect the pulse delay during its propagation along the aorta. Additionally in standard PC cine imaging, an increase in spatial resolution usually requires a longer scan time to compensate for the loss in signal to noise ratio (SNR). In this work, we implemented a radial PC MR imaging technique on a 7 Tesla animal scanner. We used asymmetric echo sampling to reduce the echo time and the repetition time. Combined with under sampling of k-space, this technique acquires higher temporal and spatial resolution flow images per given time
compared to standard PC techniques. We demonstrate the utility of this technique on an atherosclerotic mouse model (ApoE KO) by assessing the PWV and WSS in the descending aorta.

MRI has been one of the major medical diagnostic methods used during the past two decades. This method is relatively safe (low radiation) and highly sensitive to most soft tissues. New MRI applications are continuously being developed, including tumor targeting and fast imaging.

Cardiac cine MRI has served as the reference standard in measuring cardiac function, left ventricular volumes and myocardial mass for over a decade. The ability to image non-invasively in arbitrary planes and high tissue-blood contrast, and independent from geometric assumptions have all contributed to accurate and reproducible clinical MRI data. Recent advances in high-field magnets, high-performance gradient hardware and parallel acquisition methods have helped overcome long scan times that previously limited the application of MR in cardiac examinations.

In this chapter the basic concepts of MRI[7] are outlined and the typical MRI sequences used in my Ph.D. project are explained.

1.1 Basic Concept of MRI

1.1.1 Spin in an external magnetic field

MR signal is based on the interaction of proton spins and the external magnetic field. A spinning proton can be considered as a single magnetic dipole moment. As this dipole moment is placed in an external magnetic field, the dipole moment vector (spin orientation)
will not be fully aligned to the external field direction due to the thermal energy associated with body temperature. It will precess along the external field direction with a frequency calculated by equation

\[ \omega_0 = \gamma B_0 \]

Equation 1-1

where \( \gamma \) is gyromagnetic constant (in water, the constant is equal to \( 2.68 \times 10^8 \text{ rad/s/Tesla} \)) and \( B_0 \) is the external magnetic field.

At equilibrium, in ideal conditions, some of dipole moments will align with the external field \( B_0 \), either in the same direction or opposite direction according to the Boltzmann distribution, and have a net magnetization given by the equation

\[ M_0 = \frac{\rho_0 \gamma^2 h^2}{4kT} B_0 \]

Equation 1-2

where \( \rho_0 \) is the spin density, \( \hbar = h/2\pi \) in terms of Planck’s quantum constant \( h \) and \( k \) is the Boltzmann constant. This is the equilibrium state of the net magnetization of a spin voxel in an external magnetic field.

As mentioned, the MR signal is based on the interaction of proton spins and the external magnetic field. The interaction energy of a magnetic dipole \( \mu \) in any magnetic field \( B_0 \) is written quantum-mechanically as \( (-\mu \cdot B_0) \). This form of magnetic interaction is known as Zeeman interaction. The result of Zeeman interaction is the split of the energy state of a nucleus spin, as termed spin-up and spin-down. Therefore, a single proton spin can be excited to a higher energy level by absorbing a quantum of energy carried by electromagnetic radiation, or an RF pulse. When a large enough population of nuclei has been excited, the net magnetization is tilted for an angle \( \alpha \) from \( B_0 \) direction. The flipped angle \( \alpha \) can be calculated by equation

\[ \alpha = \gamma B_0 t \]

Equation 1-3
where $B_1$ denotes the RF pulse and $t$ is the duration of the pulse. When the RF pulse is turned off, the individual nuclei will start to release energy in the form of electromagnetic radiation, bringing the net magnetization back to the equilibrium status. This released energy is the MR signal collected through a nearby signal receiver. From a macroscopic point of view, when the RF pulse is turned off, the net magnetization relaxes and returns to its equilibrium state. Therefore, the MR signal can be regarded as the voltage induced by the relaxing net magnetization, and the signal receiver is exactly a Faraday coil.

However, spins do not accept all energy carried by the RF pulse. Energy will be accepted only when the quantum of energy carried by RF pulse equals the energy difference between the two split energy levels. Quantum-mechanically, the magnetic moment component along the external field can be written as

$$
\mu_z = \gamma m
$$

Equation 1-4

where $m=I, (I-1), (I-2), \ldots \ldots, -I$. For a proton, which is a spin $\frac{1}{2}$ particle, $m=\pm \frac{1}{2}$. The energy value given by this magnetic moment can be written as

$$
E = -\mu \cdot B = -\mu_z B_z = -\gamma m \hbar \omega_0
$$

Equation 1-5

![Figure 1-1](image)

**Figure 1-1** Two energy levels split as a result of Zeeman Interactions.

As shown in Figure 1-1, the energy difference $\Delta E$ between the two energy levels is $\hbar \omega_0$, where $\omega_0$ is the Larmor Frequency given by Equation 1-1. A proton can transit from lower
energy state to higher energy state (or the opposite way) by absorbing (or emitting) a quantum of energy of $h\omega$. From a macroscopic point of view, this absorption of energy from the RF pulse results in a tilt of the net magnetization of the voxel. RF pulses can be used to tilt the net magnetization by 90°, 180° or any value between 0° and 90°, depending on the amount of energy that is absorbed, as calculated by Equation 1-3.

1.1.2 Spin-Lattice relaxation

To illustrate the tilting of the net magnetization of a voxel due to an RF pulse, we can follow the example of a 90° pulse acting on a voxel. Before the pulse, the magnetization of the voxel is at its equilibrium state, with the longitudinal component (the component in the external field direction, usually z-axis) at its maximum, and the transverse component (the component in the plane perpendicular to the external field) at zero. After the pulse, the longitudinal component becomes zero and the transverse component shifts to its maximum. Following the absence of the RF pulse, however, the magnetization begins its return to its equilibrium state. The rate at which the longitudinal component recovers its equilibrium state is described as spin-lattice relaxation, also called $T_1$ relaxation. Mathematically, the recovery of longitudinal magnetization over time is given by

$$ M_z = M_z(0) \exp(-t/T_1) + M_0 (1 - \exp(-t/T_1)) $$

Equation 1-6

where $M_0$ is the net magnetization at equilibrium. The $T_1$ value varies, dependent on the type of human tissue and the strength of the $B_0$ field.

1.1.3 Spin–Spin relaxation
Similarly, the rate at which the transverse component reduces to zero is described as spin-spin relaxation. Mathematically, the reduction of the transverse component over time is given by

$$M_{xy}(t) = M_{xy}(0) \exp(-t/T_2)$$

Equation 1-7

where $M_{xy}(0)$ is the transverse magnetization immediately after the RF pulse. We call this decay mechanism internal relaxation.

In practice, there is another decay mechanism of the transverse magnetization, external relaxation. External relaxation is introduced by external field inhomogeneities. As shown in Figure 1-2, the field inhomogeneities lead to variations of precession frequencies among the spins. The individual spins tend to develop different phases in time, which reduce the net transverse component of the magnetization.

The total relaxation rate is the combination of internal relaxation and external relaxation. Here, we denote the contribution of external relaxation time as $T_2'$. So the total relaxation time $T_2^*$ is calculated by

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$

Equation 1-8

1.1.4 Bloch Equation
Bloch developed an equation from the macroscopic point of view to describe the motion of
the magnetization after the pulse is turned off. This equation is called the Bloch Equation.

\[
\frac{dM}{dt} = \gamma \mathbf{M} \times \mathbf{B}_{\text{ext}} + \frac{1}{T_1} (M_0 - M_z) \hat{z} - \frac{1}{T_2} M_\perp.
\]

**Equation 1-9**

To solve this equation in a constant external field case, \( B_{\text{ext}} = B_0 \hat{z} \)

\[
M_x(t) = e^{-t/T_2} (M_x(0) \cos \omega_0 t + M_y(0) \sin \omega_0 t)
\]

**Equation 1-10**

\[
M_y(t) = e^{-t/T_2} (M_y(0) \cos \omega_0 t - M_x(0) \sin \omega_0 t)
\]

**Equation 1-11**

\[
M_z(t) = M_z(0)e^{-t/T_1} + M_0 (1 - e^{-t/T_1})
\]

**Equation 1-12**

where \( \omega_0 \) is the precession frequency of the magnetization. By looking at the solution of the
Block Equation, we find the term with \( \cos \omega_0 t \) and \( \sin \omega_0 t \) are the phases introduced by
precession. These terms vanish in a rotating frame of reference with frequency \( \omega_0 \). When the
x-y plane is rotating at frequency \( \omega_0 \) around z-axis, the solution becomes

\[
M_x(t) = e^{-t/T_2} M_x(0)
\]

**Equation 1-13**

\[
M_y(t) = 0
\]

**Equation 1-14**

\[
M_z(t) = M_z(0)e^{-t/T_1} + M_0 (1 - e^{-t/T_1})
\]

**Equation 1-15**

Assuming immediately after the pulse, the magnetization is in x-z plane. Equation 1-13 and
Equation 1-15 are exactly describing spin-lattice relaxation and spin-spin relaxation. The
solutions can be written in the form of arrays

\[
\begin{pmatrix}
M_x(t) \\
M_y(t) \\
M_z(t)
\end{pmatrix}
= 
\begin{pmatrix}
e^{-t/T_2} & 0 & 0 \\
0 & e^{-t/T_2} & 0 \\
0 & 0 & e^{-t/T_1}
\end{pmatrix}
\begin{pmatrix}
M_x(0) \\
M_y(0) \\
M_z(0)
\end{pmatrix}
+
\begin{pmatrix}
0 \\
0 \\
M_0 (1 - e^{-t/T_1})
\end{pmatrix}
\]

**Equation 1-16**
1.2 **MR sequences**

1.2.5 **Spatial Encoding**

MR signals from the whole imaging slice are acquired together by the coil. To identify the different voxels, we need to uniquely label the signal of each individual voxel.

1.2.5.1 **Slice Selection**

![Figure 1-3](image)

*Figure 1-3* Only the spins located at $z = z_0 \pm \Delta z/2$ are excited. The thickness of the slice is dependent upon the bandwidth of the RF pulse after Fourier Transform.

In practice, given a 2-dimensional scan, we are only interested in the signal coming from a thin slice. Previously we discussed the properties of energy absorption of the spins, in that they only accept the quantum of energy equal to the energy difference between the split energy levels. If a magnetic field gradient is applied along the $B_0$ direction ($z$-direction), so that $B_0$ is now a function of $z$, $B_0(z) = B_0 + G_z z$. According to Equation 1-1, spins located at different positions along the $z$-axis will have different precession frequencies. When the spins are exposed to RF pulses with certain frequency $\omega_0$, only those located within the slice at $z = z_0$ are excited, therefore only signals from that slice are acquired. This process is shown in Figure 1-3.
1.2.5.2 Phase Encoding and Frequency Encoding

Phase encoding is acquired by applying gradient $G_y$ along the $y$-axis for a short period of time $\tau_y$ before data acquisition. Hence, at the beginning of a data acquisition set, the net magnetization of a single voxel enters a unique phase, $\gamma G_y y \tau_y$, depending on the $y$-position.

Frequency encoding requires applying gradient $G_x$ along the $x$-axis during the data acquisition. Precession frequency of the net magnetization in each voxel will change linearly along the $x$-axis. When one data point is taken at time $t$, magnetization at $x_0$ accumulates a phase of $\gamma G_x x_0 t$.

As a result of phase encoding and frequency encoding, each data point that represents the signal intensity at time $t_0$ can be calculated by equation

$$S(k_x, k_y) = \iint p(x, y) e^{-2\pi i (k_x x + k_y y)} \, dx \, dy$$

Equation 1-17

where $k_x = \gamma G_x t_u$ and $k_y = \gamma G_y \tau_y$. This equation is exactly the Fourier Transform equation, and since $S(k_x, k_y)$ is the signal physically detected by the receiving coil, we can easily vary
\[ \rho(x, y) = \frac{1}{2\pi} \int \int S(k_x, k_y) e^{i2\pi(k_xr + k_yi)} dk_x dk_y \]

Equation 1-18

In practice, however, \( k_x \) and \( k_y \) cannot be varied continuously, and discrete Fourier Transform must be introduced.

\[ S(k_x, k_y) = \sum_{n} \sum_{m} \rho(n, m)e^{-i2\pi(k_xn + k_ym)} \]

Equation 1-19

\[ \rho(n, m) = \frac{1}{2\pi} \sum_{k_x} \sum_{k_y} S(k_x, k_y)e^{i2\pi(k_xn + k_ym)} \]

Equation 1-20

Here, \( k_x \) and \( k_y \) are varied by a sequence of gradients in all necessary dimensions. As shown in Figure 1-4, the time period between the RF pulses of two neighboring slice selections is called a repetition period (TR). The phase encoding y-gradient is a series of horizontal lines to denote that it is being stepped regularly through increasing values during different repetition periods. Hence, different \( k_y \)s are set. Read x-gradient is turned on throughout the data acquisition window. As each data point is taken during different moments in the acquisition window, a unique \( k_x \) is set for each data point. The complete set of loops of such pulses and g radients are called pulse sequence, which is used to acquire k-space data.

1.2.6 Typical MR Sequences

1.2.6.1 Spin Echo Sequence

As shown in Figure 1-2, the ‘fan out’ of the transverse magnetization is dominated by \( T_2 \) effect. It is possible to recover the transverse magnetization, however, following the loss due
to external relaxation. Such recovery is referred to as an *echo*. The time period between the slice selection RF pulse and an echo is called *echo time (TE)*. However, the internal T₂ loss is not recoverable.

![Image](image.png)

**Figure 1-5**

The *spin echo sequence* is based on the application of two continuous RF pulses: a π/2 pulse, with respect to the x-axis (slice selection pulse), followed by a π pulse with respect to the y-axis (refocusing pulse). As shown in Figure 1-5a, immediately following the slice selection pulse, the transverse magnetization begins to fan out in a rotational frame, accumulating negative or positive phase depending on spatial location. For 0<t<Tₑ/2, assuming that the phase is zero at time 0,

\[
\phi(\vec{r}, t) = -\gamma \Delta B(\vec{r}) t
\]

Equation 1-21
Then at half $T_E$, a $\pi$ pulse is applied with respect to the $y$-axis. Immediately following this pulse, the positive phase, previously accumulated by the spins, turns negative, and vice versa. Equation 1-21 still valid, spins continue to develop phase based on their spatial location, which tends to cancel the phase that was just converted by the $\pi$ pulse, and at time $T_E$, the echo is formed.

### 1.2.6.2 Gradient Echo Sequence

A *gradient echo sequence* doesn’t include a second $\pi$ pulse, therefore it does not recover the lost external relaxation. The gradient echo sequence creates an echo by using a gradient lobe before data acquisition, spoiling the transverse component. Finally, the frequency encoding gradient also works to refocus the gradient to form the echo.

![Figure 1-6](image)

In Figure 1-6, the shaded negative gradient lobe has an area equal to that of the shaded positive lobe. As indicated by Equation 1-21, the areas of the lobes equal the phase that can be accumulated by the spins. Therefore when the positive gradient continues until complete cancellation of the negative gradient, the spins are refocused and an echo is created.
1.2.6.3 Cine Sequence

When an MR scanner acquires data, usually it does so on the k-space line in one excitation. For imaging a still object, this process continues until all k-space lines are acquired. Usually it takes seconds to finish one complete image. However, if the object changes its formation periodically, as in the case of imaging a human heart, the image will be significantly blurred. The solution is to break the k-space array into several parts. As shown in Figure 1-7, only a limited number of k-space lines are acquired within one cardiac cycle. This process only takes several dozen milliseconds, which is a small portion of the whole cardiac cycle. Therefore we can safely assume the imaging slice doesn’t move during imaging. Data acquisition for the same image starts at a fixed delay time following each peak of the ECG gating signal. The entire scan may record dozens of cardiac cycles, depending on the resolution of the image needed. By the end of the scan, we have a series of images from different moments during the cardiac cycle. This kind of sequence is called a cine sequence.
1.2.7 T<sub>1</sub>, T<sub>2</sub>, T<sub>2*</sub> and Proton Density weighted Sequence

T<sub>1</sub>, T<sub>2</sub> and proton density are intrinsic properties for different tissues. The contrast of an MR image is the result of a combination of these properties and other imaging parameters. In practice, it is necessary to get the maximum weight of one of the three properties in the signal intensity in order to get the best contrast of the image. This requires the optimization of the imaging parameter during the scan.

The signal from a spin echo sequence is given by

\[ S = \kappa p_0 (1 - e^{-TR/T_1}) e^{-TE/T_2} \]

Equation 1-22

The signal intensity depends on TE, TR, T<sub>1</sub>, T<sub>2</sub> and proton density. To minimize the influence of T<sub>2</sub>, we need to make the term \( e^{-TE/T_2} \) as close to 1 as possible, in other words, TE<<T<sub>2</sub>, and if TR~T<sub>1</sub>, this image is essentially T<sub>1</sub> weighted. On the other hand, if TR>>T<sub>1</sub>, TE<<T<sub>2</sub> (\( e^{-TR/T_1} \to 0, e^{-TE/T_2} \to 1 \)), this diminishes the importance of the difference between T<sub>1</sub> and T<sub>2</sub>, and this image is proton-density weighted. Finally, if TR>>T<sub>1</sub> and TE~T<sub>2</sub>, a T<sub>2</sub>-weighted image will be produced.

The signal from a gradient echo sequence is given by [1]

\[ S = \kappa p_0 e^{-TR/T_1} \sin \theta \left( \frac{1 - e^{-TR/T_1}}{1 - \cos \theta e^{-TR/T_1}} \right) \]

Equation 1-23

where \( \theta \) is the flip angle. Because the gradient echo sequence does not recover the external relaxation, T<sub>2*</sub> becomes more meaningful than T<sub>2</sub>. Similarly, if TE~T<sub>2*</sub>, TR>>T<sub>1</sub> gives a T<sub>2*</sub>-weighted image. If TE<< T<sub>2*</sub>, TR~T<sub>1</sub> gives a T<sub>1</sub>-weighted image. Finally, if TE<< T<sub>2*</sub>, TR>>T<sub>1</sub> gives a proton-density-weighted image.
1.3 MR Applications

1.3.1 Flow Compensation and Flow Quantification Using Phase Contrast MRI

Phase contrast mechanism is used to map the phase of the MR signal (transverse component), and flow quantification is one application of this mechanism. However, to explain flow quantification we have to discuss flow compensation first. As discussed previously, slice selection, phase encoding and frequency encoding need gradient sequences in all three directions. However, when flow exists within or through the imaging plane – i.e., there are magnetic moment vectors moving in or through the plane – and it only sees part of the gradient sequence by the time of data acquisition, the magnetization will develop extra phase because of this motion. We can use this phase to quantify the moving velocity of the vectors if the extra phase accumulation is repeatable at different repetition times. However, if the phase accumulation is not repeatable, it will eventually cause artifacts when Fourier Transform is applied to real space. Figure 1-8 is an example of flow artifact in phase-encoding direction.

To compensate for the extra phase developed by flow, a bipolar gradient is added before data acquisition. For example, to compensate the flow in x-direction, as shown in Figure 1-9, another gradient lobe is added to the read gradient (the frequency encoding gradient). The
dotted line in the plane diagram represents the phase of moving magnetic moments and the solid line represents stationary magnetic moments.

The velocity encoding is based on the flow compensation method. An extra bipolar pulse must be inserted prior to the flow compensation gradient. As shown in Figure 1-10, magnetic moment moving with constant velocity in the gradient direction will develop a phase

\[ \phi_{vz} = \mp \gamma G v \tau^2 \]

Equation 1-24

where the +/- denotes the fact that the phase changes sign if the negative lobe is applied first. According to Equation 1-24, the phase is proportional to the flow velocity of the spins. Obviously, the phase map we get from the reconstruction of the k-space array is also a flow velocity distribution map. Though the theory of measuring flow velocity from phase is straightforward, there are some practical difficulties to which attention must be given. The first one is error due to field inhomogeneity. The background phase is measured by sequence without the velocity encoding pulse, and subtracted from the velocity encoded phase image.

The second difficulty is that the phase developed by the bipolar pulse cannot exceed \( \pi \), otherwise it aliases back between \(-\pi\) and \(\pi\). Given this, the highest velocity that can be measured by the phase contrast method \( V_{\text{enc}} \), can be calculated by

\[ v_{\text{enc}} = \frac{\pi}{\gamma G_h \tau^2} \]

Equation 1-25
1.3.2 Introduction of Phase Contrast Radial Acquisition

In standard 2D Fourier MRI, data is collected in a raster-like fashion on a rectilinear grid in Fourier space (k-space) and images are reconstructed via a standard 2-dimensional (2D) Fast Fourier Transform (FFT) algorithm. Radial is an alternative data acquisition strategy in which data is collected along radial lines in k-space and images are reconstructed via either a filtered back-projection or re-gridding-type algorithm. The radial technique has unique features that can be advantageous for a number of MRI applications.
1.3.2.1 The advantages of Radial Acquisition

1.3.2.1.1 Shortened total scan time by using undersampled projection

Undersampled projection acquisition (radial acquisition) was first implemented by Rasche et al. to image joint motion using a sliding window reconstruction [8]. In radial acquisition, low spatial frequency data is acquired with a much higher density, in comparison to the higher spatial frequency data, as shown in Figure 5-2. As we know, the FOV in real space is inversely proportional to the k-space sampling interval. In the case of radial acquisition, two different sampling intervals are used: one in the radial direction, $\Delta k_r$, the other in the angle direction, $\Delta k_0$. We assume the sampling interval in radial direction, $\Delta k_r$, meets the criteria that the reconstructed image is alias-free. The sampling interval in angle direction is related to the sampling interval in radial direction as described in Equation 1-18.

$$\Delta k_0 = \frac{\pi \Delta k_r N_r}{2N_p}$$

Equation 1-26

$N_r$ is the number of sampling data points from k-zero to the edge of the outer region of k-space; $N_p$ is the number of projections. This equation assumes the projections rotate $2\pi$ around k-space center. By undersampling, fewer projections are acquired and $\Delta k_0$ increases and exceeds the limit for an alias-free image. Thus, an artifact-free image is only possible given a reduced FOV in the reconstructed image. The size of the reduced FOV ($rFOV$) is related to the number of projections according to Equation 1-19.

$$\frac{rFOV}{FOV} = \left(\frac{N_p}{N_r}\right) \cdot \frac{2}{\pi}$$

Equation 1-27

In real-space, an image reconstructed from undersampled radial acquired k-space shows well-reconstructed features within the rFOV. Radial streak artifacts appear only outside the rFOV, as shown in Figure 1-11.
1.3.2.1.2 Reduction of motion artifact

The 2D Cartesian method of k-space data acquisition uses data of uniform density throughout the plane, while the radial acquisition method over-samples the low spatial frequency data (k-space center region. In particular, motion artifact is due to either the phase shift of the object’s motion during TE, or to the amplitude perturbations resulting from through-plane motion. In both cases, the error is attributed to the low spatial frequency signal. With radial acquisition, however, over sampling of the k-space center achieves the same result as taking a signal average in this area, which is to reduce the creation of motion artifact.
Chapter 2 The Arterial Structure and Function

2.1 Introduction

There are two types of blood vessels that transport blood throughout the body. Vessels carrying blood away from the heart are called arteries; toward the heart, veins. Arteries include four different groups: elastic arteries, medium muscular arteries, small arteries and arterioles. All arteries carry oxygenated blood, except the pulmonary and umbilical arteries. These two blood vessels play a pivotal role in sustaining life, such as in the delivery of oxygen and nutrients to all human cells, the removal of carbon dioxide and waste products, maintenance of optimum pH in human cells, and so on. In this chapter, I will mainly introduce the structure, mechanics and pathophysiological changes of the arterial wall.

2.1.1 The structure of the arterial wall

Arteries usually consist of three layers. The outermost layer, called tunica externa or tunica adventitia, is composed of connective tissues. The middle layer, called tunica media or media, is made up of smooth muscle cells and elastic tissues. The innermost layer, called tunica intima, which is directly contacting the flow of blood and is composed of mainly endothelia cells. The hollow part of arteries is called lumen. Figure 2-1.
Figure 2-1  Structure of a medium-sized muscular artery

2.1.2 Mechanics of the large artery vascular wall

The arterial system is circulatory system with a very high pressure that provides a conduit for blood to reach different part of human body. However, due to the complicated structure of the cardiovascular system, the pressure and flow curves are not a simple ratio. Arterial blood flow is instead determined by blood pressure and other impedance factors of the vascular system. For example, the mechanic properties of the aortic artery walls play an important role in the transmission toward regional vascular beds of energy. As a reference, mechanical properties of the arterial wall were first characterized several decades ago. Mechanical parameters, in vivo and in vitro measurements are described and compared thoroughly in Mechanics of the large artery vascular wall [9], including compliance, distensibility, elasticity modulus, impedance, and pulse wave velocity [9].
2.2 Atherosclerosis

2.2.1 Introduction

Arterial stiffness has been acknowledged as an very important factor of cardiovascular risk [10]. There are multiple reasons that can cause arterial stiffness, among which, there are two major types of modifications that can be observed on the vascular wall: atheromatous plaque formation (atherosclerosis) and increase of wall thickness, stiffening, (arterioclerosis). Atherosclerosis is considered to be one of the common types of arteriosclerosis diseases in which the medium or larger arterial wall thickens and loses its elasticity. The common effects triggered by atherosclerosis include heart attack, stroke or even death. Atherosclerosis is possibly caused by the accumulation of various forms of atheromatous plaque, such as fatty acids, cholesterols, cellular waste products, calcium and other substances in the insides of an artery. Gradually, plaque becomes harder and harder, narrowing the arteries and leading to a decrease of the flow of blood to other parts of the body Figure 2-2.

Detailed research on atherosclerosis has shown that it is derived from low-density lipoprotein cholesterol (LDL). This lipoprotein enters through the arterial wall and is oxidized by oxygen free radicals [11]. White blood cells attempt to absorb the oxidized-LDL, but when white blood cells are dysfunctional or unable to process the oxidized-LDL, the oxidized cholesterol is able to get into the artery wall. This leads to more white blood cells and the cycle continues. Finally, the artery becomes inflamed and the cholesterol plaque causes the muscle cells to harden over the affected area. The plaque narrows the circumference of the lumen, which decreases blood flow and increases blood pressure. Other research has shown that atherosclerosis may also be caused by an infection of the vascular smooth muscle cells [12, 13]. The exact mechanisms of atheromatous plaque formation also have been studied extensively at the cellular and molecular level [14, 15], yielding the important discovery that the role of sequential divisions of smooth muscle cells (SMCs) leads to a change in their
phenotype and an increased capacity for the synthesis of extracellular matrix components, which is an important factor of atheromatous plaque progress [16].

Unlike atherosclerosis, arteriosclerosis is caused by any other increase of thickness and stiffness in medium and large arteries.

2.2.2 The pathophysiological changes during atherosclerosis

2.2.2.1 Endothelial function

Endothelial cells are the thin layer of cells that cover the interior surface of arterial wall, forming an interface between circulating blood in the lumen and the rest of the vessel wall. Endothelial cells line the entire circulatory system and reduce friction of the flow of blood, allowing blood to be pumped more efficiently. Research has shown that endothelial cells are
involved in many aspects of vascular biology, such as vasoconstriction and vasodilation, which affect blood pressure, blood clotting, atherosclerosis, etc. Endothelial cells can be found in any part of the vascular tree, in large or small veins and arteries. Atherosclerosis is a chronic, inflammatory, fibroproliferative disease primarily of large and medium sized conduit arteries [17]. The distribution of atherosclerosis is multifocal and heterogeneous. For instance, multiple atherosclerotic lesions can co-occur at different stages of progression in the same artery at a single point in time [18, 19].

2.2.2.2 Wall Shear Stress

Wall shear stress expresses the force per unit area exerted by the endothelial surface of the arterial wall on the fluid in a direction on the local tangent plane during the arterial blood flow. The distribution of wall shear stress is more and more important because emerging evidence demonstrates that increased wall shear stress is associated with vascular disease, especially atherosclerosis [20-24]. The exact implications of changes in shear stress remain unknown, but different disturbances of the laminar velocity pattern have been classified with regard to the degree and localization of atherosclerosis: low shear stress [25], low and oscillating shear stress[26].

Endothelial shear pattern is used to characterize the direction and magnitude of arterial blood flow. It is determined by the pulsatile nature of the blood flow and unidirectional with a magnitude that varies within a range of 15-70 dyne/cm² over the cardiac cycle, yielding a positive time-average. Unlike in straight arterial segments, the endothelial shear stress in coronary arteries is determined by the pulsatile in combination with the blood’s rheological properties, as well as by the complex geometric configuration of the arteries [27, 28]. In irregular areas, low or oscillatory endothelial shear stress is produced. It is unidirectional at any given point, with a fluctuating magnitude during the cardiac cycle (<10-12 dyne/cm²). Low endothelial shear stress usually occurs at the inner areas of curvatures, as well as
upstream of stenoses [29]. Oscillatory endothelial shear stress is characterized by significant changes bi-directionally and according to the magnitude of difference between systole and diastole, leading to a very low time-average, usually close to zero. Oscillatory endothelial shear stress occurs primarily downstream of stenoses [30, 31].

2.2.2.3 Role of endothelial shear stress in endothelial gene expression

Endothelial cells could be able to be stimulated by the local endothelial shear stress through several types of mechanoreceptors that are located in the luminal, junctional and basal endothelial surfaces [23, 32]. Following such stimulation, a complex network of intracellular pathways is activated, known as mechanotransduction. [23, 33]. Eventually, that activation will trigger phosphorylation of transcription factors which in turn bind positive or negative shear stress responsive elements at promoter regions of mechanosensitive genes. Gene expression will be induced or suppressed, leading to changes in cellular morphology [34]. In straight arterial regions, in which flow is not disturbed, endothelial cells express a variety of atheroprotective genes, and suppress several pro-atherogenic genes, resulting in stability and quiescence in those areas. In the regions with low or disturbed flow, the atheroprotective genes are suppressed, while the pro-atherogenic genes are upregulated, promoting the atherosclerotic process [35, 36].

2.2.2.4 Role of low endothelial shear stress in the pathophysiology of atherosclerosis

In arterial regions with disturbed flow, endothelial shear stress reduces the availability of nitric oxide through regulation at the RNA and protein levels. Endothelin-1 is a potent vasoconstrictive and mitogenic molecule that plays a negative role in endothelial function. During atherosclerosis, endothelial shear stress also increases the uptake and synthesis of low-density lipoprotein-cholesterol. The high accumulation of low-density lipoprotein
cholesterol in turn promotes the widening of the junctions between endothelial cells, therefore, increasing the deposition of LDL-cholesterol. Reactive oxidative species can be produced by endothelial shear stress through the regulation of transcriptional and post-transcriptional activity of major enzymes on endothelial cell membranes [37]. Endothelial shear stress can also decrease the intracellular reactive oxygen species (ROS) scavengers, which further promotes local oxidative stress [38].

Nuclear factor-kB (NF-kB) is also an essential variable affecting endothelial shear stress in the pathophysiology of atherosclerosis. Endothelial shear stress up-regulates the expression of several adhesion molecules following the activation of NF-kB. Adhesion molecules mediate the rolling and adhesion of circulating leukocytes on the endothelial surface.

The internal elastic lamina (IEL) separates the diseased intima from the media and then forms fibroatheromas. Breaks in the IEL create a gateway for vascular smooth muscle cells to enter the intima. Endothelial shear stress stimulates vascular smooth muscle cell migration to the intima by enhancing the endothelial gene and protein expression. Neovascularization also plays an important role in determining the natural history of atherosclerosis. Inhibition of neovascularization prevents the progression of atheroclerotic lesions [38]. Endothelial shear stress promotes intimal neovascularization by inducing intimal thickening.

2.3 Arterial wall stiffening

Arterial stiffness has recently been recognized as an important cardiovascular risk marker. It is a dynamic parameter that can be controlled by vascular contraction and other factors. In particular, endothelial cells play an important role in the functional regulation of arterial stiffness.
2.3.1 The pathophysiological mechanism of arterial wall stiffening

Arterial stiffness is a term used to define an artery’s capacity to expand and contract during the cardiac cycle.

The stiffness, or rigidity, of the arterial wall has been recognized for several centuries. Arterial wall stiffening has been proposed to be an important determinant of cardiovascular risk [39]. Pathophysiologically, arterial stiffening is based on dys-regulation of the balance between collagen and elastin towards excessive elastin breakdown and overproduction of abnormal collagen [40]. The imbalance between collagen and elastin mainly is caused by the population of the matrix producing vascular smooth muscle cells, and the activity of the matrix degrading proteases such as matrix metalloproteinases (MMPs) [41]. For those factors, in some way, elastolysis prevails against collagenolysis, and then decreases the elastin content of the wall, and gradually promotes arterial stiffening [40]. Endothelial damage or dysfunction, such as the quantification of circulating endothelial cells, leads to the increased arterial stiffness of arteries [42].

The association of endothelial dysfunction and arterial stiffening in the early stages of atherosclerosis shows that vessel distensibility can be used as an early marker of endothelial dysfunction, and possibly as a predictor of future atherosclerosis [10]. Some other factors, such as the existing wall material, by arterial smooth muscle, may also contribute to arterial stiffness [43]. Mediators involved in arterial wall stiffness have not been determined. But factors such as nitric oxide (NO) [44] and endothelin (ET) have been investigated and characterized.

Insulin, a hormone with wide effects on human metabolism, has also been shown to be associated with arterial stiffness. Westerbacka [45] demonstrated that high physiological concentrations of insulin diminish large artery stiffness in a short time in nondiabetic men. Given this finding, the resistance of large arteries to stiffness becomes another facet of insulin resistance that could strengthen the association between insulin resistance and
cardiovascular disease. Growth hormone deficiency (GHD) also was reported to be associated with endothelial dysfunction and increased large-artery stiffness [46]. Hypertension and smoking are also important factors affecting arterial stiffness [47, 48]. Taken together, arterial stiffness is not only determined by the structure of the extracellular matrix, but by endothelial cell function and vascular smooth muscle cell tone as well. The latter variable is affected by a number of factors, such as shear mechanical stress and the paracrine mediators angiotensin II, endothelin and NO [49].

2.3.2 Methods for measurement of arterial stiffness

It has been known that the characteristics of the arterial pulse change with age. Assessment of the arterial pulse is an important factor in the clinical examination of the patient. The first method used in assessing arterial pulse was the sphygmograph, which registered the arterial waveform. Later, the mercury sphygmomanometer was developed by Riva-Rocci and focused on the absolute systolic and diastolic blood pressure. The newly developed non-invasive methods, such as the Pulse Wave Velocity (PWV) and Arterial Stiffness Index (ASI) measurement, are derived from the blood pressure, pulse and ECG waves. These novel techniques provide simple, time-saving ways to evaluate arterial stiffness with clinical significance and accuracy. Here, I will focus on pulse wave velocity. Most factors involved in arterial stiffness are measured by pulse wave velocity. In Figure 2-3, a schema shows the experimental preparation with pulse wave velocity. Arterial stiffness was determined directly by the measurement of the pulse wave velocity intravascularly [50].

2.3.3 Pulse pressure

Before measuring pulse wave velocity, pulse pressure should be defined. Pulse pressure is the difference between systolic and diastolic blood pressure and is the consequence of cardiac contraction. It is strongly influenced by the properties of the arterial trees [51]. Since
the pulse pressure is primarily determined by cardiac output, aortic and large artery stiffness and pulse wave reflection, it is an important marker for arterial stiffness.

2.3.4 The measurement of pulse wave velocity

Pulse wave velocity is used as an indicator of arterial stiffness. It refers to the speed at which the blood pressure pulse travels from the heart to the peripheral artery following contraction. The methods commonly used to determine pulse wave velocity include: ECG-gated tonometry, ultrasound and Doppler. Given that pulse wave velocity increases with stiffness of the arteries, it is a well established technique for measuring arterial stiffness between two locations in the arterial system. More commonly, pulse wave velocity is measured between the carotid and femoral peripheral artery sites in order to provide a measure of aortic stiffness. This aortic pulse wave velocity can increase dramatically when coupled with age, diseases and other factors.
To assess arterial stiffness using aortic pulse wave velocity, aortic pulse wave velocity is calculated as distance/transit time (in centimeters per second) of the pulse wave. The pulse waves at each site (the carotid and femoral peripheral arteries) are measured by a tonometric sensor. Pulse transit time is determined by the average of 10 consecutive beats. The distance traveled by the pulse wave is determined by the participant’s torso.

The association between wall stiffness and PWV is calculated via the Moens-Kortweg formula, the equation being as follows: $PWV = (Eh/2uR)^{1/2}$, where $E$ is Young’s Modulus of the arterial wall, $h$ is wall thickness, $R$ is arterial radius at end-diastole and $u$ is blood density. From this equation, PWV is proportional to the square root of the elastic modulus. A change in PWV is not a particularly sensitive measure of change in physical arterial properties [52, 53]. Recently, ultrasound technology (using a wall echo-tracking device) has been developed to track the changes in arterial diameter following an observed change in pulse pressure. This was applied to the study of the elasticity of the walls of the major peripheral arteries in humans [54], and to measure the elastic properties of the wall of the rat carotid artery [55] and aorta [56]. This method can provide useful values for the elastic modulus [57].

As mentioned above, pulse wave velocity is used as an index for vascular stiffness and is valuable for the diagnosis of atherosclerosis. Age is the most important factor contributing to an increase in pulse wave velocity. However, position is also an important factor. For instance, pulse pressure varies across the entire arterial system because of the differences in vessel stiffness and the phenomenon of wave reflection. Usually, pulse pressure in the central arteries is a better predictor of left ventricular mass and carotid-intima thickness than is the peripheral pulse [58].

Therefore, assessment of pulse wave velocity is relatively simple and the method has been widely applied and found to be both robust and reproducible. It is also very promising to see that aortic pulse wave velocity is a powerful independent predictor of mortality in diabetic and elderly population samples.
Chapter 3 MRI in Arterial Disease diagnostic and Its Advantages

3.1 MRI of Vascular Function

One non-invasive measure of arterial compliance is pulse wave velocity (PWV). Aortic PWV > 13 m/s is a particularly strong predictor of cardiovascular mortality in hypertension[58]. By measuring aortic PWV using Doppler flow recordings, previous studies have independently predicted mortality in patients with end-stage renal disease (ESRD) [59, 60]. The benefit associated with blood pressure control in ESRD, either by adjustment of dry weight or the use of anti-hypertensives, was also independently related to change in aortic PWV, such that a reduction in PWV of 1 m/s was associated with a relative risk of 0.71 for all-cause mortality[60].

Functional assessments of blood vessels provide important prognostic and therapeutic information beyond that provided by traditional blood pressure measurements. It is well known that the compliance of large arteries diminishes with age and disease[61]. Raised PWV, a measure of arterial stiffness, occurs with a range of established cardiovascular risk factors[62], including hypercholesterolemia[63], type II diabetes[64] and a sedentary lifestyle[65]. A recent study suggests that abnormalities in the pulsatile characteristics of arteries occur early in the disease processes associated with increased cardiovascular risk[1]. It has also been suggested that low wall shear stress (WSS) – the drag force of blood on the vessel wall – and oscillations in shear stress can cause localization of atherosclerotic lesions in the carotid bifurcation, coronary arteries and aorta[66, 67]. In contrast, elevated flow and WSS induce direct structural changes resulting in inhibition of atherosclerosis[67]. Such evidence
suggests that WSS is an important marker of early atherosclerosis disease[2, 68]. Furthermore, the relationship between WSS and the development of atherosclerosis has been studied using wall WSS values derived in vivo from phase-contrast MR imaging, pulse Doppler sonography and quantitative arteriography.

### 3.2 The measurement of PWV using Ultrasound

PWV can be measured both invasively and non-invasively by Ultrasonic probes. In the work of Wang et al [5], PWV was measured among a group of ApoE-KO mice and a controlled wild mice group. In order to measure PWV in the mice, two pressure transducers were placed at the aortic arch and abdominal aorta respectively, via surgery. The distance along the abdominal aorta between the two transducers was measured at the same time. To reliably measure PWV, the arterial path length must be determined accurately. The pressure waves from both transducers were recorded simultaneously for at least 30 minutes. The propagation time for the pulse wave moving from the aortic arch to the abdominal aorta was measured by the time delay between the upstrokes of each pressure wave front. The average of the time delay was taken from at least 10 consecutive cardiac cycles. The ratio of the distance between both transducers and the delay time of the pressure wave is the abdominal aorta PWV in mice.

The advantages of this method are two-fold. Firstly, it has a very high temporal resolution. Samples were acquired at a rate of 1000 Hz, which can be further improved because the transducers that were used in this experiment had a frequency response from 0 to 10000 Hz. Secondly, the length between both transducers was able to be measured precisely. The disadvantage for this method is that the measurement is taken invasively, so that observing the change of PWV in the blood vessels over the course of development of diseases is not possible.
In a slightly later work published by Hartley et al [5], the PWV was measured non-invasively using Ultrasonic probes. The data acquisition and analysis were similar to the previous work, however, instead of surgically placing the probe inside the mouse body, the transducers were placed on the animal surface. The distance between the two measuring position was acquired by taking the straight distance between the two marked places where the flow velocities were measured. This estimation of distance ignored the internal geometry of the abdominal aorta, however, and introduced significant error in PWV measurement.

Figure 3-1 shows the data acquisition and calculation of PWV measurement in mouse abdominal aorta using invasive methods.

**Figure 3-1.** Velocity/Pressure measurements are suppose to be made at aortic arch and descending aorta. The delay of upstroke(foot) between the velocity/pressure waves at both positions is going to be measured. PWV is calculated by dividing the separation distance by the pulse delay.
3.3 The measurement of PWV using MRI

3.3.1 The measurement of PWV using MRI

As introduced in 1.2.6.3 and 1.3, MR Phase Contrast Cine Imaging can acquire images with great soft tissue contrast as well as blood flow information as a function of time during one cardiac cycles. Typically, the PWV is defined as how fast the pressure wave travels along the blood vessel. This physical property can be transferred to either how dramatic the vessel lumen area change during the cardiac cycle[69], or how fast the pulsatile flow profile travels along the vessel, this makes it possible to utilize MR Cine imaging in calculating PWV.

3.3.2 Method 1, measure the PWV by the variation of the vessel cross-section area

This method[69] of calculating the PWV is based on one assumption: during early systole, aortic pressure and flow waves do not contain reflection waves, hence the early systole is unidirectional and reflectionless. For a unidirectional wave, the ratio between pressure variation ($\Delta P$) and flow variation ($\Delta Q$) is equal to the characteristic impedance $Z_c$:

$$Z_c = \frac{\Delta P}{\Delta Q}$$  \hspace{1cm} \text{Equation 3-1}

By definition, the local area compliance ($C_A$) is given by

$$C_A = \frac{\Delta A}{\Delta P}$$  \hspace{1cm} \text{Equation 3-2}

where $\Delta A$ is the variation of the vessel cross-section area. Given the formula

$$Z_c = \sqrt{\frac{\rho}{A C_A}}$$  \hspace{1cm} \text{Equation 3-3}

where $\rho$ is the blood density and $A$ is the vessel cross sectional area at the diastole, eliminating $\Delta P$ from all above equations, we have

$$C_A = \left(\frac{\Delta A}{\Delta Q}\right)^2 \frac{A}{\rho}$$
Equation 3-4

\[ C_A \text{ is related to } PWV \text{ by} \]
\[ PWV = \frac{A}{\rho C_A} \]

Equation 3-5

Therefore,
\[ PWV = \frac{\Delta Q}{\Delta A} \]

Equation 3-6

In this method, it is not necessary to measure the length of the blood vessel, hence eliminating the possible introduction of errors due to such measurements. The accuracy of this PWV measurement does, however, rely on the accuracy of measuring the cross-section of the blood vessel. Since it is assumed that the wave is unidirectional, the flow has to be measured at some positions a certain distance away from any blood vessel bifurcation. In the case of the abdominal aorta, measurements must be taken close to the aortic arch. At the aortic arch, the blood flow is extremely fast and complicated, which can easily create flow artifact in MRI and reduce the measurement precision.

3.3.3 Method 2, 1-dimensional projection velocity method

A brief summary of this method,[70] the raw data is not reconstructed into conventional MR images, but instead is analyzed as a time-resolved sequence of 1-dimensional (1D) spectra.
In this sequence, one axial slice is excited by each RF pulse. After adjusting for slice selection gradient, the frequency encoding gradient is turned on in the same direction as the slice selection. This same frequency encoding gradient also acts as the slice selection gradient for the next repetition period. In this system, each RF pulse excites a certain amount of blood, this same amount of blood then moves in the direction of the frequency encoding gradient, and the flow velocity is encoded. After 1D Fourier Transformation, the flow velocity can be calculated based on the phase of the real space data. Data from two separate positions along the blood vessel are analyzed. The distance between the two positions, divided by the delay of the arriving of the wave pulse, gives the PWV.

In this method, the temporal resolution of the measurement is significantly increased by eliminating the unnecessary gradients. However, the increase is gained by sacrificing any 2-dimensional (2D) flow pattern information. Furthermore, this method requires that the flow of information inside the excited axial slice be as simple as possible, so that there can be no more than two blood vessels traveling through a slice.
3.3.4 Method 3, measure PWV using MR tagging

In comparison with the previous method, this method[71] excites a slice perpendicular to the blood flow direction in each repetition period. As show in Figure 3-3, A column of blood within a specific blood vessel is tagged using the combination of a SPAMM (SPAtial Modulation of Magnetization) excitation and a 2D-selective excitation, followed by a series of 1D projections (same as method 2) along the blood flow direction that provided the measurement of blood displacement. By exciting only the amount of blood inside the chosen blood vessel, more complicated flow information in the entire imaging slice does not compromise the resulting PWV measurement. However, this method requires that the segment of blood vessel through which the tagged blood travels, during the series of 1D projections, is fairly long and straight.
3.3.5 Method 4, measure PWV using phase contrast MRI

Phase contrast MRI can measure the 2D flow pattern through an imaging slice. To measure PWV using phase contrast MRI[72], multiple imaging slices are chosen along the blood vessel and 2D flow is measured at each image slice. The arrival of the wave pulse is determined with respect to the ECG signal. The positions of all slices along the blood vessel are plotted against the arriving moments of the wave pulse. The curve is fitted using a linear model, the slope of which gives the PWV. The most commonly picked imaging slice position is at the aortic arch, as shown in Figure 3-4 [73], so that the flows in both the ascending and descending aortas are measured simultaneously, eliminating the error of the variation of ECG signal. The strategy of imaging multiple slices along the descending aorta is also popular because having multiple points to plot in the fitting of the linear model can significantly reduce the systematic error.

Figure 3-3. Sequence diagram of MR tagging combined with 1D projection for blood flow measurement.
3.4 The Measurement of WSS using MRI

In nonpulsatile flow in a straight vessel, fluid does not move at the same velocity at every point in the vessel. Instead, fluid flow is fastest at the center and slowest close to the vessel wall. The fluid velocities assume a parabolic profile referred to as the laminar flow profile. This pattern of flow is the result of friction with the vessel wall and is related to the fluid viscosity. This friction creates a tangential force on the surface of the vessel and is referred to as the wall shear stress (WSS). The pattern of blood flow is much more complex in vivo, where the flow is pulsatile and the curvature of the blood vessel may change the flow dynamics. Thus, the WSS could be linked to the pathogenesis of atherosclerosis. Vessel segments with low WSS or highly oscillatory wall shear stress appear to be at the highest risk for development of atherosclerosis. Multiple methods have been used to measure WSS in vivo[2].

3.4.1 Method 1, Measure WSS using ultrasound probe and Hagen-Poiseuille formula

In the study of Sho et al [74] and Guzman et al [75], ultrasound probe and Hagen-Poiseuille formula were used to calculate the WSS in abdominal aortas of mice. For a Newtonian fluid, shear stresses can be derived from the gradient of velocity field distribution and the blood
viscosity. In the studies mentioned above, the mean blood flow was measured using ultrasound probe, and it was assumed that the flow was ideal parabolic flow. Under this assumption, the Hagen-Poiseuille formula Equation 3-7 is valid where $\tau_{mean}$ is the temporal and spatial average shear stress, $Q$ is the total volume flow, $R$ is the lumen radius and $\mu$ is the dynamic viscosity of blood.

$$\tau_{mean} = \frac{4 \mu Q}{\pi R^3}$$

Equation 3-7

There are several limitations of this model in vivo. First, this method does not capture the spatial variations in shear stress; second, the parabolic flow was assumed. Parabolic flow requires the lumen to be nearly circular or elliptical. However, in practice, it is preferable to measure WSS at positions where plaques are most likely to be deposited. Where plaque exists, the vessel lumen is no longer nearly circle or elliptical. Finally, blood flow in vivo is very complicated and hard to predict, and the assumption of parabolic flow may significantly reduce the accuracy of WSS measurement. For example, in pulsatile flow, the flow is never fully developed and will not have a parabolic profile during much of the cardiac cycle.

### 3.4.2 Method 2, Measure WSS using Lagrangian interpolation functions

In Cheng et al’s study [76], a method using Lagrangian interpolation functions to calculate WSS was developed. This model is built on the information of the 2D flow pattern of the blood, MRI is bay far the only non-invasive imaging technique that can provide this information. In this method, it is assumed that the blood is an Newtonian Fluid, the total stress of which on the vessel wall can be calculated by equation

$$\overline{\sigma} = -pI + 2\mu D = -pI + \mu [\nabla u + (\nabla u)^T]$$

Equation 3-8
where \( p \) is the pressure, \( I \) is the identity matrix, \( \mu \) is the viscosity, \( D \) is the rate of deformation tensor and \( \nabla u \) is the velocity gradient. The traction vector is defined as \( t = \sigma n_s \) where \( n_s \) is the regional normal vector. The tractor vector can be decomposed into normal and tangential components. When we subtract out the normal component, the left side of the equation is called *surface traction vector* \( t_s \).

\[
t_s = t - (t \cdot n_s)n_s
\]

**Equation 3-9**

This surface traction vector is defined as the WSS, \( \tau_w \). We can further assume that when the blood vessel is long enough and the flow is only in \( z \) direction, so that the normal unit vector \( n_s \) is in \( x-y \) plane, the equation to calculate the WSS can be simplified as

\[
\tau_w(x, y) = \mu[\nabla u_z(x, y) \cdot n_s(x, y)]
\]

**Equation 3-10**

According to Equation 3-10, to calculate WSS, the velocity gradient has to be obtained first. A 2D flow pattern with 16 nodes is created for each pixel within the vessel area along the vessel boundary. The velocity value for each node is calculated from interpolation of the velocity values of the surrounding image pixels. Once the nodal velocity values are assigned, the velocity value for the pixel is given by

\[
u_x = \sum_{i=1}^{16} N_i(x, y) \cdot v_i
\]

**Equation 3-11**

where \( N_i \) are the cubic Lagrange polynomial shape functions and \( v_i \) are the nodal velocities. Then the velocity gradient is calculated by

\[
\nabla u_z(x, y) = \sum_{i=1}^{16} \left[ N_{i,x}(x, y) \cdot v_i \right] \nabla \left[ N_{i,y}(x, y) \cdot v_i \right]
\]

**Equation 3-12**

where \( N_{ix} \) and \( N_{iy} \) are the derivatives of \( N_i \) with respect to \( x \) and \( y \).
In this method, the spatial resolution of the 2-D flow pattern is very important for the accuracy of the calculation. In Cheng’s paper, the influence of the spatial resolution was evaluated. As shown in Figure 3-5.

![Figure 3-5. Time dependent WSS averaged over the lumen for increasing image resolutions (This is the same graph from the reference with the authorization from the author [76]).](image)

In this phantom experiment, average WSS over the lumen was measured for the same flow phantom at different image resolutions. The number of pixels across the lumen area increased from 20 pixels to 65 pixels. The WSS value significantly differs with such variation of the imaging resolution.

The method developed by Cheng [76] is accurate and without any assumption of the flow pattern. However, when performing the same measurement in small animals, current MR techniques lack enough spatial resolution to accurately calculate WSS. In Greve et al’s [4] work, Computational Fluid Dynamic (CFD) simulation was used to achieve high enough spatial resolution for the calculation of WSS. In a recent work by Fukui et al [77], it was
shown that the axial wall motion reduces the relative speed of the blood, and further reduces WSS by up to 15%. The largest effect of wall motion occurs when the axial and elastic waves coincide, which can reduce the WSS by 30%. This study shows, therefore, that CFD is not necessarily suitable for improving the spatial resolution in WSS measurements.

3.5 Summary

Several approaches have been developed to measure PWV and WSS accurately in vivo. The most popular methods used now to measure PWV and WSS all require a 2D flow pattern at the cross section of the vessel lumen. To perform these measurements and make accurate calculations of PWV and WSS in small animals, both temporal and spatial resolution must be improved.
Chapter 4 Aortic PWV quantification in Children Using Peak Velocity

4.1 Introduction

In the standard 2-D cine flow technique\[7\], phase contrast cine flow images are obtained at several locations along the aorta. The velocity is encoded in the through plane direction. The PWV is calculated as the ratio of length along the aorta (D) to the time interval (ΔT) between the arrivals of the pulse wave at different planes, \( \text{PWV} = \frac{D}{\Delta T} \). Conventionally, \( \Delta T \) is the time lag between mean velocity time curves of the respective locations along the aorta measured at the half maximum velocity.

The mean velocity at a given time point is the average velocity of all pixels within the aortic lumen derived from the cine flow images. By representing the ante grade flow by the mean velocity it is implied that all pixels within the lumen simultaneously “feel” the passage of the pulse wave (i.e. all pixels within the lumen accelerate and decelerate equally as the pulse wave passes the axial slice). However numerous investigations on the flow distribution in the aortic arch contradict this assumption. As shown in previous studies,\[78-81\] in the aorta and other largely curved vessels, in early systole ante grade flow develops a skewed profile, with higher velocities closer to the inner curvature of the aorta. As blood accelerates, the peak ante grade flow migrates towards the outer curvature while slow secondary flow move towards the inner curvature. This give rises to local retrograde flow in the distal arch during mid to late systole as the net flow is interrupted. It is also clear from these studies that the ante grade
pulse wave is localized in the lumen in a time dependent manner. Therefore the *mean velocity* of all pixels within the lumen as a function of time does not accurately characterize the passage of the pulse wave, in the aortic arch. Since determination of ΔT relies on the shape of the velocity-time curve, inaccurate representation of the pulse wave dynamics leads to unreliable PWV measurements.

To improve the accuracy of PWV estimation from MRI flow data, I developed an algorithm to selectively map the pulse wave in time and space using an automated, *peak velocity* tracking technique on phase contrast cine images. The *peak velocity-time* curves were subsequently used to derive the time interval, ΔT. Additionally, software was developed to automatically calculate the distance (D) along the aorta between two scan planes from user-defined lumen edges and to find the time interval (ΔT) at the half maximum velocity using velocity–time curves. The new technique was assessed in a group (n=30) of young healthy children aged between 5 to 10 years. The results were compared with that of traditional method of measuring the time interval i.e. by using the *mean velocity-time* curve and the *mean flow-time* curve.

### 4.2 MATERIALS AND METHODS

30 healthy children of age between 5-10 years (mean age=7.3 years, 15 boys, 15 Girls) were studied after the project was approved by the institutional review board. A written consent was obtained from one of the parents after the child assented to the study. This study was part of a larger study designed to assess the cardiac function of healthy children which included cine imaging of the left ventricle, myocardial tagging, flow imaging etc. Imaging was performed on a 3T scanner (Trio, Siemens, Erlangen, Germany). Studies were done with no sedation. First, TrueFISP images were acquired in a double oblique plane (long axis view) that visualized the greatest portion of the ascending and the descending aorta. Second, a phase contrast (PC) cine MRI was performed in a plane perpendicular to the long axis view.
Figure 4-1a) depicting both the ascending and the descending aorta using a velocity encoded segmented FLASH cine sequence. PC MRI parameters were: Minimum Venc = 150 cm/sec, number of segments=3, TE/TR=4.8/7.5, slice=6mm, flip=15, Matrix size = 256 x 160, in plane resolution=1.1x1.1 mm. The Venc value was raised when necessary. Twenty two phase images were reconstructed with prospective gating with an average temporal resolution of 29ms. Phase and magnitude DICOM images were transferred to a remote workstation for post processing. Post processing was done using software developed in house using the IDL (ITT visual information solutions, Boulder, CO) environment.

Eddy current induced fields and concomitant fields can result in spatially dependent phase off-set errors in phase contrast images[82]. These errors are evident in the stationary tissue as a non zero phase. By fitting a surface to a collection of ROIs chosen from stationary tissues in the phase images, the spatial dependence of the phase off-set can be determined[83]. ROIs were manually drawn on the stationary tissue on the PC images and the mean values of which were assigned to the centroids of the ROIs. The coordinates of the centroids were then fitted to a surface of two degree polynomials at each time frame. The phase off-set was subtracted from the PC images.

**Peak Velocity Tracking:** The ante grade flow is represented by a region of high velocity within the lumen at a given time frame. However, simple thresholding does not ensure that all selected pixels form a contiguous region as it should if it were to represent the pulse wave. In this study, we considered the antegrade flow to be represented by a contiguous region of highest velocity within the lumen. We used the following algorithm to track this region over time: The aortic lumen was defined on the magnitude PC MR images using a semi automated active contour method based on gradient vector flow[84]. The same contours were used to segment the lumen in the velocity/phase images. For each time frame \( t \) in the velocity images, contours of velocities, \( C_{v,i}(t) \) were defined within the lumen for levels \( v=0,1,2..V_{\text{enc}} \) cm/sec. Where \( C_{v,i}(t) \) is the \( i^{\text{th}} \) contour representing level \( v \). Each contour defines a closed region with velocity greater than the level \( v \) from its surroundings. For each level \( v \), the
contour region \( i \), having the maximum number of pixels was chosen (=\( C_v \)). This step effectively forces the tracking along the major streamlines of the aortic flow and also eliminates any pixel with erroneous phase being considered since phase error normally occurs only in a small number of pixels. The number of pixels within each \( C_v \) when normalized by the total number of pixels within the lumen, represents a complementary cumulative distribution function of \( v \); which we used to find the 90\(^{th}\) percentile velocity, \( v' \). The 90\(^{th}\) percentile velocity was chosen because higher thresholds reduced the number of pixels within \( C_v \), to less than 10 in some cases. The average velocity of the contour \( C_v \) was taken to represent the velocity peak hence the pulse wave at time \( t \).

The mean peak velocity was plotted as a function of time. The half maximum peak velocity was identified and a straight line was fitted to the closest 4-5 data points within the half maximum velocity. The arrival time was determined from the intersection of this line and the half maximum peak velocity[85]. The time interval, \( \Delta T \) was calculated by subtracting the arrival time at the ascending aorta from the descending aorta. The Peak velocity tracking, curve fitting and the \( \Delta T \) calculations were fully automated. For comparison, \( \Delta T \) was also calculated using the mean velocity-time and the mean flow-time curves. The instantaneous flow was calculated by multiplying the mean velocity by the lumen area.

**Length of the aortic arch:** The following method was used to calculate the distance between the ascending and the descending aorta along the aortic arch (D): First, the line of intersection between the PC image plane and the long axis view plane was displayed on the long axis view image. Using this display, a line was manually traced along each edge of the aortic arch from the ascending to descending aorta. Each edge was sampled by approximately 100 spatial points. For each point on the outer edge, a point on the inner edge was found such that the distance between the two points was a minimum. This ensured that the segments were approximately perpendicular to the edges. When joined, the mid points of all such segments defined the length, D of the arch between the ascending and the descending aorta. The length D was calculated by summing the Euclidean distance between the mid points.
Finally the PWV was calculated as: \( D/\Delta T \). The effect of convection was corrected by subtracting the local blood velocity. For each subject, the PWV was calculated by three methods corresponding to different methods of measuring \( \Delta T \): **Method 1** using mean velocity-time curves, **Method 2** using flow velocity-time curves and **Method 3** using peak velocity-time curves.

The results were summarized using descriptive statistics. Parametric paired-t tests and nonparametric Wilcoxon signed rank tests were used to compare means and medians respectively between any two methods. A Bonferroni’s method was used to adjust for each paired comparison and ensure an overall type-1 error of 0.05 in the multiple comparisons. In order to derive robust estimates of mean, standard deviation and coefficient of variation, and their confidence intervals (CI’s) of the PWV, a bootstrap re-sampling method was used. In particular, we generated a total of 1,000 replicates in bootstrapping, with each replicate being consisted of \( n=30 \) samples drawn from empirical distributions of the 3 methods. The association of PWV with age, gender, body mass index (BMI) and pulse rate was assessed using a simple linear regression model for each method. All statistical computations were performed using a SAS 9.1 software (SAS, Cary, NC) package. P-values < 0.05 were considered statistically significant.

### 4.3 RESULTS

Figure 4-1c shows the results of peak velocity tracking. The contours of 90th percentile velocity plotted over the phase images depict the time dependent axial displacement of the peak flow in the descending aorta. As seen, the position of the contour varied smoothly between time frames demonstrating the robustness of the peak velocity tracking algorithm. The PWV calculated from the three methods are summarized in Table 4-1. A total of 30 subjects were studied, with a median (range) of age 8 (5, 10) years old, and a male/female
ratio of 1:1. The medians (ranges) of BMI and heart rates were 17 (13, 26) and 93 (67, 125) bpm respectively.

Figure 4-1 a) The long axis view of the aorta showing the line of intersection of the flow image plane. b) The velocity profile of the descending aorta at mid systole features a skewed distribution with retrograde flow near the inner curvature of the aortic arch. c) The contours of 90th percentile velocity in the descending aorta are shown superimposed on the velocity maps obtained during the systole. The sequential order is indicated on the top left hand corner.

The mean PWV derived from method 3 (1.81 ms⁻¹) was significantly (p<0.05) lower than that using methods 1 (2.91 ms⁻¹) and method 2 (2.78 ms⁻¹). Figure 4-2 shows the standard deviations of PWV and their 95% CI’s; 2.79 (1.83, 3.81), 2.16 (1.56, 2.79) and 0.87 (0.64, 1.12) for methods 1, 2 and 3 respectively, using bootstrapping re-sampling calculations. The upper bound of the method 3 was lower than the lower bounds of methods 1 and 2, suggesting that method 3 had smaller variation than the others. The coefficient of variation,
defined as the ratio of the standard deviation and the mean, also suggest that the results of method 3 had smaller variation compared to the other methods.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Method 1</th>
<th>Method 2</th>
<th>Method 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistics estimated from original data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.91*</td>
<td>2.78*</td>
<td>1.81</td>
</tr>
<tr>
<td>Std</td>
<td>2.53</td>
<td>1.92</td>
<td>0.85</td>
</tr>
<tr>
<td>CV</td>
<td>0.87</td>
<td>0.69</td>
<td>0.47</td>
</tr>
<tr>
<td>Median</td>
<td>2.16**</td>
<td>2.44**</td>
<td>1.63</td>
</tr>
<tr>
<td>Min</td>
<td>0.24</td>
<td>-2.09</td>
<td>0.06</td>
</tr>
<tr>
<td>Max</td>
<td>12.22</td>
<td>7.05</td>
<td>3.88</td>
</tr>
<tr>
<td>Skewness</td>
<td>2.54</td>
<td>0.21</td>
<td>0.94</td>
</tr>
<tr>
<td>Statistics derived using bootstrapping methods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.83 (1.90, 3.81)</td>
<td>2.80 (2.05, 3.60)</td>
<td>1.71 (1.39, 2.06)</td>
</tr>
<tr>
<td>Std</td>
<td>2.79 (1.83, 3.81)</td>
<td>2.16 (1.56, 2.79)</td>
<td>0.87 (0.64, 1.12)</td>
</tr>
<tr>
<td>CV</td>
<td>1.01 (0.68, 1.41)</td>
<td>0.79 (0.55, 1.16)</td>
<td>0.51 (0.37, 0.66)</td>
</tr>
</tbody>
</table>

*: The mean of method 1 (or method 2) was statistically different from that of method 3 with a p<0.05, using a parametric paired t-test.

**: The median of method 1 (or method 2) was statistically different from that of method 3 with a p<0.05, using a non parametric Wilcoxon signed rank test.

Table 4-1 Summary of description of method 1-3

<table>
<thead>
<tr>
<th>Method</th>
<th>Predictor</th>
<th>OLS estimate†</th>
<th>Slope ± se</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age (year)</td>
<td>0.37 ± 0.35</td>
<td>0.301</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.17 ± 0.16</td>
<td>0.309</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>0.03 ± 0.03</td>
<td>0.363</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>1.20 ± 0.91</td>
<td>0.200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age (year)</td>
<td>0.19 ± 0.27</td>
<td>0.480</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>0.06 ± 0.12</td>
<td>0.637</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>0.01 ± 0.02</td>
<td>0.591</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Gender</td>
<td>-0.01 ± 0.71</td>
<td>0.986</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age (year)</td>
<td>-0.01 ± 0.12</td>
<td>0.942</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>-0.03 ± 0.05</td>
<td>0.564</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>0.01 ± 0.01</td>
<td>0.390</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Gender</td>
<td>0.19 ± 0.31</td>
<td>0.541</td>
<td></td>
</tr>
</tbody>
</table>

† Estimates were from simple linear regression models. A estimate of the slope indicated changes of PWV in response to one unit increase of the predictor.

Table 4-2 Summary of linear regressing analysis
Table 4-2 compares PWV with subjects’ characteristics for each method. Age, gender, BMI and pulse rate were not associated with the PWV in all 3 methods.

![Figure 4-2](image)

Figure 4-2 Plots of standard deviation (STD) and coefficient of variation (CV) of PWV using bootstrap methods. The solid square represents the mean of STD (or CV) and the solid whisker line indicates the 95% confidence interval of the mean.

4.4 DISCUSSION

In this study I modified the conventional 2-D cine flow technique of PWV measurements by implementing a method to track the peak velocity of the antegrade flow (method 3). The results suggest that the precession of the aortic arch PWV may be improved by representing the dynamics of the pulse wave by the *peak velocity-time curve* (method 3). All subjects were healthy and the PWV was not found to be associated with age, BMI or heart rate in this cohort. Therefore the large variations in method 1 and 2 (Figure 4-2) compared to method 3 are most likely inherent to the techniques themselves. In contrast to the peak velocity-time
curve, by definition, the mean velocity-time and the mean flow-time curves include retrograde flow. The spatially asymmetric axial velocity profile of the descending aorta in one subject is seen in Figure 4-1b. This velocity map obtained at mid systole, features retrograde flow near the inner curvature of the aorta. The retrograde flow in the distal arch at mid to late systole has been previously observed in healthy subjects[78, 80]. The retrograde movement coincides with regions of relatively high non-axial, helical velocity indicating oblique backward flow. These regions are typically located near the inner curvature[80] of the aortic arch and may not be seen in axial slices distal to the aortic bend. Therefore the degree of retrograde flow in the PC images depends on the positioning of the slice and the geometry of the descending aorta. Hence it is likely that by taking the mean value of all pixels within the lumen, retrograde flow affects the velocity-time and the flow-time curves to varying degrees on different subjects. This variability probably caused the variability in the PWV measured by mean velocity (method 1) and mean flow methods (method 2).

It is well known that the PWV increases as the aorta stiffen with age[86, 87]. To my knowledge the aortic arch PWV measurement has not been performed in the past in this specific age group (i.e. 5-10 yrs). Rogers et al[87] in an MRI based study of healthy subjects of ages between 21 to 72 years (n=24), predicted that the PWV in the proximal descending aorta increased linearly with age as PWV = 0.15*age(years) + 1.074 (r=0.8, p<0.0001). By substituting the mean age of the present cohort (=7.3 year) the above equation yields a PWV value of 2.17 ms⁻¹ which agrees well with the peak velocity-time curve (method 3) derived value of 1.8 ms⁻¹ in the present study. However further cross-sectional studies are needed to validate this linear model.

The focus of this study was to improve the post processing aspect of the 2-D phase contrast flow imaging technique. Improvements on temporal resolution can significantly increase the precision of ΔT and therefore of PWV[85]. These modifications should be considered in future studies.
The peak velocity tracking method introduced in this study can be used effectively to minimize errors in aortic arch PWV measurements using phase contrast MRI data. With improved sensitivity, MR based measurement of PWV will provide a non-invasive diagnostic marker to use in risk stratification, treatment monitoring, and as surrogate endpoint in studies examining the therapeutic value of new interventions in cardiovascular disease.
Chapter 5 Implementation of Radial Phase contrast cine imaging at 7 Tesla

5.1 Pulse Sequence

The pulse sequence for a 2D phase-contrast radial acquisition sequence [88] is shown in Figure 5-1.

![Figure 5-1 Radial acquisition phase-contrast pulse sequence.](image)

The bipolar gradient is used to encode the flow in the slice selection direction. The gradient can be positive or negative. The strength and duration of the bipolar gradient determines the maximum flow velocity that can be encoded, which is indicated by Equation 5-1.

\[
\phi_{rz} = \mp G v (\tau + \tau_n) (\tau + 2 \tau_n)
\]

Equation 5-1

This is the equation to calculate the phase that is developed with a constant velocity in the bipolar gradient direction for trapezoidal gradients, where \( G \) is the gradient strength, \( \tau \) is the duration for a single gradient lobe and \( \tau_n \) is the ramp time. The \( \pm \) denotes that the phase value changes sign if the negative lobe applies first. In practice, \( \phi \) cannot exceed the range...
between $-\pi$ and $\pi$, otherwise it wraps back to this range. Hence, the maximum velocity ($v_{enc}$) that can be encoded is calculated by

$$v_{enc} = \pi /[\Delta G(\tau + \tau_r)(\tau + 2\tau_r)]$$

Equation 5-2

Since steady state is not achieved at the end of each repetition period, a spoiler gradient is applied in all three directions.

![Figure 5-2 Diagram for projection angular sampling scheme](image.png)

The projection rotates 360° around the k-space center. Figure 5-2 shows the projection angular sampling scheme. As shown by this figure, the fractional echo is applied, so that the any two angular distributions are not equivalent. The orientation of each projection is determined by the gradient strength ratio and the signs of the gradients in read and phase directions, respectively, as indicated by

$$\tan \theta = \frac{G_{\text{read}}}{G_{\text{phase}}}$$

Equation 5-3

To eliminate the effect of the steady phase introduced by eddy current, a projection is acquired twice, once with the bipolar gradient turned on, again with the gradient turned off, and using the same orientation for both acquisitions. The two images need to then be reconstructed using projections with and without bipolar gradients. The phase of the image reconstructed from projections acquired without bipolar gradients is considered with phase
errors only, and should be subtracted from the phase of the image reconstructed from projections with bipolar gradients.

In this project, Velocity encoding was done in the slice direction using a bipolar gradient. Dephasing gradients were added to the read-out gradients so that an echo was formed at 15% of the read-out duration. Projections were acquired in a 2D rotating mode over 360 degrees to obtain uniform sampling in the outer regions of k-space [88]. The k-space projections of the velocity encoded image and the reference image (i.e. non-encoded) were acquired at alternate cardiac cycles.

5.2 Reconstruction [89]

5.2.1 Density compensation

Two-dimensional Fourier Transform in Cartesian coordinate is

\[ R_{(x,y)} = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} S_{(k_x,k_y)} e^{2\pi i \frac{k_x x}{\lambda}} e^{2\pi i \frac{k_y y}{\lambda}} \, dx \, dy \]

Equation 5-4

while the counter part in Polar coordinate is

\[ R_{(r,\theta)} = \int_{0}^{2\pi} \int_{0}^{\infty} S_{(k,\theta)} e^{2\pi i \frac{k r}{\lambda}} k \, dk \, d\theta \]

Equation 5-5

Between the two equations, \( dx \, dy \) is equivalent to \( kd \, d\theta \). Both terms represent the unit area in k-space for which each data point stands. From Equation 5-5 we should be able to figure out that a term \( |k| \) needs to be multiplied by each data point in a radial acquired k-space dataset to compensate for the density difference between the k-space center and its outer region. Lack of this density compensation may result in the blurring of the image after reconstruction.
5.2.2 Centering the projection trajectory

In practice, the gradients in all x/y/z directions do not turn on simultaneously; there are delays as small as several microseconds among them. Such delays can result in missing the k-space center in an angular dependent manner for different projections [90] (as shown in Figure 5-3).

![Figure 5-3. Result of a simulation of the trajectory in the presence of gradient delays of 3.7µs and -1.5µs. The figure is the same one from the citation with authorization. [90]](image)

The amount that each k-space projection misses the k-space center can be calculated from the integral of the gradient between the assumed echo positions and the effective echo positions as shown in Figure 5-4 and Equation 5-6, 5-7 and 5-8.

![Figure 5-4. The time delay between the center of data acquisition and the effective echo in x and y directions.](image)

\[ \Delta A_x(\theta) = t_x \cdot G_x(\theta) \]

Equation 5-6
\[
\Delta A_y(\theta) = t_y \cdot G_y(\theta)
\]
Equation 5-7

\[
\Delta K = \frac{\gamma}{2\pi} [\bar{i} \Delta A_x(\theta) + \bar{j} \Delta A_y(\theta)]
\]
Equation 5-8

Gradient delay can be measured by taking projections in different orientations. The amount that each projection misses the k-space center can be broken down into two components: one perpendicular to the projection, the other parallel to the projection, as shown in Figure 5-5.

In Figure 5-5, the \(k_{//}\) and \(k_{\perp}\) can be calculated by the following equation series (Equations 5-9 through 5-11).

\[
G_{\text{read}} = \sqrt{G_x^2 + G_y^2}
\]
Equation 5-9

\[
\Delta K_{//}(\theta) = G_{\text{read}} \frac{\gamma}{2\pi} [t_x \cdot \cos^2(\theta) + t_y \cdot \sin^2(\theta)]
\]
Equation 5-10

\[
\Delta K_{\perp}(\theta) = G_{\text{read}} \frac{\gamma}{2\pi} (-t_x + t_y) \cdot \cos(\theta) \cdot \sin(\theta)
\]
Equation 5-11

Theoretically, it takes the measurement of \(\Delta k_{//}\) and \(\Delta k_{\perp}\) of only one projection to determine the time delay in the x and y directions. However, in practice, it is much easier to measure
versus measuring $\Delta k_0$. Therefore, the strategy most often used is to measure $\Delta k_0$ for two projections of different orientations, then calculate the gradient delay. Any algorithm that can provide the shift parallel to the projection can be used. Here the algorithm described by Ahn and Cho is explained [91].

Typical phase errors associated with MR acquisition include field inhomogeneity, electronic filters and data acquisition delays (gradient delay). Consider the two primary phase errors: zero and first order, $\varepsilon_1$ and $\varphi_0$, respectively. The zeroth order is mostly a result of field inhomogeneity and electronic filters. Given the principle of Fourier Transform, a shift in k-space will result in a linear change of phase in real-space. Therefore, the first order is mainly caused by gradient delay. The reconstructed image with both zeroth and first phase errors can be expressed as

$$\tilde{I}(r) = I(r)e^{i\varphi_0}e^{i\varepsilon_1 r}$$

Equation 5-12

where $I(r)$ is the ideal image. For the estimation of the first order, the phase difference between each pixel and its adjacent pixel is taken. The phase difference is determined by the equation

$$\rho(r) = \tilde{I}(r)\tilde{I}^*(r+1)$$

Equation 5-13

$\tilde{I}^*$ denotes the conjugate of $\tilde{I}$. The statistical expectation is calculated by considering all the pixels along one projection direction. The delay time can be calculated as

$$\varepsilon_1 = -\text{phase}[\text{Statistical}[\rho(r)]]$$

Equation 5-14

$$\Delta K_\theta = \text{FOV}_{k-space} \cdot \frac{\varepsilon_1}{2\pi}$$

Equation 5-15

$$t_\theta(\theta) = (\text{FOV} \cdot \Delta K_\theta) / 2 \cdot BW$$

Equation 5-16
The gradient delay error can be corrected either by implementing a fixed delay, as described in the method of x/y gradient turn-on time, or using the calculated delay time to correct the coordinates of each data point using the following re-gridding step.

In general, relative gradient delays in the order of few micro seconds can be measured by the linear phase shifts that it cause in the k-space, provided that there are no other sources of phase errors [90, 91]. However at high magnetic fields, phase shifts can also result from B0 and RF inhomogeneities and eddy currents that are not easily resolved; rendering gradient delays measured from k-space data un-reliable. Therefore in this project we used an empirical method to determine the gradient delay. A standard Gd doped water phantom with 2cm in diameter and 8cm in length was scanned with the same acquisition parameters as used in the in-vivo experiments. A series of images were reconstructed by applying relative delays to the read out gradients between -10 to +10 us in the correction algorithm. The reconstructed images using different delays were evaluated qualitatively for signal-to-noise ratio, image artifacts and sharpness. The delay that resulted in the best quality image was chosen as the relative delay. Eddy current induced fields and concomitant fields can result in spatially dependent phase off-set errors in phase contrast images [82]. These errors are evident in the stationary tissue as a non zero phase. The phase-offset was calculated by a linear fit of several ROIs in the surrounding skeletal muscle. The offset was subtracted from the phase of the region of interest.

5.2.3 Re-gridding

To take advantage of the convenience of Fast Fourier Transform, the k-space data must lie on a Cartesian grid. The re-gridding step is the process of convolving the data that was acquired in a polar coordinate into a 2D array. This process is done by multiplying each density-compensated data point by a convolution window function (a few grid points in width),
evaluating the result at each grid point within the window, and adding the result into the 2D array.

The most important part of this step is the selection of the convolution function. One study showed that the optimal gridding method is convolution with a sinc function with infinite extent. However, in practice, too wide a window width can result in an unacceptably long processing time. Jackson et al evaluated the results for different convolution window functions, and considered both performance of the function as well as the time required to generate the function. With an optimum combination of function parameters (window width and $\beta$), the Kaiser-Bessel window function was determined superior. The Kaiser-Bessel function is defined as follows:

$$W_\beta(n) = \begin{cases} 
\frac{I_0[\beta(1-\left[\frac{2n}{N-1}\right]^2)]}{I_0(\beta)} & -(N-1)/2 \leq n \leq (N-1)/2 \\
0 & \text{otherwise} 
\end{cases}$$

$$I_0(x) = 1 + \sum_{L=0}^{\infty} \frac{(x/2)^{2L}}{(L)!^2}$$

Equation 5-17

$I_0$ is the zeroth order Bessel function. Usually the function is expanded to only 20 decimal places.

In this project, The reconstruction process included: density compensation, gradient delay correction [90], re-gridding and FFT. The real and imaginary channels of the projections were re-gridded separately using a Kaiser-Bessel window.
Figure 5-6 Left: T1w axial image show flow enhanced blood vessels. Right: A velocity encoded radial PC MR phase image of the abdomen show no under-sample artifacts in the aortic lumen.

Figure 5-6 shows the magnitude and the phase map of an axial slice in the ascending aorta. Although streaking artifacts due to under-sampling of k-space are evident in the outer regions of the FOV, the aortic lumen is minimally affected by it.
Chapter 6 Quantification of Aortic Compliance in Mice Using Radial Phase Contrast MRI

6.1 MATERIAL AND METHOD

6.1.1 Pulse Sequence and Reconstruction:

A phase-contrast, under-sampled, radial acquisition cine sequence [88] was implemented (as described in Chapter 5) on a 7T Bruker MR scanner (Bruker Medical GMBH). Reconstruction was done on a stand-alone computer using custom made software written in IDL (ITT visual information solutions, Boulder, CO).

A linear, single-turn-solenoid (STS) radio frequency (RF) coil [92] (length=35mm ID=29.7mm) was fabricated for this study. In the STS design, the traditional multi-turn solenoid was replaced by a solenoid having a single turn consisting of a wide conductive sheet. To validate the MR measurements, we measured steady flow using a simple flow phantom. The PC MR derived average flow (=velocity × area of flow tube) was compared with that measured from the volume of Gd doped water collected during a given time period.

6.1.2 In vivo experiment:

We used the radial PC MR sequence to measure flow velocity in the descending aorta of mice. The study was conducted under a protocol approved by the Institutional Animal Care and Use Committee. Two nine-month-old groups were studied: ApoE KO mice (n=10) and C57BL/6/J wild type mice, WT (n=10). Mice were obtained from the Jackson Laboratory.
(JAX® Mice and Services, 610 Main Street Bar Harbor, Maine 04609 USA). All mice were fed a normal chow diet. Mice were anesthetized with Isoflurane (2% volume O2). The scans were prospectively gated for ECG and respiration (SA Instruments, Inc. Stony Brook, NY). The core body temperature was maintained at 37±0.5°C by an MR-compatible, small rodent heater system (SA Instruments, Inc. Stony Brook, NY). The following imaging parameters were used: TE/TR = 1.9/5.2msec, flip angle = 30°, pixel size = 0.093 × 0.093 mm, number of projections = 128, echo position = 15%, VENC = 180 cm/sec, slice thickness = 1mm, number of cine frames = 20-25 (depending on the heart rate). We used both sagittal and coronal images of the aorta to ensure that the imaging planes were perpendicular to the blood flow. Temporal resolution was doubled by interleaving two sets of MR data with an ECG delay of TR/2 [18]. All scans were performed at approximately the same time of the day.

6.1.3 Ex vivo experiment

To validate the non-invasive MRI method to quantify the aorta compliance, we carried out a follow up ex vivo experiment on the same group of ApoE and Wild Type mice. The expected outcome of the ex vivo experiment is to observe significant difference of aorta compliance between ApoE and Wild Type mice by measuring the elastic modulus. WT and ApoE mice were euthanized by CO2 asphyxiation. Aorta were excised, placed in ice-cold physiological saline solution, and derided of loose fat and connective tissue, and prepared for measurement of isometric force as previously described in detail [93]. Each aorta was separated into two sections as thoracic and abdominal. Each section was mounted isometrically and the length was increased in steps of 200,200,100,100,100,100 μm until attained a maximum passive force of approximately 30mN. For the aorta, the applied tension was chosen to approximate that attributable to 100 mmHg. Data were obtained with Acquire hardware and analyzed using AcqKnowledge Software (Biopac).
The normalized force, \( (F/A) \) data were plotted against the relative circumferential length change, \( (\delta C/C) \). The data were fitted to a function of the form:

\[
y = ax^{b} + c
\]

**Equation 6-1**

the best fit values of the constants \( a, b \) and \( c \) were determined for each section at force generation. Figure 6-1 is an example of average force-length curves for passive force generation.

Based on the curve shown on Figure 6-1, we can estimate the incremental elastic modulus using the linear elastic theory and assuming an isotropic homogeneous elastic material for the aortic wall [94]. According to the equation below

\[
E_{inc} = 0.75 \frac{d\sigma}{d\varepsilon}
\]

**Equation 6-2**
where $\sigma$ represents stress and $\varepsilon$ represents strain. We can estimate the $E_{\text{inc}}$ by taking derivative of equation Equation 6-1 with respect to $x$ ($\delta C/C$). Based on the fact that we observed during the experiment, the internal radius of the blood vessel changes approximately 30% during one cardiac cycle, we take $\delta C/C = 0.3$ in this calculation.

$$E_{\text{inc}} = 0.75 \times a \times b \times \varepsilon_{\text{inc}}^{(bc)} \bigg|_{c=0.3}$$  

Equation 6-3

6.1.4 Calculation of PWV:

![Figure 6-2 Sagital view of a mouse aorta depicting PC MR imaging planes.](image)

Blood flow was measured at eight to ten axial slices along the descending aorta with 2mm gaps (Figure 6-2). The acquired raw data was reconstructed into a series of 2D magnitude
and phase images. The aorta was segmented on the magnitude image using a semi-automatic snake algorithm [84]. For each time frame, the mean velocity among the pixels with velocity greater than a pre-set threshold (=80% maximum velocity in the lumen) was taken. The baseline aortic flow velocity, measured from the flow at end diastole was subtracted from the mean velocity. In order to improve temporal resolution the systolic velocity-time data were fitted to a 6th order polynomial of time. The order of the polynomial was determined based on a goodness-of-fit of $r^2 > 0.9$. The arrival time was defined as the point of half maximum velocity of the fitted data. The Figure 6-3 shows examples of velocity-time curves obtained from an ApoE KO mouse and a WT mouse at two locations on the descending aorta. The relative distance (D) from the superior most slice to different slice locations along the descending aorta were plotted against the corresponding arrival times (T) of the pulse wave at each location (Figure 6-4). The pulse wave velocity of each animal was calculated from the slope of the curve D vs. T by a linear fit.
Figure 6-3 Examples of velocity-time curves obtained from a WT mouse (top) and an ApoE KO mouse (bottom) at two locations, 17 mm apart, on the descending aorta. The shorter time difference (ΔT) at half maximum velocity between the superior (solid line) and inferior (dotted line) locations in the ApoE KO mouse compared to that of WT indicates higher PWV of the ApoE KO mouse.

Figure 6-4 A typical plot of D vs T for an ApoE-KO (O) mouse and a WT (+) mouse. D=distance to the measured slice from the superior most slice location. T = time elapsed from the ECG trigger to half maximum velocity. The PWV of each subject was measured from the slope of the linear fit. The 95% confidence intervals of the calculated PWV are shown in brackets.

6.1.5 Calculation of WSS

The flow was measured in four contiguous axial slices in the suprarenal abdominal aorta at approximately 2.0 cm distal to the aortic arch. The WSS was calculated from the velocity gradient along the aortic lumen using a Lagrangian interpolation function [76]. The aorta was segmented on the magnitude image, using a semi-automated SNAKE algorithm. First, 16 two-dimensional nodal velocities were created for each pixel along the vessel boundary by
bi-cubic interpolation. Once the nodal velocity values were assigned, the pixel wise velocity
gradient was calculated using;

\[
\nabla U_z(x, y) = \sum_{i=1}^{4} \left[ N_{ix}(x, y) \cdot v_x + N_{iy}(x, y) \cdot v_y \right]
\]

Equation 6-4

where \(N_{ix}, N_{iy}\) are the derivative of the cubic Lagrange polynomial shape functions [95] with
respect to x and y. Finally the WSS was calculated as;

\[
WSS(x, y) = \mu (\nabla U_z(x, y) \cdot n_c(x, y))
\]

Equation 6-5

where \(\mu\) is the viscosity, \(n_c\) is the regional normal vector. In this study, \(\mu = 4cP\). First, the
mean \(WSS(x, y)\) of the lumen boundary was determined for all phases throughout the cardiac
cycle. Then the average of all phases was calculated to represent the WSS of each subject.

To test the reproducibility of the PWV and WSS measurements, a separate cohort of
C57BL/6/J mice (n=4) were studied. Each animal was imaged 4 times during a two-week
time period using the same scan parameters as used in the ApoE-KO study. The heart rate
was measured from ECG (SA Instruments, Inc. Stony Brook. NY). The tail cuff blood
pressure was obtained using a computerized apparatus (Visitech Systems, Apex. NC). The
mean and the standard deviation of PWV and WSS (PWV_{mean}, PWV_{std} and WSS_{mean} WSS_{std})
for repeated measures were calculated for each mouse. The reproducibility was assessed by
the average value of \(PWV_{std}/PWV_{mean}\%\) and \(WSS_{std}/WSS_{mean}\%\) among the group.

6.2 RESULTS

The radial PC MR derived steady flow measurements of the phantom agreed to within 3% of
the actual values (results not shown). Results of the in vivo reproducibility test are given in
Table 1. The mean percentage of standard deviation among the study group was 10.1% for
PWV and 25% for WSS. No appreciable physiological changes were observed during the
study (mean standard deviation systolic blood pressure = 102.99 ± 9.7 mmHg, heart rate = 428 ± 32 bpm).

<table>
<thead>
<tr>
<th>subject</th>
<th>PWV (m/s)</th>
<th>Std dev/mean (%)</th>
<th>WSS (Pa)</th>
<th>Std dev/mean (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.48 +/- 0.26</td>
<td>10.4%</td>
<td>1.1 +/- 0.2</td>
<td>22%</td>
</tr>
<tr>
<td>2</td>
<td>3.57 +/- 0.36</td>
<td>10.1%</td>
<td>1.4 +/- 0.3</td>
<td>22%</td>
</tr>
<tr>
<td>3</td>
<td>3.84 +/- 0.32</td>
<td>8.3%</td>
<td>2.1 +/- 0.3</td>
<td>17%</td>
</tr>
<tr>
<td>4</td>
<td>3.73 +/- 0.43</td>
<td>11.5%</td>
<td>0.8 +/- 0.3</td>
<td>38%</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td>10.1%</td>
<td></td>
<td>25%</td>
</tr>
</tbody>
</table>

**Table 6-1** The results (mean +/- standard deviation) of repeated measures. Each 6 month old WT mouse was scanned four times.
Figure 6-5 Comparison of spatial resolution and temporal resolution between Cartesian acquisition and radial acquisition. a: Magnitude image acquired by Cartesian acquisition with TR=5.6ms, scan time~1min b: Magnitude image acquired by radial acquisition with TR=5.6ms, scan time~1 min c: In vivo pulsatile flow measurement by Cartesian acquisition and radial acquisition with the same spatial resolution.

Figure 6-5 shows the comparison of temporal and spatial resolution between Cartesian and Radial acquisitions. Figure 6-5a and Figure 6-5b are magnitude images acquired by Cartesian and Radial sequences with identical TR and scan time. The radial image shows better spatial resolution for the same scan time (13 pixels across the lumen in the radial image vs. only 9 in the Cartesian image). Figure 6-5c show mouse aortic flow velocity as a function of time measured using Cartesian and the radial sequences. Both measurements were based on the phase maps which had the same spatial resolution. However, keeping all other imaging
parameters the same, the radial sequence provided a higher temporal resolution measurement and resulted in a more detailed flow pattern shown on the curve.

In vivo results showed the average PWV of the ApoE KO mice (5.83±2.15 m/s) to be significantly higher (p=0.0164) than that of the wild type mice (3.54±0.97 m/s) indicating impaired aortic compliance in the ApoE KO mice. We also found the average WSS of the ApoE KO mice (1.44±0.31 Pa) to be lower than that of the wild type mice (1.55±0.36 Pa). However, the difference was not significant (p=0.47).

Ex vivo results showed the average Increment Elastic Modulus for ApoE mice at both portion of the aorta are higher than the value for wild type mice indicated in Table 6-2. However, based on the T-test result, the difference is not significant. (p=0.12 for Ab_aorta, p=0.1015 for Th_aorta).

6.3 DISCUSSION

In this study we implemented an under-sampled radial cine phase contrast technique on a 7 Tesla scanner for in vivo high resolution flow quantification in mice. This study demonstrates that radial phase contrast MR imaging can be reliably used to measure blood flow velocity in small animal models (Figure 6-5c). Compared to conventional MR methods, our method provides the advantage of higher temporal and spatial resolution. Under the current hardware limitations on our scanner, for an in-plane resolution of about 100µm, using 15% fractional echo causes the TR to drop from 8.3ms to 5.2ms. Therefore the use of fractional echo improved the temporal resolution by 37%. Although fractional echo can be used in conventional Cartesian sampling, the asymmetry in k-space can cause undesired blurring, whereas in radial acquisitions with 360 rotations, it is not detrimental because the outer region of k-space is acquired uniformly [88]. We used 128 projections with 192 samples in each projection. To achieve a similar intrinsic resolution using a Cartesian sampling scheme
344 phase encoding lines must be acquired costing approximately 3 times the scan time. The use of a fractional echo shortened the TE to 1.9ms. A shorter TE increases SNR and helps mitigate misregistration effects [96] due to blood flow. The under-sampling of k-space significantly reduced the scan time however as noticed in Figure 5-6, the aortic lumen is free of any streaking artifacts.

### 6.3.1 Pulse Wave Velocity of ApoE-KO mice

The PWV of the ApoE-KO mice was higher than that of the wild type, which indicates stiffening of the aorta in ApoE-KO. Our results are similar to that found by Hartley et al [5] (3.79±0.10 m/s for wild type mice and 4.28±0.15 m/s for ApoE KO) using Doppler Ultrasound. In Doppler Ultrasound, the PWV is calculated based on the time delay between two probes placed at two points along the aorta. However, since there are no anatomical images, the distance between the two probes cannot be measured precisely unless measured invasively. This and the fact that the mouse’s descending aorta is tortuous, can lead to significant errors in PWV measures by Doppler Ultrasound compared to MRI. According to the Moens-Korteweg equation, the PWV can be related to the incremental elastic modulus (E\text{inc}) as:

$$PWV = \sqrt{\frac{E\text{inc} \times h_m}{2\delta \times R_m}}$$

Equation 6-6

where $h_m = 30\mu m$ [97] is the mean vessel wall thickness, $\delta = 1055kg/m^3$ [98] is blood density, $R_m = 0.65mm$ [99] is the mean internal radius of the blood vessel. As indicated in Equation 6-6, the PWV is theoretically related to the Increment Elastic Modulus. The theoretical PWV calculated by substituting $E\text{inc}$ measured ex vivo in to equation 6-6 is given in Table 6-2. As evident, the PWV derived by Equation 6-6 are much higher than the experimental values. One of the reasons for this discrepancy may be that $E\text{inc}$ measured in the ex vivo experiment
was related to the axial strain while the aortic PWV may be more affected by the longitudinal strain. From our ex vivo experiments, we observed a higher mean $E_{\text{inc}}$ among ApoE mice. This result indicates the accuracy of our PWV measurement using Radial PC MRI.

<table>
<thead>
<tr>
<th></th>
<th>ApoE_ab</th>
<th>WT_ab</th>
<th>ApoE_th</th>
<th>WT_th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean $E_{\text{inc}}$ (Mpa)</td>
<td>27.1</td>
<td>21.2</td>
<td>24.7</td>
<td>16.6</td>
</tr>
<tr>
<td>Std Dev of $E_{\text{inc}}$</td>
<td>9.3</td>
<td>5.7</td>
<td>10.8</td>
<td>10.8</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>19.9</td>
<td>17.6</td>
<td>18.9</td>
<td>15.6</td>
</tr>
</tbody>
</table>

**Table 6-2**

### 6.3.2 Wall Shear Stress of ApoE-KO mice

In the abdominal aorta, a correlation between atherosclerosis and areas of low shear stress has been well established in human studies [100, 101]. Correspondingly, the mean abdominal aortic WSS of the atherogenic, ApoE-KO mice was less than that of the wild type mice even though the difference was not statistically significant. Our results are consistent with Sho’s [74], but significantly lower than that of Guzman’s [75] and Greve’s [4]. Our values may have been underestimated due to limited spatial resolution (~15 pixels across the vessel diameter). The WSS was calculated from the velocity gradient at the vessel wall. Large imaging voxels can underestimate the velocity gradient as confirmed by Cheng et al [75]. In Greve’s [4] work, computational fluid dynamic (CFD) simulations were used to reconstruct the aortic blood flow pattern assuming that the vessel wall was rigid. However, we noticed that the aortic lumen area increased up to 30% during systole in mice. Therefore by neglecting the vessel wall compliance, CFD simulations can significantly overestimate the WSS [77].

To our knowledge, this is the first study to demonstrate the feasibility of measuring aortic PWV of mice using MRI. It is also important that we were able to detect a significant change in PWV in ApoE mice at nine months of age even with a standard diet. On a standard diet,
significant functional impairment in the aorta has thus far only been detected in older ApoE mice (~1 year). However, Maguire et al [102] demonstrated that vascular reactivity to endothelin-1 is significantly enhanced in the aortas of young ApoEKO mice that have not yet developed atherosclerotic lesions. Their finding, which complements our results, suggests that alterations in the endothelial system and arterial stiffness may occur in the early stages of disease. In studies using animal models of vascular disease, radial PC MR derived PWV could be potentially used as a surrogate marker for impaired vascular function.

6.4 Future Direction

Despite our advances in diagnosis and treatment, atherosclerosis is a leading cause of death worldwide. Atherosclerosis remains clinically silent for a long time; therefore detecting it in a sub-clinical phase provide the best opportunity to reduce or even reverse its progression. However, tools that can detect early signs of atherosclerosis and distinguish successfully treated patients from those remaining at risk are not well developed. Although considerable progress has been made in MR imaging of atherosclerotic plaque, no preventive therapeutic study has been conducted where both arterial stiffness and plaque burden has been tracked serially. Animal studies have clearly indicated that alterations in the endothelin system occur in the early stages of atherosclerosis. Hence, there is a strong rationale to quantify the extent to which measures of both arterial stiffness and plaque burden can improve risk stratification. The work presented here could be extended to characterize MRI derived variables of vascular structure and function in a well known hypercholesterolemic (low density lipoprotein receptor knockout, LDLr-KO) mouse model at various phases of the disease and at post-preventive therapy. These studies will test the hypothesis that 1) the functional impairment of the aorta is predominant in the early phase of atherosclerosis and that 2) the prediction of the differential risk for atherosclerosis at post therapy is superior with the combination of plaque burden and arterial dysfunction than plaque burden alone. A serial study would be conducted.
in which LDLr-KO mice will be fed a fatty diet followed by different therapeutic dietary interventions including HMG-coA reductase inhibitors ("Statins"). The plaque burden and arterial function will be serially measured using high-resolution black blood MRI and velocity encoded radial cine MRI respectively.
Reference


