Improving Assessments of Hemodynamics and Vascular Disease

Magnus Ziegler

Linköping University
Medical Dissertation No. 1675

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Cover: Stylized streamline visualization of blood flow through an abdominal aortic aneurysm.

We will never be here again.

Abstract

Blood vessels are more than simple pipes, passively enabling blood to pass through them. Their form and function are dynamic, changing with both aging and disease. This process involves a feedback loop wherein changes to the shape of a blood vessel affect the hemodynamics, causing yet more structural adaptation. This feedback loop is driven in part by the hemodynamic forces generated by the blood flow, and the distribution and strength of these forces appear to play a role in the initiation, progression, severity, and the outcome of vascular diseases.

Magnetic Resonance Imaging (MRI) offers a unique platform for investigating both the form and function of the vascular system. The form of the vascular system can be examined using MR-based angiography, to generate detailed geometric analyses, or through quantitative techniques for measuring the composition of the vessel wall and atherosclerotic plaques. To complement these analyses, 4D Flow MRI can be used to quantify the functional aspect of the vascular system, by generating a full time-resolved three-dimensional velocity field that represents the blood flow.

This thesis aims to develop and evaluate new methods for assessing vascular disease using novel hemodynamic markers generated from 4D Flow MRI and quantitative MRI data towards the larger goal of a more comprehensive non-invasive examination oriented towards vascular disease. In Paper I, we developed and evaluated techniques to quantify flow stasis in abdominal aortic aneurysms to measure this under-explored aspect of aneurysmal hemodynamics. In Paper II, the distribution and intensity of turbulence in the aorta was quantified in both younger and older men to understand how aging changes this aspect of hemodynamics. A method to quantify the stresses generated by turbulence that act on the vessel wall was developed and evaluated using simulated flow data in Paper III, and in Paper V this method was utilized to examine the wall stresses of the carotid artery. The hemodynamics of vascular disease cannot be uncoupled from the anatomical changes the vessel wall undergoes, and therefore Paper IV developed and evaluated a semi-automatic method for quantifying several aspects of vessel wall composition. These developments, taken together, help generate more valuable information from imaging data, and can be pooled together with other methods to form a more comprehensive non-invasive examination for vascular disease.

Populärvetenskaplig Sammanfattning

Kardiovaskulär sjukdom är den vanligaste dödsorsak i Sverige och skapar en stor utmaning för vårt sjukvårdssystem. Kärlsjukdomar, till exempel aortaaneurysm och åderförfattning kan utvecklas utan symptom. Därför behöver vi teknik för att kunna undersöka dessa sjukdomar.

Våra blodkärls form och funktion påverkas och skapas delvis av de krafter som blodet skapar på grund av blodtryck och friktion mellan blod och kärlvägg. Att mäta och undersöka dessa krafter och flödesmönster kan hjälpa oss förstå och förutsäga vad som kan hända. Flödesmönster i friska men framförallt sjuka kärl är mycket komplexa. Flödet kan vara turbulent och därmed karaktäriseras av oregelbundenhet och intensiva fluktuationer, snarare än välordnat och laminärt.

Kliniskt används idag flera olika metoder för undersökning av kärlsjukdomar, till exempel: ultraljud, datortomografi, och magnetisk resonanstomografi (MRT). Varje teknik har för- och nackdelar, men MRT verkar att ha störst potential att undersöka båda form och funktion. Blodkärlets form kan mätas och kvantifieras i tre-dimensionella bilder med hjälp av kontrast-förstärkta angiografibilder, och vi kan även kvantifiera kärlväggens innehåll med hjälp av så kallade Dixon-bilder. Funktionen av kärl, blodflödet, kan kvantifieras med hjälp av tre-dimensionella, tidsupplösta bilder skapade med så kallad 4D flödes-MRT. Därför, med en kombination av olika MRT-genererade bilder kan vi skapa en fullständig bild av kärlsjukdom. I avhandlingen beskrivs flera studier som fokuserar på utveckling och validering av nya metoder som tillsammans tar oss närmare målet att ta fram en mer fullständig MRT-baserad undersökning av kärlsjukdom. De metoder som utvecklats i avhandlingsarbetet visar potential för att tillhandahålla unik information som är kliniskt relevant för diagnos och uppföljning av patienter med kärlsjukdom.

Acknowledgments

While my name stands alone on the cover, this thesis was undoubtedly a team effort.

I feel quite lucky to have had Petter Dyverfeldt as my main supervisor and mentor throughout this work, not only because of the freedom he entrusted me with, but also for his constructive and pragmatic advice throughout my studies. Thank you for giving me this opportunity.

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To my friends in Linköping, thank you for livening up this city with fun dinners, bbqs, parties, drinks, rides, and hockey. To my family and friends scattered across other countries and timezones, thank for you support throughout.

A stylized, handwritten signature in black ink, appearing to read 'Magnus'.

Magnus, Linköping, April 2019

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List of Papers

This thesis is based on the following papers, which will be referred to by their Roman numerals:

- I Visualizing and Quantifying Flow Stasis in Abdominal Aortic Aneurysms in Men using 4D flow MRI**
Ziegler M, Welander M, Lantz J, Bjarnegård N, Lindenberg M, Länne T, Ebbers T, Dyverfeldt P. *Magnetic Resonance Imaging*, 2018
- II Age-related Vascular Changes Affect Turbulence in Aortic Blood Flow**
Ha H, Ziegler M, Welander M, Bjarnegård N, Carlhäll CJ, Lindenberg M, Länne T, Ebbers T, Dyverfeldt P. *Frontiers in Physiology* 2018, 9:36
- III Assessment of Turbulent Flow Effects on the Vessel Wall using Four-Dimensional Flow MRI**
Ziegler M, Lantz J, Ebbers T, Dyverfeldt P. *Magnetic Resonance in Medicine* 2017; 77 (6), 2310-2319.
- IV Automated Quantification of Fat and R_2^* in Carotid Atherosclerosis**
Ziegler M, Good E, Warntjes M, Engvall J, de Muinck E, Dyverfeldt P. *In manuscript*.
- V Exploring the Relationship between Carotid Geometry and Hemodynamic Wall Shear Stresses**
Ziegler M, Alfraeus J, Good E, Engvall J, de Muinck E, Dyverfeldt P. *In manuscript*.

Papers I-III are reproduced with permission.

In addition, the following peer-reviewed papers were published in connection to work performed in this thesis:

- **Assessment of turbulent viscous stress using ICOSA 4D Flow MRI for prediction of hemodynamic blood damage**
Ha H, Lantz J, Haraldsson H, Casas B, Ziegler M, Karlsson M, Saloner D, Dyverfeldt P, Ebberts T. *Scientific Reports* 2016.
- **Estimating the irreversible pressure drop across a stenosis by quantifying turbulence production using 4D Flow MRI**
Ha H, Lantz J, Ziegler M, Casas B, Karlsson M, Dyverfeldt P, Ebberts T. *Scientific Reports* 2017.

Nomenclature

2D	Two-Dimensional
3D	Three-Dimensional
4D	Four-Dimensional
AAA	Abdominal Aortic Aneurysm
AS	Aortic Stenosis
CE	Contrast-Enhanced
CEMRA	Contrast-Enhanced MR Angiography
CFD	Computational Fluid Dynamics
CMR	Cardiovascular Magnetic Resonance Imaging
CNN	Convolutional Neural Network
CoA	Coarctation of the Aorta
ECG	Electrocardiogram
FF	Fat Fraction
FOV	Field-of-View
IP	In-Phase
IPH	Intraplaque Hemorrhage
IVSD	Intravoxel velocity standard deviation
KE	Kinetic Energy
LRNC	Lipid Rich Necrotic Core
MP-RAGE	Magnetization-Prepared Rapid Acquisition with Gradient Echo
MRA	MR Angiography
MRI	Magnetic Resonance Imaging
OP	Out-of-Phase
OSI	Oscillatory Shear Index

PC	Phase-Contrast
PD	Proton Density
qMRI	Quantitative MRI
Re	Reynolds Number
RT	Residence Time
SNR	Signal-to-Noise Ratio
SVM	Support Vector Machine
TAWSS	Time Averaged Wall Shear Stress
TKE	Turbulent Kinetic Energy
TOF	Time-of-Flight
tWSS	Turbulent Wall Shear Stress
VENC	Velocity Encoding Range
VNR	Velocity-to-Noise Ratio
WSS	Wall Shear Stress

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Chapter 1

Introduction

The form and function of the cardiovascular system are intrinsically linked, each strongly affecting the other. The forces exerted by blood flow dictate a continuous remodeling of the heart and vessels, and these forces appear to remodel the vessel for efficient flow. As a result, the healthy cardiovascular system has largely laminar flow in vessels without abrupt changes in size, shape, or direction. At the same time, the forces exerted by blood flow play a significant role in the pathophysiology of many common cardiovascular diseases. Through remodeling and other compensatory mechanisms, flow irregularities and the forces they generate can lead to a cascade of increasingly more severe abnormalities or conditions.

Therefore, to improve diagnosis, treatment, and the understanding of cardiovascular disease, the quantification of the abnormal hemodynamics that drive the remodeling processes associated with many vascular diseases is of interest. For example, hemodynamic markers such as the wall shear stress may help determine the development or rupture risk of both atherosclerotic plaques and abdominal aortic aneurysms. Similarly, we can measure the degree of turbulence present in the carotid bifurcation, as a measure of the flow efficiency or the impact of stenoses.

The composition of the wall is another aspect that presents an opportunity for quantification, as the material properties of the vascular wall may be altered as a result of the flow-induced stresses or other disease. For example, the rupture risk of an atherosclerotic plaque is known to be linked to its composition. Whether or not the composition is associated with hemodynamic stresses is unknown, however.

Currently, vascular disease is frequently assessed using imaging modalities such as ultrasound, x-ray angiography, and computed tomography. While many of these modalities can provide images about the structure of the vascular system, they are limited in their ability to assess the flow and its impact on the vascular wall. Magnetic Resonance Imaging (MRI) unlocks these assessments. With 4D Flow MRI, a technique that acquires the time-resolved three-dimensional flow field in a volume of interest, we can quantify the flow using a wide range of hemodynamic markers in vivo and investigate how they are linked to the form and function of the cardiovascular system. In addition, with quantitative MRI (qMRI) techniques such as the Dixon sequence, we can describe the material properties of the vascular wall that change as a result of cardiovascular

disease.

In this work, we develop and evaluate new methods for assessing vessel wall disease using novel hemodynamic markers generated from 4D Flow MRI and quantitative MRI data towards the larger goal of a more comprehensive non-invasive examination oriented towards vascular disease.

Chapter 2

Aims

The aim of this thesis is to develop new methods for assessing vascular disease using novel hemodynamic markers generated from 4D Flow MRI, and compositional information from quantitative MRI data, to examine vascular disease in a more comprehensive manner. Specifically we aimed to:

- Develop and evaluate methods for quantifying and visualizing flow stasis
- Investigate where and the degree to which turbulence is present in the aorta
- Develop and evaluate a method for quantifying the effect of turbulence on the vessel wall
- Examine the flow-induced stresses acting on the wall in vivo
- Develop and evaluate a method for extracting compositional information from the vessel wall

Chapter 3

Physiological Background

The vascular system has one deceptively simple function: to act as a conduit for blood. However, it is not a static conduit and its form is influenced by the flow itself, which in turn influences the flow in a feedback loop. This feedback loop is dictated by the hemodynamic forces generated by the blood flow, and the distribution and strength of these forces appear to play a role in the initiation, progression, severity, and the outcome of vascular disease.

This chapter will describe the structure of the vascular wall, as well some common vascular diseases where imaging plays an important role. This thesis primarily examined the arterial portion of the vascular system, and so this section will not discuss the anatomy or pathologies of the venous system.

3.1 Anatomy

An artery is a blood vessel that carries oxygenated blood away from the heart to the rest of the body¹, and therefore responsible for the delivery of oxygen and nutrients throughout the body [1–3]. Blood is pumped through the arterial system at a higher pressure and velocity than the venous system [2]. As the vessels become more distant from the heart, their size decreases. A schematic of the arterial tree is shown in Figure 3.1.

The aorta is the largest artery in the arterial tree, receiving blood directly from the left ventricle of the heart through the aortic valve. The aorta extends through the abdomen to its bifurcation into the common iliac arteries. Given the size of this vessel, different anatomical regions of the aorta are often described: the ascending aorta, extending from the aortic valve to the peak of the aortic arch; the descending aorta, from the peak of the aortic arch to the diaphragm and the abdominal cavity; and, the abdominal aorta, from the diaphragm to the iliac bifurcation². Each region has localized, clinically relevant considerations and pathologies that tend to present there. For example, aneurysms are much more common in the abdominal aorta versus the thoracic aorta [4].

¹With the exception of the pulmonary and umbilical arteries

²Other definitions for these regions are often used. For example, the aortic arch itself is often defined as a region on its own, and under these definitions contains the three upward arterial branches for the brachiocephalic trunk, the left common carotid artery, and the left subclavian artery.

Figure 3.1: Schematic of the arterial tree.

Of particular relevance to this thesis are the carotid arteries. They originate at the aortic arch (left common carotid) and the brachiocephalic trunk (right common carotid³) and supply the head and neck with blood. Both left and right carotid arteries terminate at the carotid bifurcation, where they split into the internal and external carotid arteries. The internal carotid artery takes a deeper path and supplies the skull and brain, while the external takes a more superficial path and supplies the neck and face. The carotid bifurcation induces complex hemodynamics, and atherosclerotic plaques are common in this region [2, 5].

The structure of the arterial wall can be seen in Figure 3.2. The cavity through the centre of the artery is known as the lumen, while the wall itself is composed of three layers: the tunica externa, the tunica media, and the tu-

³A common anatomical variation has the right common carotid originating independently from the aortic arch instead of the brachiocephalic trunk.

nica intima. The outermost layer, the tunica externa, is composed primarily of collagen fibres and some elastic tissue. The middle layer, the tunica media, is primarily composed of smooth muscle cells. The innermost layer, the tunica intima, is mainly composed of endothelial cells. The endothelial cells are in direct contact with the circulating blood and are involved with various physiological processes, such as inflammation, vaso -constriction and -dilation, in addition to their role as a barrier between the lumen and surrounding tissue. The endothelial cells perform mechanotransduction, transforming mechanical stresses into biological reactions.

Mechanotransduction on the endothelial surface is initiated by ion channels (K, Ca, Na, Cl), cell membrane receptors, caveolae, and the plasma membrane lipid layer [6]. Moreover, the lumen is lined with glycocalyx, a structure that was found to be specifically responsible for shear stress-moderated nitric oxide (NO) production [6, 7]. When these signaling pathways are consistently activated over a prolonged period of time, vessel remodeling can occur, to reduce the hemodynamic stresses. For example, the vessel wall downstream from stenotic jets often dilates and aneurysms can form. Changes in shear stresses appear to play larger roles than changes in pressure because the pressure changes are relatively minor compared to the changes in shear. As a result, the endothelium appears more sensitive to changes in shear than changes in pressure [6, 7].

Figure 3.2: Anatomy of an artery. Reproduced with permission from [8].

3.2 Vascular Disease

Innumerable diseases impact the vascular system, ranging from rare congenital defects and genetic disorders to common atherosclerosis. Some vascular diseases that are relevant to this thesis will be briefly summarized here.

Aneurysms

An aneurysm is typically defined as a focal and permanent dilation of an artery to 150% or more than the diameter of an unaffected arterial segment [5], though precise definitions vary with location. Aneurysms can present throughout the arterial tree, though some locations are more frequent than others. Common sites for aneurysm are the abdominal aorta (Figure 3.3), the thoracic aorta, and the internal carotid artery. Aneurysms can be caused by a variety of factors: degenerative, inflammatory, congenital, among others. The diameter of the aneurysm is also commonly used for predicting the growth rate and rupture risk [4, 9–12], even though it is not strongly predictive of either [10, 13]. Risk factors for aneurysms include smoking, male gender, age, atherosclerosis, and connective-tissue disorders (e.g. Marfan Syndrome) [4, 14]. Surgical treatment tends to be decided by the diameter of the aneurysm, while also considering the age of the patient [14]. Patients with smaller aneurysms that do not warrant surgery should receive regular surveillance imaging [4]. Even if an aneurysm has been identified, predicting the rupture risk is extremely challenging as the precise relationship between flow-induced forces acting on the vessel wall, the mechanical strength of the wall, and other risk factors is still unknown [12]. This challenge, coupled with the silent-progression of aneurysmal disease produces the poor survival rates associated with ruptured aortic aneurysms [9, 15, 16]. An abdominal aortic aneurysm (AAA) is depicted in Figure 3.4 and compared against a disease-free aorta.

Figure 3.3: Schematic depiction of an abdominal aortic aneurysm, with the aneurysm marked using the arrow. Reproduced with permission from [8].

Figure 3.4: Example images from healthy young volunteer (A, B) and patient with AAA (C, D). (A) and (C) show balanced-images of the abdominal cavity, and (B) and (D) show the contrast-enhanced MR angiography for the same subject. The aorta is marked using red arrows in (A) and (C). The dashed red lines in (B) and (D) depict the level of the aorta shown in (A) and (C). The AAA is clearly visible in (D).

Atherosclerosis

Atherosclerosis is the number one cause of death worldwide, primarily by causing myocardial infarctions and strokes [17, 18]. Simply put, atherosclerosis involves the accumulation of lipids and fibrous tissues in the large arteries. Atherosclerosis most often develops asymptotically, though in the later stages of atherosclerosis, the large plaques force vessel remodeling that in turn, causes stenoses. Stenoses can radically alter the blood flow through the vessel in question, potentially causing high-velocity jets and turbulent flow, which may damage the vessel wall. However, the primary risk is dictated by the rupture risk of the plaque and the emboli generated. Plaque composition and structure can be used to help determine the risk posed by the plaque. For example, plaques with a large lipid rich core have a higher rupture risk. A simplified depiction of the progression of atherosclerosis is shown in Figure 3.5.

Figure 3.5: Simplified depiction of the progression of atherosclerosis through time.

Chapter 4

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) provides an unparalleled ability for investigating the human body. MRI can generate anatomical images with excellent soft-tissue contrast in any area of the body, without ionizing radiation. Complementing those abilities, MRI can generate functional images that describe the physiology of the subject, describing, for example, the passage of blood through the heart or the brain’s response to visual stimuli. Merging anatomical information such as the diameter of the thoracic aorta with physiological information such as the amount of turbulence in that same region provides clinicians and researchers the opportunity to understand the mechanisms behind a large range of pathologies.

This chapter will describe the basic principles behind image generation in MRI, the goals and challenges of MRI investigations of the cardiovascular system, and the three major types of imaging used in this thesis: Contrast-Enhanced (CE) MR angiography, Dixon, and 4D Flow MRI. This chapter is primarily based on the following texts: [12, 19–25] .

4.1 Basic MRI Principles

Sub-atomic particles like electrons and protons are magnetic. As a result of this, they spin and have a spin angular momentum and a magnetic moment. The spin angular momentum and magnetic moment are proportional to each other by the gyromagnetic ratio (γ). Considering the hydrogen proton, $\gamma = 2.68 \cdot 10^8$ rad/s/T. Exposing the protons to an external magnetic field B_0 causes the magnetic moments, or spins, to align and precess about that field. The rate of angular precession is described by the Larmor equation:

$$\omega_0 = \gamma B_0 , \tag{4.1}$$

where ω_0 denotes the Larmor frequency. Field strengths of 1.5, 3, and 7 T are used in whole-body MRI scanners, and therefore the Larmor frequencies are approximately 64, 128, and 298 MHz, respectively. Changing the magnetic field, and therefore the Larmor frequency, is used in MRI to generate images.

Instead of considering spins individually, it is more convenient to aggregate them and consider “packets”. With this choice, a classical physics representation can be used, and the packet of spins can be described using its net magnetization

vector M . Normally, M is aligned with the external magnetic field B_0 , and this is known as the “relaxed state”, but when radio-frequency (RF) pulses that match the Larmor frequency are applied, the orientation of M can be altered. As the RF pulse stops, the magnetization undergoes a relaxation period and re-aligns itself with the B_0 field. The relaxation and re-alignment of M is described using the Bloch equation:

$$\frac{dM}{dt} = \gamma M \times B - \frac{M_x}{T_2} \hat{x} - \frac{M_y}{T_2} \hat{y} - \frac{M_z - M_0}{T_1} \hat{z}, \quad (4.2)$$

where T_1 is the spin-lattice (or longitudinal) relaxation time and T_2 is the spin-spin (or transversal) relaxation time. T_1 describes the time it takes for the longitudinal component of the magnetization vector M to recover to 63 of its original value M_0 . T_1 measures the return of excited or perturbed spins to their natural, relaxed state. T_2 describes the time it takes for the transverse component to decay to 63% of its original value. T_2 decay is a result of the loss of phase-coherence (or synchronicity in spin) within the packet of spins. T_1 and T_2 are both tissue-specific parameters that are exploited to generate contrast and distinguish between different tissues in the body. To generate the images and use T_1 or T_2 contrast patterns to distinguish between tissues, the time-varying signal generated by the magnetization vector returning to alignment is measured by the receiving coils of the MR scanner. This signal is called the free-induction decay signal, and electromagnetic induction is used by the receiver coils to measure it.

To generate useful images, the signal generated by the relaxation of spin packets must be spatially located. To do this, magnetic field gradients are used. These gradients cause the magnetic field to vary spatially over the object being imaged and therefore change the Larmor frequency of the spin packets as a result of their spatial position. Spins will also accumulate a phase-shift as a result of these gradients and the length of time they are exposed to the gradients.

Using a combination of magnetic field gradients in different directions across the object in the scanner and appropriate timing of the RF excitation pulses, signal can be generated that is able to be spatially localized in the object. The order and manner in which the gradients and RF pulses are applied is known as the pulse sequence. The signal induced in the receiver coil(s) of the scanner are split into real and imaginary components and stored in a spatial-frequency domain known as k -space. The resulting complex signal is a function of the applied gradient waveform and the object being imaged. This complex-valued signal is also the Fourier transform of the tissue-slice in that particular spatial location.

k -space is constructed as a grid with two dimensions (for a 2D image, three for a 3D image, and so on), k_x and k_y , that correspond to the horizontal and vertical axes in an image. Each dimension represents the spatial frequencies of the image in that direction. The centre of k -space contains the lowest spatial frequencies, and the outer-regions contain the higher spatial frequencies. The centre, therefore, contains most of the key image information and is generally regarded as most important. The pulse sequences for a specific MR acquisition are designed to fill k -space, by acquiring data that corresponds to all spatial frequencies, so that the image can be constructed. After k -space is filled, taking the inverse Fourier transform yields the complex-valued data in the image domain. The modulus of this data yields the commonly used magnitude images.

The complex component (i.e. the phase), is also often of value, in particular for phase-contrast MRI.

The physical space that the image represents is known as the field-of-view (FOV). The number of samples in k -space along a particular dimension and the FOV determine the actual resolution of the image. The FOV in a particular direction is inversely proportional to the number of samples in k -space in that direction. For direction n , $FOV_n = 1/\Delta k_n$, where Δk_n is the spacing between two adjacent k -space samples in direction n . Similarly, the spatial resolution in an image in a given direction, δ_n is inversely proportional to the size of k -space in that direction: $\delta_n = 1/(k_{n,max} - k_{n,min})$. Combining these two equations allows for the calculation of the minimum number of samples necessary for the desired FOV and resolution:

$$N_n = \frac{FOV}{\delta_n} = \frac{(k_{n,max} - k_{n,min})}{\Delta k_n}. \quad (4.3)$$

In 2D imaging, the spatial resolution is discussed in terms of pixel size (i.e. $\delta_x \cdot \delta_y$) and the slice thickness. In 3D imaging, the voxel size (i.e. $\delta_x \cdot \delta_y \cdot \delta_z$) is commonly reported.

4.2 MRI of the Cardiovascular System

Cardiovascular MRI (CMR) has become valuable in assessing cardiovascular disease and function, as a result of its non-invasive nature, excellent soft-tissue contrast, ability to create anatomical and functional imagery, and lack of ionizing radiation. Many techniques have been developed specifically for cardiovascular applications, and CMR has come to include a range of imaging techniques including angiography, T_1 and T_2 mapping, fat mapping, flow imagery, strain imagery, and static- or cine-images of the heart. However, CMR presents several specific challenges, for example, cardiac and respiratory motion, that add an additional layer of complexity to the task at hand. Each technique has its own practical requirements, though CMR techniques commonly require cardiac and respiratory gating to reduce or remove motion artifacts and acquire temporally resolved data. Therefore, cardiac gating and respiratory gating will be described in this section.

4.2.1 Cardiac Gating

Several CMR acquisitions require data acquisition in synchrony with the cardiac cycle, to ensure the heart is at the same location when all spatial frequencies of the image are recorded, and to generate time-resolved flow data for the entire heartbeat. Typically, data from an ECG (preferred), or pulse oximeter is used to detect the heart beat and provide timing information. There are two general strategies for cardiac gating: prospective gating, which uses a predefined acquisition time-window and therefore only allows data acquisition under a specific fraction of the cardiac cycle [26]; and, retrospective gating, which permits the acquisition of data during the entire cardiac cycle (Figure 4.1) [27, 28].

Prospective gating, also known as “triggering”, often uses the R-wave of the ECG to determine when to begin data acquisition. This type of gating is common for single-timeframe images of the heart, where the image is acquired

Figure 4.1: Prospective Gating (also known as triggering) acquired data only during specific windows. Retrospective gating continually collects data and groups the data according to the phase of the cardiac cycle during image reconstruction.

between beats to minimize motion. Retrospective gating acquires data during the entire cardiac cycle, and uses the ECG signal to reconstruct the data after all the data was acquired. The heart rate is not a constant signal, so the number of acquired timeframes can vary from beat-to-beat. During reconstruction, a temporal sliding-window approach is often used to reconstruct the data into a set of evenly distributed timeframes. Retrospective cardiac gating is typically used for cine-imaging.

4.2.2 Respiratory Motion Suppression

Similar to cardiac gating, many CMR acquisitions require respiratory motion suppression to prevent artifacts and blurring as a result of respiratory motion [29]. Acquisitions with shorter scan times can be performed by instructing the subject to hold their breath for a short period of time (15-20 seconds maximum), during which the scan is performed. However, this creates difficulty for many subjects or is simply not possible because the acquisition takes too long. Therefore, to monitor the subject's respiration and decide when to acquire data, bellows or navigator scans are commonly used. Respiration bellows are placed on the subject while inside the scanner, and they physically monitor the movement of the chest or belly using pressure sensors. Respiratory navigator scans are typically pencil-beam or cross-pair excitation scans that acquire an image that represents the motion of the diaphragm through the cardiac cycle. These scans acquire a column of voxels across the lung-liver interface, so as to monitor the motion of the diaphragm. Using either navigator scans or bellows, data acquisition is only allowed if the current respiratory position falls within a specified acceptance window. This acceptance window is typically defined around the end-expiratory phase. The size of this window is a tuneable parameter, where larger acceptance windows would incur more respiratory motion in the final image (and therefore a degradation in image quality), but increase the efficiency of the scan as data can be acquired for longer periods of time.

4.3 Phase-Contrast MRI

Flow assessment is widely used in the evaluation and grading of cardiovascular disease. For example, the severity of stenoses in the aortic valve are often graded with respect to the peak velocity measured using ultrasound. MRI also offers the ability to investigate hemodynamics in vivo, with numerous advantages over other techniques. The ability to retrospectively examine data, plan investigations irrespective of acoustic windows, and the decreased observer dependencies make MRI flow-investigations valuable. 4D Flow MRI is a phase-contrast (PC)-MRI technique that measures the velocity of fluids in three spatial dimensions and three velocity dimensions through time [22, 23, 30, 31]. 4D Flow MRI was developed from the more commonly used two-dimensional (2D) PC-MRI technique that is used clinically to measure velocities through a pre-positioned plane [32–35]. MRI-based flow imaging is commonly used to, for example: examine congenital heart conditions, aortic pathologies, aneurysms in cerebral or thoracic circulation, and the effects of valvular pathologies, among other uses [11, 22, 31, 36–49].

In this section, the working principles behind MRI based flow measurements will be described. Following this, the extension of the basic principles to create 4D Flow MRI will be described, as well as typical scan properties and considerations. Finally, the unique possibility to map turbulence using 4D Flow MRI will be presented.

4.3.1 PC-MRI Velocity Mapping

PC-MRI flow imaging is based on the fact that spins moving in parallel to a magnetic field gradient will acquire some phase shift, proportional to their velocity [30, 32–35]. This provides MRI with an inherent sensitivity to motion. In some scenarios, this motion must be compensated for as it degrades the image quality, but for PC-MRI velocity mapping, this is critical.

The phase shift accumulated by the spin packet, ϕ , is proportional to its velocity. A specific motion sensitivity is normally desired, and so the motion sensitivity is controlled by adding bipolar gradients and other gradients. Assuming a symmetric distribution of velocities about the mean velocity U , the phase shift is related to the mean velocity and the motion sensitivity k_v according to:

$$\phi = k_v U + \phi_{add}, \quad (4.4)$$

where ϕ_{add} represents an additional phase-shift incurred due to inhomogeneities in the B_0 magnetic field. ϕ_{add} is independent of k_v and can be eliminated using the phase-shifts from two sets of data, known as flow-encoding segments, if they are generated using different motion sensitivities. Using the two datasets, the mean velocity can be calculated as:

$$U = \Delta\phi / \Delta k_v. \quad (4.5)$$

Practically speaking, one of the critical parameters for velocity mapping is the velocity encoding range (VENC), which relates the flow sensitivity k_v to velocity value which yields a full phase-shift of π radians:

$$VENC = \frac{\pi}{k_v}. \quad (4.6)$$

If the true velocity is larger than $\pm VENC$, the measured velocity is aliased and wraps back into that range (phase-wrapping), preventing it from being unambiguously determined. Therefore, this scan parameter is set with care before the acquisition to minimize phase-wrapping. However, selecting a $VENC$ that is too large has a negative effect on the velocity-to-noise ratio (VNR). The VNR is related to the signal-to-noise ratio (SNR) (as measured in the magnitude data, not the phase data) and $VENC$ by:

$$VNR = \frac{VENC}{SNR}. \quad (4.7)$$

This technique must be extended in the temporal domain to create useful data in vivo. This entails the creation of the temporal domain. Put simply, this requires the acquisition of a full k -space dataset for each point in time required. Data is acquired as described in Sections 4.1 and 4.2.2. This process can be lengthy, requiring several thousand cardiac cycles without acceleration techniques.

4.3.2 4D Flow MRI

Extending the flow-encoding technique to consider three velocity directions throughout the cardiac cycle in a volume involves the use of additional flow-encoding segments to create a 3D velocity vector through time for each voxel¹[30]. This results in an acquired dataset that contains four four-dimensional complex-valued volumes from which the following are normally generated: the magnitude volume which depicts anatomy, and three velocity encoded volumes (Figure 4.2). This section will detail specific considerations for the use of 4D Flow MRI, including acceleration techniques, signal quality, and background phase-offsets.

Figure 4.2: Example dataset from 4D Flow MRI. The four flow-encoding segments, generated at each point in the cardiac cycle, create maps of the mean velocity in each direction (V_x, V_y, V_z), and turbulence intensity maps ($\sigma_x, \sigma_y, \sigma_z$).

Non-accelerated 4D Flow MRI acquisitions have impractically long scan times, and therefore clinical use of this technique demands the use of acceleration

¹3 Spatial dimensions of velocity information, plus the temporal dimension yields the '4D Flow' moniker.

techniques [22]. For example, an acquisition with a 112×48 phase-encoding lines would require 5376 cardiac cycles (assuming 1 k -space line per beat). At a steady 60 beats per minute and with 100% respiratory navigator efficiency this acquisition would take roughly 90 minutes. There are few healthy volunteers who can tolerate such a scan time, let alone patients.

To improve scan time, several strategies exist. One way to reduce the acquisition time (T_{acq}) is to increase the number of k -space lines (often called “segments”, N_{seg}) acquired per cardiac cycle. Doubling this, to 2 k -space lines per cycle, would reduce T_{acq} by a factor of 2, but cause a reduction in the minimum temporal resolution (estimated by: $T_{res} = 4 \cdot T_R \cdot N_{seg}$). Additionally, the size of k -space can be reduced by not acquiring the outer edges. This incurs a SNR penalty and will affect the spatial resolution, but it can yield substantial T_{acq} reductions, potentially 20-25%. Parallel imaging techniques such as SENSE (SENSitivity Encoding), which uses coil-sensitivity maps to reconstruct partial FOV images from each coil, or GRAPPA (GeneRalized Auto-calibrating Partial Parallel Acquisition), which under-samples the phase-encoding directions and attempts to compensate for this in k -space, are commonly used in 4D Flow MRI. Both strategies can also be combined with acceleration in the temporal direction, resulting in the kt -SENSE and kt -GRAPPA techniques. Combining all of these techniques, acceleration factors >5 are possible without significant reduction in data quality, and have been used in a clinical setting, bringing down T_{acq} towards the 10-15 minute range [23].

PC-MRI velocity mapping techniques have several common data quality issues, including: Maxwell terms and eddy currents causing phase errors, gradient field distortions causing phase-offset errors, phase-wrapping causing velocity aliasing, and low SNR/VNR as a result of high scan acceleration. Appropriate data processing is required to correct or compensate for these errors and ensure accurate quantification of hemodynamics is possible.

Errors from Maxwell terms are a result of using switching magnetic fields for spatial and velocity encoding [22, 23]. Switching the gradient generates additional transverse magnetic field components that cause the underlying B_0 field vector to be misaligned. These additional components are called “concomitant field” or “Maxwell term” errors. These errors can be estimated with knowledge of the applied gradients and corrected for during reconstruction of the 4D Flow acquisition.

Eddy currents are similarly caused by the switching of the magnetic field gradients, though in this case, the switches result in changes in magnetic flux and induce eddy currents in the conducting components of the scanner. These eddy currents can cause changes in the desired gradient strengths and duration and cause spatially varying phase-errors. Eddy currents need to be corrected for in post-processing, and correction strategies often use weighted fits to static tissue [50–52].

Gradient field distortions are deviations from linearity in the magnetic field gradients that tend to increase with distance from the isocentre of the magnet. These distortions cause image warping in the magnitude images, but also phase-offsets causing velocity errors. These errors must be can be substantial, especially when the FOV is large and there are areas of interest distant from magnet isocentre (e.g. infrarenal AAAs in whole-aorta acquisition volumes). Correction for gradient field distortions can be done during image reconstruction, using knowledge of the non-linearities [22, 23].

Phase-wrapping, or velocity aliasing, is a result of the real velocity being larger than the VENC. VENC is set prior to acquisition², to some maximum value that corresponds to a maximum phase difference of $\pm\pi$. Therefore, if the velocity is greater than this level, the phase will be aliased (i.e. it falls out of the $[-\pi, +\pi]$ interval) and is wrapped back onto itself. This obviously causes issues during flow quantification. VENC can be set based on the estimated maximum velocity with a safety margin to prevent wrapping, though at the cost of VNR (Equation 4.7). This implies that VENC should be set as low as possible, given the expected maximum velocities, to optimize VNR. This approach sometimes leads to velocity aliasing, because the expected maximum was too low. Post-processing steps can attempt to correct for aliasing by comparing the wrapped voxel to the surrounding region, and assuming that the phase-change between adjacent areas is less than π , though in some cases manual corrections may be required.

As previously discussed, VENC should optimally be set as low as possible to optimize the VNR [22]. However, in some acquisitions, there is a large range of expected flow velocities which causes the maximum expected velocity to rise and put slower-flow areas at risk of being dominated by the effects of noise. Whole-aorta acquisitions that provide coverage of the aortic valve, with its high velocity jet flow, and the much slower flow in the distal areas of the abdominal aorta, are a prominent example. A hypothetical subject presenting with both an aortic stenosis, causing extreme jet flows, and an AAA, with areas at risk of flow stasis constitutes an extreme case. In this example, the jet flow would dictate a high VENC but such a choice would likely substantially increase the noise in the AAA and prevent accurate flow analysis there. This case could merit of two separate acquisitions, each focused on a different anatomical regions to ensure adequate VNR and minimal velocity aliasing. Fortunately, the development of multi-VENC acquisitions enables a single-acquisition volume while conserving (and potentially improving) VNR. Unfortunately, as tradeoffs are common in MRI, a multi-VENC acquisition will increase T_{acq} . In addition to multi-VENC strategies, VNR/SNR can be improved by using gadolinium-based contrast-agents. The use of contrast-agents can compensate for parallel acquisition strategies that decrease VNR/SNR.

4.3.3 Turbulence Mapping

Velocity measurements using 4D Flow MRI represent the mean velocity from a given voxel [53–56]. However, turbulence is characterized by chaotic, random fluctuations in velocity magnitude and direction. The velocity in a given voxel, u , can therefore be described as having a mean and a fluctuating velocity (U and u' , respectively):

$$u_i = U_i + u'_i, \quad (4.8)$$

where i represents an arbitrary direction. The turbulent intensity in each direction, σ_i , is defined as the standard deviation of the fluctuating component:

$$\sigma_i = \sqrt{(u_i'^2)}. \quad (4.9)$$

²VENC has typical values of 120-180 cm/s for thoracic or cardiac acquisitions, though it can be higher if flow jets are present and of interest.

The mean value of u'_i is zero by definition. This approach for statistical separation of the mean and fluctuation components of velocity is known as Reynolds decomposition [57].

While the mean velocity in a voxel can be accurately measured using 4D Flow MRI, current temporal and spatial resolutions are insufficient to measure u' . However, the presence of disturbed and turbulent flows attenuates the MRI signal magnitude as a result of the distribution of velocities (spins) within that voxel. The strength of signal attenuation depends on the characteristics of the bipolar gradients used during imaging, and the spread of velocities. Modeling the spread of velocities using a gaussian distribution, and given known gradients, we can use the magnitude of the signal to estimate the intravoxel velocity standard deviation (IVSD). IVSD is a measure of turbulence intensity. IVSD can be calculated as:

$$IVSD = \sigma_i = \frac{1}{k_v} \sqrt{2 \cdot \ln \left(\frac{|S_i(0)|}{|S_i(k_v)|} \right)}, \quad (4.10)$$

where $S_i(0)$ and $S_i(k_v)$ are the signals acquired with zero motion sensitivity and k_v motion sensitivity, respectively. This technique is known as IVSD- or turbulence-mapping, and is depicted in Figure 4.3. It enables estimation of the turbulence intensity in any desired direction. σ_i is also known as the Reynolds or Turbulent Normal Stress in direction i and forms the diagonal of the Reynolds Stress tensor $\mathbf{R}$:

$$\mathbf{R} = \overline{\rho u'_i u'_j} \sim \rho \begin{bmatrix} \overline{u_1'^2} & \overline{u_1' u_2'} & \overline{u_1' u_3'} \\ \overline{u_2' u_1'} & \overline{u_2'^2} & \overline{u_2' u_3'} \\ \overline{u_3' u_1'} & \overline{u_3' u_2'} & \overline{u_3'^2} \end{bmatrix}, \quad (4.11)$$

where ρ is the fluid density. This tensor is 2nd order symmetric and describes the average momentum flux as a result of the velocity fluctuations.

However, it is often convenient to have a non-directional estimate of the turbulence intensity, and therefore the turbulent kinetic energy (TKE) is also of interest. TKE is a direction-independent measure of the energy of the fluctuating velocity components, and can be calculated as:

$$TKE = \frac{1}{2} \rho \sum_{i=1}^3 \sigma_i^2, \quad (4.12)$$

where σ_i is the turbulence intensity in each principal direction $i = x, y, z$ in a given voxel. Using this technique, a voxel-by-voxel map of the TKE can be created alongside the velocity information.

As IVSD-mapping uses the magnitude of the MRI signal, instead of the phase, as would be the case for velocity mapping, there are different considerations for optimizing data quality. The VENC parameter defines the dynamic range of velocities that can be measured without phase-aliasing, but also has some effect on IVSD-mapping. It can be shown that VENC defines the point of maximum IVSD sensitivity, $\tilde{\sigma}$:

$$\tilde{\sigma} = \frac{1}{k_v} = \frac{\pi}{VENC}. \quad (4.13)$$

When the optimal VENC values for velocity- and IVSD-mapping are similar, both quantities can be accurately reconstructed from the same acquired data.

Figure 4.3: Schematic description of turbulence mapping approach. Two datasets are used, one with low (or zero) motion sensitivity and a second with high motion sensitivity. The loss in signal magnitude between these two images is used to calculate the turbulence intensity.

4.4 Contrast-Enhanced MR Angiography

Contrast-Enhanced MR angiography (CEMRA) acquisitions are designed to produce bright-blood images of the vasculature. CEMRA can be performed on just about any scanner and used for a wide range of clinical questions. Compared to Time-of-Flight (TOF) or PC-MRA techniques that are also used for examining vasculature, they are faster, with better spatial resolution even while having a larger FOV [19]. In addition, they create images that are independent of flow characteristics. However, they require the use of often expensive and potentially harmful contrast-agents and intravenous access. Finally, implementing a first-pass contrast-enhancement protocol can be challenging given the variance in patients' cardiac output. In this section, the acquisition parameters will be discussed alongside the challenge of contrast timing, and the uses for this data.

CEMRA acquisitions are typically T_1 -weighted 2D or 3D spoiled gradient echo sequences. Gadolinium-based contrast agents are used to significantly shorten the T_1 relaxation time of blood. This implies that the blood with which the contrast-agent has mixed with has the strongest signal compared to the surrounding tissue. T_E and T_R are typically as short as possible, with T_E typically 1-2 ms, and T_R 2-5 ms. Flip angles are typically between 15-40°, where higher flip angles increase the background suppression but can also attenuate some of

the signal in the vessels of interest. Partial k -space acquisitions and those that initially fill the centre of k -space are preferred to minimize the acquisition time to ensure the image contains only the arterial phase. Typically, CEMRA of the carotid arteries are acquired using a sagittal slab, with the anterior-posterior direction having the shortest FOV to minimize one of the phase-encoding directions. Similarly, scans of the thoracic aorta or AAAs are oblique sagittal slabs oriented in parallel to the aortic arch. Example CEMRA images of the abdomen and the neck are shown in Figure 4.4.

Figure 4.4: Example maximum intensity projections of CEMRA acquisitions for the abdomen of a subject with AAA (A), and the neck of a healthy subject (B).

For a high-quality CEMRA, the acquisition must be synchronized with the duration of arterial enhancement and to precede venous involvement (Figure 4.5). For this reason, first-pass contrast enhancement is used to ensure that the arterial system has the strongest signal enhancement. “First-Pass” refers to the first time the contrast bolus passes through the arterial circulation after leaving the heart. Contrast dosage, injection rate, and timing are all key factors that determine image quality.

Contrast dosage is standardized by subject mass. A typical single dose is 0.1 mmol/kg of body mass, with an upper limit of 0.3 mmol/kg. For whole-aorta or AAA investigations, a double dose is preferred to ensure that the amount of contrast is sufficient to enhance the entire FOV.

The injection rate affects the amount of contrast dispersion, peak intensity of arterial enhancement, and the circulation time (Figure 4.6). As contrast is injected intravenously, the contrast material mixes with un-enhanced venous blood and a certain amount of contrast-dispersion occurs en route to the heart. Increased contrast dispersion decreases the peak arterial enhancement. Increasing the injection rate lowers the amount of dispersion and therefore the peak arterial enhancement is increased because the peak contrast concentration is maximized. However, increasing the injection rate means that the contrast bolus transits to the vasculature of interest faster (i.e. shortened circulation time).

Timing the acquisition to coincide with arterial enhancement is a key determinant of CEMRA quality [19, 58]. Various strategies exist for timing the start

Figure 4.5: Ideal contrast and acquisition timing. Data should be acquired in synchrony with the first pass of the contrast material through the arteries of interest. Circulation time, and therefore the scan delay, are partially tuneable through the injection rate, but are mostly determined by the subject’s cardiac output.

of the acquisition after beginning the contrast injection: guessing the circulation time; the test bolus method; or a bolus-detection method. The circulation time could be guessed based on estimates of the cardiac output of the patient or from experience based on prior acquisitions. This is generally a poor strategy given the variance in cardiac output among subjects. Improving upon the guess-method, the test-bolus method involves the injection of small contrast dose and while measuring the time until peak enhancement. However, a test bolus will decrease the peak contrast enhancement in the subsequent image because of the diluted contrast material in the blood and surrounding tissue. The bolus-detection method is a further improvement, and it involves using real-time or rapidly acquired images displayed to the MR technician so that they can follow the contrast bolus through the venous system, heart, and into the arterial system and trigger the acquisition at the appropriate time. Fluoroscopy-style imagery is normally created using a 2D gradient echo sequence that rapidly fills the centre of k -space. An example fluoroscopy-style bolus-tracking image is shown in Figure 4.7a alongside the maximum intensity projection of the resulting image. This correctly timed image does not show venous involvement. Figure 4.7b shows an example of a poorly timed CEMRA. In this subject, the contrast enhancement is seen in the cerebral circulation at the point when the acquisition was triggered. As a result, the CEMRA shows significant venous involvement.

Figure 4.6: The injection rate controls not only the length of arterial enhancement, but also the peak arterial enhancement. Faster injection rates result in shorter circulation times, higher intra-arterial contrast concentrations, and shorter enhancement periods, all else being equal.

Generating high spatial resolution images of the vasculature makes CEMRA valuable for the identification of stenoses, dissections, or aneurysms. In addition, these bright-blood images are useful for vessel segmentation. These segmentations can be used for geometric analyses or registered to other acquisitions for use in a variety of analyses. Their large FOV also makes CEMRA data a useful target for registering multiple images together.

(a) Contrast bolus leaving the heart (left, red arrow), and the maximum intensity projection of the resulting correctly timed CEMRA which shows minimal venous involvement (right).

(b) Contrast bolus entering the cerebral circulation (left, red arrow), and the maximum intensity projection of the resulting CEMRA which shows significant venous involvement (right).

Figure 4.7: Bolus-track images and resulting CEMRA. Figure 4.7a depicts a well-timed CEMRA acquisition, where the bolus-track image depicts the contrast material leaving the heart. Figure 4.7b depicts a sub-optimal CEMRA, and the bolus-track image depicts the contrast entering the cerebral circulation. Red arrow indicates the location of the contrast bolus at the start of image acquisition.

4.5 Dixon

The Dixon technique is an MRI sequence that exploits the fact that water and fat molecules precess at different rates in order to generate fat-only and water-only images [24, 59]. These images can be used for a variety of investigations, for example, distinguishing between various types of abdominal lesions by examining the fat content. The fat-only images could also be used to examine the amount of abdominal fat a subject has. This section will describe the Dixon technique, outlining how fat- and water-only images are generated, and discuss

common challenges related to its use.

A fundamental assumption of most Dixon techniques is that water and fat are the only two chemical species in the object that generate signal [24]. Using this assumption, the Fourier transform of the acquired signal S can be expressed as:

$$S(x, y, z) = [W(x, y, z) + F(x, y, z) * e^{i\alpha}] * e^{i\phi(x, y, z)} * e^{i\phi_0(x, y, z)}, \quad (4.14)$$

where (x, y, z) is the spatial coordinate of the voxel, W and F are real and non-negative numbers representing the magnitude of the magnetizations at a given location for water and fat. α is the phase angle of fat relative to water given their chemical shift difference, ϕ is the phase error due to field homogeneity, and ϕ_0 is a second phase error term representing other system imperfections. The accumulated signal can be visualized in a vector form (Figure 4.8). The primary objective of Dixon techniques is to determine W and F from the acquired image(s) that encode the chemical shift difference into the signal phase, that are represented by S in Equation 4.14.

Figure 4.8: Vector representation of the complex signal S for a given voxel that is generated by the two components fat (F) and water (W). α is the phase angle of fat relative to water, ϕ is the phase error due to magnetic field inhomogeneity, and ϕ_0 is additional phase error caused by other system imperfections.

Figure 4.9: Phase-cycling of fat and water protons. At $t=0$, and $t=4$ they are in-phase, though at $t=2$ they are out-of-phase with each other.

As previously noted, water and fat protons have slightly different resonance frequencies, which causes their spins to go in- and out- of phase with each other. The period of this phase-cycling is proportional to the field strength of the magnet and the gyromagnetic ratio. Figure 4.9 shows the phase-cycling of fat and water protons. At time $t = 0$, the spins are aligned and in-phase (IP) as the RF pulse is triggered. As the fat and water molecules spin, their phase difference grows until $t = 2$, at which point they are out-of-phase (OP), and continues to $t = 4$ where they are IP with each other. The images obtained at $t = 2$, or $t = \frac{1}{2} * T_E$ are known as the OP images, while the images at $t = 4$, or $t = n * T_E$ are known as the IP-images. Using a combination of the IP and OP images, the fat- and water-only images can be generated. By definition: $IP = Water + Fat$ and $OP = Water - Fat$. Using these definitions, we can obtain the water-only image (W):

$$\frac{1}{2}(IP + OP) = \frac{1}{2}[(W + F) + (W - F)] = W ,$$

and similarly, the fat-only image (F):

$$\frac{1}{2}(IP - OP) = \frac{1}{2}[(W + F) - (W - F)] = F .$$

Therefore, using only a pair of acquired images, four images with different contrast patterns are generated: one IP, one OP, plus the fat-only and water-only images. This is known as a 2-point Dixon sequence as the acquisition only uses two images generated at two different echo times. Unfortunately, the usability of a 2-point Dixon sequence is limited because it assumes that the B_0 field is perfectly homogenous and there are no significant local changes in susceptibility. With adequate shimming of the B_0 field, and post-processing, 2-point Dixon sequences can be used and are offered as standard sequences by most vendors. However, numerous changes have been proposed for the technique, including using multiple images and combining the extra data with modeling based approaches for the binary separation of fat and water [60–62].

For example, in the study by Koppal et al [63], a 4-point Dixon sequence is used with an OP, IP, OP, IP scheme at echo times of $n * 3.6$ [ms]. The use of an additional echo enables the estimation of T_2^* relaxation (a measure of phase-dispersion) times for each voxel. In that study, the T_2^* relaxation rate, R_2^* was

modeled using the signal magnitude S at each T_E as follows:

$$S(T_E) = W + F \cos\left(\frac{2\pi T_E}{2.4}\right) \exp(-R_2^* \cdot T_E), \quad (4.15)$$

where 2.4 is the period of the oscillating signal caused by the frequency difference between water and fat at 3T. Therefore, in that study, each Dixon acquisition generates the following images: 2×IP, 2×OP, fat-only, water-only, and R_2^* . The fat and water fractions on a per voxel basis can also be calculated by the division of the fat or water component by the sum of the two. The sum of the fat-only and water-only images creates a proton density (PD) image.

Dixon acquisitions often suffer from one common artifact, that is known as the “fat-water swap” artifact (Figure 4.10). This artifact is aptly named and manifests itself as regions in the image where fat and water values are reversed. This can occur in particularly heterogeneous areas of tissue, such as the neck, or near any metallic implant. This artifact arises from the non-homogenous B_0 fields that cause an additional phase-shift (ϕ in Figure 4.8). The phase can only take the range of $[-\pi, \pi]$ and therefore any additional phase-shifts could cause the signal to “wrap”. These phase-wraps have the effect of swapping the voxel from fat to water or vice-versa. No general solution exists, though several different post-processing strategies exist to unwrap the phase and attempt to remove the fat-water swap. One common approach is to use region-growing techniques that identify areas of high-confidence water or fat signals and use these to locate neighboring areas that are falsely labelled [64, 65]. With multi-point Dixon acquisitions, modeling approaches can also be used for unwrapping [61, 66]. These methods use an iterative least-squares process with the initial assumption of a zero phase-shift (i.e. a homogenous B_0 field) [24]. Minimum-norm, and path-following methods also exist [24]. The successful use of Dixon techniques for binary fat-water classification is dependent on adequate phase-unwrapping solutions, and so therefore this is a key area of research.

Figure 4.10: Example of the fat-water swap artifact. In this image the left kidney has been identified as composed of fat instead of water. *Image Courtesy of Allen D. Elster, MRIquestions.com*

Chapter 5

Methods and Results

This chapter will describe the analysis methods used in this thesis, as well as the results we generated while pursuing the aims outlined in Chapter 2.

5.1 Quantifying and Visualizing Flow Stasis

Flow stasis is characterized generally by very slow or recirculatory flow, and can be created as a result of pathologically driven vessel remodeling. Regions of flow stasis or recirculation play a role in the development of atherosclerosis, thrombosis, and aneurysms [67], because in these regions there is ample opportunity for platelet adhesion and thrombus formation.

Given the basic definition of flow stasis as a region that has abnormally slow flow velocity, an Eulerian approach that examines a region of interest and statistically analyzes the regional and temporal distribution of velocities is a logical method. The most direct application of this approach would be to measure the proportion of a volume of interest (e.g. the left atrial appendage, or AAA) that has temporal mean velocities below a predefined velocity threshold [68, 69]: $P_{stasis} = \frac{V_{stasis}}{V_{total}}$, where V_{stasis} is the volume inside region V_{total} with temporal mean velocity $\bar{v}$ below v_{stasis} . Another strategy is to measure the time for which a given volume (e.g. a voxel) has a velocity below the threshold value, normalized to the length of the cardiac cycle [70, 71]: $r_{stasis} = \frac{n_{stasis}}{N_{Total}}$. The duration for which a given region has sub-threshold velocity can also be considered [71]. However, an obvious difficulty with these strategies is the definition of the v_{stasis} threshold value, and the use of this strategy in regions with substantial wall motion is conceptually challenging.

Flow stasis has often been studied using Lagrangian particle tracking approaches which indicate where particles accumulate, and the time they reside there (e.g. [72–77]). In this method, particles are typically seeded either across the entire volume of interest or released from the inlet, and their movements are tracked forwards in time for several cardiac cycles or until all particles have left the volume of interest. The volumetric residence time (VRT) can then be calculated as the total time any given particle resides within a local volume of interest. The total time spent by a given particle in the entire fluid domain, or particle residence time (PRT), can also be evaluated.

With the goal of quantifying flow stasis in mind, in **Paper I** we studied thir-

teen subjects with AAA and examined three methods for visualizing and quantifying flow stasis. AAAs often present with complex geometry that generates a patient-specific flow pattern that can include recirculatory regions, vortices, and stagnation zones. These flow patterns can lead to flow stasis. In **Paper I**, the aneurysmal geometry and flow profiles from one subject were used as input for a CFD simulation, to generate noise and artifact free data that would serve as a test bed for flow stasis quantification methods. Five levels of gaussian noise and five levels of background phase-offset errors were added to the CFD-generated artifact-free data to test the three methods in various data quality scenarios. This testing procedure ensures that the methods tested are suitable for use in clinically acquired 4D Flow MRI data.

The first method studied was VRT, where virtual particles are released into the AAA and traced forward in time several cycles while their positions are recorded. VRT was strongly impacted by all levels of background phase-offsets, with R^2 dropping to below 0.35 in each test. The VRT method was more robust against noise, however. To assess the global impact of these artifacts on VRT, the clearance rate of the particles from the aneurysm per cardiac cycle was also measured. As particles need to be traced through several cardiac cycles using the VRT method, the excessive accumulation of error limits the applicability of this method in 4D Flow MRI.

Two methods expected to be more suitable for 4D Flow MRI were therefore investigated. TDA, which measures how far particles travel from a given voxel, and MVA, which measures the temporal mean velocity in a voxel. TDA was more strongly affected by background phase-offsets than MVA, as it is a particle-tracking method, though it performed better than VRT as it tracks particles over only one cardiac cycle and can therefore minimize error accumulation. With respect to noise, TDA was less affected than MVA. Examining the identified stasis volumes for both methods, it is evident that MVA is less suitable for extremely low SNR scenarios. This is likely a result of the static stasis velocity threshold approaching the increasing mean noise level as SNR drops. Alternate definitions for the velocity threshold may alleviate this issue. The TDA and MVA volumes for a subject with saccular AAA is depicted in Figure 5.1.

In addition to the quantitative testing of TDA and MVA using the computationally generated flow fields, they were qualitatively tested using data from thirteen subjects with AAA. Figure 5.2 depicts the identified stasis regions for two subjects using the TDA and MVA methods. As there is no gold-standard method for identifying flow stasis, we compared the regions identified as flow stasis using the automated approaches to the regions identified by an observer using conventional pathline visualizations. Two observers assigned scores based on pairwise agreement between the methods. Qualitative testing indicated that TDA had better agreement to conventional flow visualizations than MVA, and only poor agreement was found between MVA and TDA.

The results of **Paper I** indicate that flow stasis can be quantified and visualized using 4D Flow MRI-specific methods. Quantification of flow stasis may present another avenue for assessing the rupture risk and growth rate of AAAs.

Figure 5.1: Example mean travel distance (top) and mean velocity (bottom) volumes for a subject with saccular AAA.

Figure 5.2: Example stasis regions identified by TDA and MVA methods for two subjects (A, B). Red regions are defined as "in stasis" by the respective method.

5.2 Quantifying Turbulence and its Effects

Given that the complete time-resolved 3D velocity field is acquired using 4D Flow MRI, detailed analyses of the hemodynamics of a subject can be performed. Describing how blood flows in the cardiovascular system is complex, and requires different parameters to describe different aspects of the flow in question. For example, different metrics are used to describe bulk properties of the flow and how the flow interacts with the vessel wall.

To gain a general understanding of the hemodynamics, several parameters are routinely used:

- **Speed:** The magnitude of the velocity vector, per voxel. Various descriptive statistics are often reported to describe the speed of the blood flow in a given volume at a specified point in time. For example, the maximum or mean speed in the ascending aorta at peak systole.
- **Flow Volume:** The surface integral of velocity over a given surface. Most often, the amount of blood that passes through a plane that cuts a vessel in a given amount of time. For example, the flow volume through the internal carotid artery. The cardiac output of a subject is a similar parameter.
- **Kinetic Energy:** The amount of energy possessed by an object due to its motion. In hemodynamics analyses, the object of interest is the blood in a specific volume, most often an anatomically defined volume or voxel. The voxelwise kinetic energy (KE) of blood can be calculated as: $KE = \frac{1}{2}mv^2$, where m is the mass, and v is the blood's speed. The mass of the blood is calculated using the density of blood (ρ) and the volume in question (dV), typically the voxel-volume: $m = \rho dV$.

However, the hemodynamics of the cardiovascular system are complex, and these simple parameters do not comprehensively describe it. Therefore, further parameters are necessary, particularly when turbulent flows are considered.

Flow can typically be characterized as either laminar or turbulent, where in laminar flows the fluid travels in a streamlined manner with parallel layers and turbulent flow is typically described as random and chaotic. Cardiovascular flows are predominantly laminar, though turbulent flows can be found in subjects with vessel or valve stenoses.

One of the most common parameters used when describing turbulent flows is the Reynolds number (Re). This dimensionless parameter describes the ratio of inertial (or body) forces to viscous forces and can be expressed as:

$$Re = \frac{UL}{\nu}, \quad (5.1)$$

where U is the mean velocity, L is the characteristic length (e.g. the diameter of a pipe), and ν is the kinematic viscosity of the fluid. It is commonly used to describe flows, or predict the transition between laminar and turbulent regimes [57, 78].

As described in Section 4.3.3, a framework has been developed to exploit this definition that enables MRI-based estimation of turbulence intensity [53–56, 79]. Turbulent kinetic energy (TKE), the turbulent analog to kinetic energy,

can be described using this method as:

$$TKE = \frac{1}{2}\rho \sum_{i=1}^3 \sigma_i^2, \quad (5.2)$$

where σ_i is the IVSD in direction i , and ρ is the fluid density. TKE can be used to describe the energy content of turbulent flow and is a direction-independent measure of the intensity of velocity fluctuations. However, TKE does not describe turbulence production or dissipation rates [80]. TKE has been employed to examine mitral regurgitation [81], as a marker of dysfunction in the right ventricle [37], the left ventricle [82], and has been investigated for use as a measure for pressure loss in stenotic vessels [83, 84].

Investigating the extent of Turbulence in the Aorta

Turbulent flow is often discussed in a pathological context, but an understanding of where and how much turbulence is developed is missing. Therefore, to map the presence and degree of turbulence, in **Paper II** we quantified the amount of turbulent flow in 22 young men (23.7 ± 3.0 years old) and 20 older men (70.9 ± 3.5 years old), in four different anatomical regions of the aorta (ascending, descending, suprarenal and infrarenal). As the aorta also changes in shape and structure through age, examining two age-cohorts also allows us to examine how aging affects turbulence development.

4D Flow MRI was used to non-invasively measure the blood flow and turbulence in each aortic region, alongside basic geometric descriptions like the vessel diameter. The maximum Reynolds number was also calculated for each region.

All subjects in this study displayed elevated levels of TKE in systole when compared to diastole, and the overall levels of turbulence were similar between the two groups, though there were regional differences. Total TKE ranged from 2.7 to 18.8 mJ. This total TKE value is, as expected, lower than previously examined cohorts that included subjects with aortic stenoses [83], with that cohort generating between 13 and 52 mJ. Interestingly, while there was no difference in peak total TKE between the cohorts when the entire aorta was considered, the older subjects had 73% higher peak total TKE in the ascending aorta. The older subjects also had larger ascending aortas than the younger subjects. In the descending aorta and abdominal aortic regions, the age-related dilation of the aorta decreased the average flow velocity and appears to have suppressed the development of turbulence.

The maximum Reynolds number, which is often used as an indicator for turbulence, was more strongly correlated to the peak total TKE in young subjects than older subjects across each region. Considering the entire cohort, the correlation was strongest in the descending and suprarenal aorta. Results indicated that indirect assessment of turbulent blood flow using the Reynolds number was only feasible for young subjects.

Quantifying the Stresses on the Vessel Wall

Flow induced shear stresses are important hemodynamic parameters, thought to influence the function of endothelial cells and play a role in pathologically driven vessel remodeling, for example in atherosclerosis and thrombosis. Blood flow

causes two forces acting over the surface area of the vessel wall: the normal force, causing pressure, and the tangential force, causing wall shear stress (WSS). These stresses are depicted in Figure 5.3.

Figure 5.3: Schematic of fluid-induced forces acting on the vessel wall.

In a Newtonian fluid, the WSS is proportional to the shear rate of the fluid, where the fluid's viscosity is the constant of proportionality. The shear stress (τ) on a surface element parallel to the flow is given by:

$$\tau(y) = \mu \frac{du}{dy}, \quad (5.3)$$

where μ is the dynamic viscosity of the fluid, u is the fluid velocity, and y is the distance to the surface. Non-newtonian fluids, like blood, do not have a constant viscosity. Blood is often modeled using the Carreau-Yasuda model, which models blood as Newtonian at low shear rates, followed by a power-law fluid at intermediate shear rates, and finally as a Newtonian fluid again at high shear rates.

WSS is often studied using CFD, though 4D Flow MRI enables non-invasive in vivo estimation. However, the temporal and spatial resolution of 4D Flow MRI limits the accuracy of these estimations [85, 86]. To calculate the WSS vector on a 3D surface, first the inward normal vector at each point on the surface is determined, and subsequently the velocity at several points along that vector is sampled. After defining the velocity at the wall to be zero (no-slip condition), and fitting a smoothed spline to the velocity measurements along the normal vector, the slope of this curve can be calculated to generate

the shear rate. Finally, multiplying by the shear-dependent viscosity yields the WSS vector at that point on the surface. Repeating this process throughout the cardiac cycle generates the time-resolved WSS vector.

From the WSS vector, innumerable other parameters can be calculated to describe the stress patterns, and some relevant to this thesis will be described here. Perhaps the most commonly used parameter is the time averaged WSS (TAWSS):

$$TAWSS = \frac{1}{T} \int_0^T |\vec{\tau}| dt, \quad (5.4)$$

where T is the period of the cardiac cycle. The TAWSS vector and its magnitude are commonly used to describe the predominant stresses acting on a region or specific point on the vessel wall.

Given the pulsatile nature of cardiovascular flows, the TAWSS vector cannot describe the direction nor magnitude of the changes in WSS through the cardiac cycle. The Oscillatory Shear Index (OSI) is a measure of how much the WSS vector is aligned with the TAWSS vector throughout the cardiac cycle, and is defined as [87]:

$$OSI = \frac{1}{2} \left(1 - \left(\frac{|\int_0^T \tau dt|}{\int_0^T |\tau| dt} \right) \right). \quad (5.5)$$

An OSI of 1 indicates that the WSS vector is perfectly aligned with the TAWSS vector throughout the cardiac cycle, where a value of 0 indicates no alignment.

OSI can be used to examine the effect of laminar and periodic oscillations through the cardiac cycle, but cannot represent the chaotic oscillations in WSS generated because of turbulent flow. Turbulent WSS (tWSS) does just this. tWSS describes the intensity of the turbulent fluctuations in WSS about the mean WSS. Analogous to the Reynolds Decomposition of the velocity signal in 4.3.3, the WSS signal can be decomposed as:

$$WSS = \overline{WSS} + wss', \quad (5.6)$$

and substituting in the definition of WSS from Equation 5.3:

$$WSS = \mu \frac{dU}{dy} + \mu \frac{du'}{dy}. \quad (5.7)$$

The standard deviation of WSS is used as a measure of tWSS:

$$tWSS = std(WSS) = std\left(\mu \frac{dU}{dy} + \mu \frac{du'}{dy}\right). \quad (5.8)$$

As the standard deviation of the mean WSS is 0 by definition, this term is removed, and Equation 5.8 is simplified to: $tWSS = std\left(\mu \frac{du'}{dy}\right)$. Assuming a linear velocity gradient at the wall yields $tWSS = std\left(\mu \frac{u'_2 - u'_1}{dy}\right)$, where u'_1 is the fluctuating velocity at the wall and u'_1 is the fluctuating velocity at distance dy . The no-slip condition at the wall implies $u'_1 = 0$, and therefore:

$$tWSS = \frac{std(u'_2)}{dy}. \quad (5.9)$$

As explained in Section 4.3.3 the numerator is measured as the IVSD in vivo using MRI.

To build on our understanding of the location and intensity of turbulent flow in the aorta (**Paper II**), we investigated methods to quantify the way in which these rapid and chaotic fluctuations in velocity create shear stresses on the vessel wall. The predominant method for estimating the WSS on the vessel wall using 4D Flow MRI fails to capture these turbulent stresses. A method to estimate tWSS in vivo would therefore be of value.

In **Paper III**, CFD was used to simulate turbulent flow in two models, representing an aortic stenosis (AS) and an aortic coarctation (CoA), at two different flow rates each. With both models, each using two flow rates, we generated simulated models with Reynolds numbers between 3000 and 9000 CFD data that acted as ground-truth, and input data for 4D Flow MRI simulations¹.

Using the CFD data, we estimated tWSS using data extracted from progressively larger distances from the wall. Results indicated that voxel sizes an order of magnitude smaller than current 4D Flow MRI voxels (i.e. ~ 0.2 mm) were necessary to have an acceptable level of error. This result was confirmed using the simulated 4D Flow MRI data, where we estimated tWSS and found strong underestimation only moderate correlation to CFD-derived ground-truth values.

Moving forward, we hypothesized that the amount of turbulence dissipated near the vessel wall would be correlated to tWSS. The former can be measured, as near-wall TKE (nwTKE). Therefore, we developed a method that samples the TKE near the vessel wall and maps this value to the vessel wall, depicted in Figure 5.4. Testing this method using the simulated 4D Flow MRI data revealed that nwTKE appears to have a linear relationship to the tWSS, and we found strong correlations between nwTKE and tWSS across the testing scenarios, with the exception of the coarctation model in the lower turbulence flow condition. This work therefore showed that nwTKE can be used in vivo to indicate areas of high tWSS.

Examining the Stresses acting on the Vessel Wall in vivo

Atherosclerosis, one of the most common vascular diseases, tends to affect specific areas of the arterial tree with particular preference towards vessel bifurcations, recirculation zones, and areas of stasis. Therefore, subject-specific arterial geometry and hemodynamics are thought to be links in the chain towards atherosclerotic development. In **Paper V** we explored the relationships between geometric and hemodynamic wall stress parameters, as well as the inter-relationships between hemodynamic parameters in the carotid arteries from a cohort of 191 subjects.

In **Paper V** we expanded upon the geometric parameters analyzed in **Paper II**, to include vessel tortuosity, bifurcation angle, and the ratios between the downstream and upstream branch diameters, in addition to the vessel diameter. Geometric parameters were extracted from branch-level segmentations automatically generated using a convolutional neural network. With respect to hemodynamics, we estimated temporally resolved WSS, OSI, and for the first

¹In **Paper II**, our results indicated that the Reynolds number in subjects without stenotic aortic valves or coarctations of the aorta were 4408 ± 1084 for young healthy volunteers in the ascending aorta (Table 1).

Figure 5.4: Volumetric Rendering of TKE in CoA model (left), and nwTKE (right).

time in vivo, nwTKE. The relationships between geometric and hemodynamic parameters were tested using the Spearman rank-correlation coefficient.

Examining the geometric parameters for this cohort showed that carotid geometry can take a wide range of forms, with the bifurcation angle, for example, having a coefficient of variation of 51%. Interestingly, the data did not reveal any substantial relationships between the geometric parameters and hemodynamic parameters.

Examining the inter-relationships in hemodynamic parameters revealed several relationships of interest. With respect to the time-resolved hemodynamic parameters, we found moderate correlation between WSS and nwTKE ($\rho = 0.53$), and that nwTKE has a stronger relationship to the 10% WSS value ($\rho = 0.77$) than it does to the 90% value ($\rho = 0.45$). This may be explained by the development of turbulence during flow deceleration. Examining the cohort-mean WSS and nwTKE through time also revealed that peak WSS and nwTKE are temporally co-located, and that nwTKE has a more pronounced second peak value that may be a result of the diastolic notch and wave reflection (Figure 5.6). Figure 5.5 depicts the WSS and nwTKE at peak systole and diastole for an example subject. In our cohort-mean data, the CCA artery displayed the largest WSS though a large portion of the cardiac cycle, though the ECA displayed the largest nwTKE. The CCA also displayed the largest coefficient of variation throughout the cardiac cycle when considering WSS, while the ECA had the largest coefficient of variation with respect to nwTKE. Considering the temporal development of the coefficient of variation through the cardiac cycle, WSS variation peaks during peak systole, while nwTKE variation is largest during diastole and decreases during peak systole. This is depicted using the mean coefficient of variation from the cohort in Figure 5.7.

In addition to the temporally-resolved parameters, we examined parameters

Figure 5.5: WSS (top) and nwTKE (bottom) depicted during diastole (left) and at peak systole (right) for an example subject. Flow rate through time is depicted in upper-right corner of each panel, and the marker represents the time-point visualized.

Figure 5.6: Cohort-mean branch specific WSS (left) and nwTKE (right) through the cardiac cycle.

Figure 5.7: Cohort-mean coefficient of variation through the cardiac cycle for both WSS (left) and nwTKE (right).

that describe the whole cardiac cycle, such as TAWSS, TANwTKE, OSI, and SA80. Correlation analyses revealed that TAWSS and nwTKE have a moderate correlation ($\rho = 0.50$), and that TAWSS was correlated to both OSI ($\rho = -0.54$) and SA80 ($\rho = 0.89$). TANwTKE and OSI were not correlated. This signals that TANwTKE and OSI reveal different hemodynamic features when considering the entire cardiac cycle. TANwTKE highlights the regions that would experience the most turbulence throughout the cardiac cycle, while OSI indicates the regions where laminar oscillations cause the WSS vector to change alignment.

Paper V provided data that describes the large variation in geometry of the carotid bifurcation in a statistically powerful cohort. Moreover, the data indicates that the commonly assumed link between carotid geometry and hemodynamic stresses may be counterintuitive, requiring complex measures to identify, or simply not present. Finally, this study examined nwTKE and WSS together in vivo for the first time.

5.3 Assessment of Vessel Wall Composition

A comprehensive examination of the hemodynamics and stresses acting on the vessel wall (**Papers I, II, III, V**) should be paired to investigations about the state of the vessel wall itself. Therefore, quantifying the composition of the vessel wall can be seen as an important building block towards such a comprehensive examination. Such a comprehensive examination would be particularly valuable for assessing atherosclerosis. Atherosclerosis is widespread and causes more deaths worldwide than any other disease. It is also a disease that progresses silently. Non-invasive imaging can therefore have a crucial role to chart the development of the disease. As atherosclerosis progresses from fatty streaks in the vascular wall towards plaques causing stenoses, the composition of the vessel wall changes. Similarly, plaques themselves undergo changes in composition, and plaque composition is predictor of cardiovascular events.

MRI has excellent soft-tissue sensitivity, allowing tissues to be characterized. For example, as shown in Figure 5.8, images can be generated with various contrasts to highlight or suppress various tissues (e.g. T_1 -weighted, T_2 -weighted, CEMRA, PD, TOF, MP-RAGE [88], etc.). Using a multi-contrast approach, different tissues can therefore be identified determined by their intensity relative to a known tissue in the image.

Carotid artery atherosclerosis is commonly examined this technique, to identify plaque components such as the lipid rich necrotic core (LRNC), intraplaque hemorrhage (IPH), fibrous tissue, and calcifications [89, 90]. The sternocleidomastoid muscle is often selected as the reference tissue. This technique has been validated using histology, and offers valuable information, but is has limited clinical application because it relies on time consuming post-acquisition assessments. These assessments are often manually performed, and this leads to operator-dependent analyses. In addition, image artifacts can impact the reference tissues, generating further errors. Table 5.1 provides an overview of the expected MR characteristics for various plaque components using several popular contrast weightings [90].

Table 5.1: Carotid MR characteristics

Component	TOF	T1w	CE-T1w	T2w	PD
Intraplaque Hemorrhage	+	+	N	+/-	-/+
Lipid-Rich Necrotic Core	○	○	N	-	-/○
Calcification	-	-	N	-	-
Fibrous Tissue	○	○	○	○	○

Note: + indicates hyper-intensity; ○ indicates iso-intensity; - indicates hypo-intensity; Y indicates enhancement on contrast-enhanced imagery; N indicates enhancement absent on contrast-enhanced imagery

qMRI techniques are those that use the contrast information to generate information that quantifies specific parameters of the physical tissue [91]. One such technique is the Dixon gradient-echo sequence, which takes advantage of the fact that fat and water will have in-phase/out-of-phase signal shifts when comparing images acquired with slightly different echo times, as described in Section 4.5. From this information, water- and fat-only images can be produced, describing where in the image fat or water are located. From the same images,

Figure 5.8: The neck of a subject with stenoses of the carotid arteries, viewed using T_1 -weighted, contrast-enhanced T_1 -weighted, TOF, MP-RAGE, and CEMRA images. Red crosshair denotes stenotic vessel.

by measuring the signal loss due to phase dispersion, the T_2^* relaxation time can be quantified. The relaxation rate, R_2^* (i.e. $1/T_2^*$) can be viewed as a measure for the presence of iron (heme)², and therefore a measure of blood [63]. The R_2^* signal can therefore be used as a measure of IPH. The fat images can be used to generate a fat-fraction (FF) map and subsequently used to quantify the LRNC in carotid plaques, or to estimate the fat content of the vascular wall. Using this technique, operator-dependent selections of reference points are not necessary. This technique therefore lends itself well to automatization. Figure 5.9 depicts a cross-section from the neck with the T_1 -weighted, fat, and R_2^* images.

Figure 5.9: T_1 -weighted (left), Dixon Fat-only (centre), and R_2^* images (right) of the neck. Red squares mark carotid arteries.

In **Paper IV**, we designed and evaluated a method for automating the extraction of compositional information from the vessel wall. To do so, we used support vector machines (SVM) to segment the vessel lumen using bright-blood CEMRA data and subsequently delineate a vessel wall region, registered this mask to quantitative Dixon data, and extracted the compositional data. We validated our method using comparisons against manual analyses.

²Iron increases R_2^* because it creates local magnetic field disturbances.

Testing showed that our SVM-based segmentation method compared favourably to manually-performed segmentations in both quantitative and qualitative testing. With a Dice score of 0.89, a true positive ratio of 0.93 in ten vessels, and median qualitative score of $\frac{4}{5}$ across 30 vessels, the SVM-segmentation method was considered appropriate for use. We validated the definition of our vessel wall region by measuring the overlap between the automated segmentations and those generated manually on T_1 -weighted images. The mean overlap across 10 vessels was 0.84. This was considered acceptable for use, as during this test, the CEMRA segmentations were registered to T_1 -weighted images and some error may be introduced. This registration pairing does not exist in the automated workflow.

FF and R_2^* data was extracted using the automated and manual workflows and compared for ten subjects. Bland-Altman analysis for FF assessments showed good correlation, $R^2 = 0.83$, and a small positive bias of 3.2%. Comparing R_2^* assessments using the same approach showed moderate correlation of $R^2 = 0.51$ and a positive bias of $8.2[\frac{1}{s}]$. Using a histogram-based method to examine cohort-wide results, we found that the lower range of FF and R_2^* had more error than the clinically relevant higher range.

This study showed that automated approaches for extracting compositional information are comparable to manually performed analyses. The method developed here can be seen as a building block towards enabling large-cohort studies that use automated methods to reduce necessary observer input and the variance in data that produces.

5.4 Segmenting Vessels and Quantifying Geometry

In order to investigate vascular disease using MRI, the vessel in question must be located in the image. This is a non-trivial task for experienced observers in many scenarios, let alone automated methods. However, the studies included in this thesis demonstrated an evolution from primarily manual or assisted segmentation techniques to fully automatic state-of-the-art techniques.

Papers I and II employed a semi-automatic segmentation approach that relies on the relatively large difference in signal intensity between the bright-blood CEMRA or PC-MRA and the surrounding tissue. However, in large FOV acquisitions like those of the entire aorta, the signal intensity of the vessel lumen is rarely uniform, and often exhibits a large range of signal intensity because of uneven contrast material distribution, acquisition timing, or receiver-coil artifacts (e.g. Figure 4.4A). As a result, segmentations generated using this method often require time-consuming manual editing.

Segmentations generated manually or semi-automatic techniques are valuable for use as training data for more advanced machine learning segmentation methods. This strategy was employed in **Paper IV** to create the SVM classifier that was used to segment the carotid arteries from CEMRA data. That classifier attained Dice and true positive ratio scores of 0.89 and 0.93, respectively, using a small set of ten subjects for training. While manual edits are often still required when using this classifier, the time required to generate a segmentation that is ready to use for analysis is substantially reduced when compared to a

Figure 5.10: Fat Fraction (upper panel) and R_2^* maps (lower panel) for an example subject.

full manual segmentation procedure.

Feeding results forward once again, segmentations generated using the SVM classifier were used to train the convolutional neural network (CNN) used in **Paper V**. The CNN classifier is able to automatically segment the carotid arteries, as well as divide the bifurcation region into component branches. Examining the segmentations for all vessels included in **Paper V**, we found that the majority of vessels (250/382, 65%) did not require any manual edits (Table 5.2). Figure 5.11 depicts a typical segmentation of the carotid bifurcation generated using the CNN. Moving forward, the CNN can be further improved by continuously retraining when new segmentations are confirmed correct.

Aside from using these segmentations to describe hemodynamics or vessel wall composition, they can also be used to quantify vessel geometry. For example, using the segmentations of the carotid bifurcation generated by the CNN in **Paper V**, the bifurcation angle, branch diameters and diameter ratios, and vessel tortuosity are quantified without observer input.

Figure 5.11: Comparison of automatically generated segmentation of the carotid bifurcation generated using the CNN (bottom panel) versus manually generated ground-truth segmentation (top panel).

Table 5.2: Qualitative Assessment of Segmentation Results

Score	Description	Count
4	No adjustments required for further analysis use	250 (65%)
3	Minor adjustments (i.e. 2 minutes) required for further analysis use	87 (23%)
2	Substantial adjustments (i.e. 5 minutes) required for further analysis use	22 (6%)
1	Major adjustments (i.e. 10 minutes) required for further analysis use	7 (2%)
0	Segmentation Failure; one or more branches incorrectly labelled or missing, manual segmentation required	16 (4%)

Chapter 6

Discussion

This thesis explored various topics related to hemodynamics and vascular disease, towards the ultimate aim of a more comprehensive MRI examination that can describe the hemodynamics of the vessel, their effect on the wall, and the composition of the wall itself. As a result, we: developed and evaluated methods for visualizing and quantifying flow stasis in abdominal aortic aneurysms; increased understanding of the presentation of turbulence in the aorta; developed and evaluated a method for quantifying the turbulent shear stresses acting on the vessel wall and compared them to common measures of shear stress; and, developed and evaluated a method for quantifying the composition of the vessel wall.

This chapter will discuss the results of the work included in this thesis, highlight its contributions, and discuss future work.

6.1 Quantifying and Visualizing Flow Stasis

Routine investigations of flow stasis do not currently exist, in part due to the lack of a consensus definition for stasis but also because standardized approaches for quantifying and visualizing flow stasis are not available. **Paper I** lent effort towards the latter, in hopes that the methods developed can be used to establish a definition for this interesting feature of aneurysmal flows.

The results from **Paper I** indicated that traditional Lagrangian particle-tracking methods (e.g. volumetric residence time [73] and particle washout [75, 76]) for examining flow stasis in AAAs were not suitable for use in 4D Flow MRI, and this spurred the examination of two methods more suitable for 4D Flow MRI. The TDA and MVA methods presented in **Paper I** both generate scalar data for each voxel in the AAA which is ultimately classified as being “in stasis” or not (Figures 5.1 and 5.2). The two methods approach the task of binary classification differently, using a patient- or cohort-relative threshold value. TDA classifies voxels as being “in stasis” if their mean travel distance is below 25% of the maximum value for that subject, while MVA flags voxels with mean velocity below 5 cm/s as being “in stasis”. Both methods present benefits and drawbacks, as discussed in **Paper I**. Electing to classify voxels as “in stasis” or not, as opposed to directly using the scalar values from TDA or MVA, respectively, as a risk metric is important for visualizing and quantifying

stasis even though the precise definition of each respective threshold value can be debated. Flow stasis is a relatively unexplored area with respect to the hemodynamics in the cardiovascular system, and therefore threshold selection is an ongoing challenge.

This conceptual challenge was also encountered when Markl et al [68, 70, 92], and Cibis et al [71] sought to examine flow stasis in the left atrium and left atrial appendage. These studies both used a velocity thresholding method that classified voxels as being “in stasis” if their velocity was below a threshold value for the duration of the cardiac cycle. This is conceptually similar to the MVA method discussed in **Paper I**. However, the application of this method in regions with substantial wall movement, like the atrium and its appendage, is conceptually difficult. New strategies that involve time-resolved segmentations and a consideration for the wall’s effect on the flow are likely necessary for these anatomical regions.

The methods discussed in **Paper I** can be used to replace manual examinations of the flow fields using conventional visualization tools, in favour of more repeatable methods. Requiring no operator input, these methods would lend themselves well to longitudinal or large-cohort studies of aneurysmal hemodynamics, both of which would be valuable for understanding the role hemodynamics play in the growth of AAAs.

6.2 Quantifying Turbulence and its effects

Building on the work of Dyverfeldt et al [53–56, 79], which enabled non-invasive investigations of turbulence using 4D Flow MRI, in **Paper II** we examined the effects of aging on the presentation of turbulence in the aorta of healthy men using two age-based cohorts.

Aging brings several changes to the aorta, including increased vascular stiffness, tortuosity, and vessel size. The age-related dilation of the ascending aorta corresponded to a higher peak TKE when comparing the two cohorts, but the increased vessel diameters elsewhere in the aorta served to suppress the development of turbulence. This is likely because the flow in the ascending aorta resembles jet flow more than the other sections of the aorta that resemble pipe flow.

This finding was echoed in our analyses of the Reynolds number for each region of the aorta. We found that the Reynolds number was more strongly correlated to the levels of turbulence in the younger cohort than the older cohort. The Reynolds number, defined for simple geometries, does not appear to be reflective in the tortuous vessels of older subjects. Geometric complexities, alongside the wide range of mechanical properties, flow pulsatility, and hemorheological parameters reduce the ability of the Reynolds number to indicate turbulence in vivo. This suggests that measures like TKE have utility and should be considered while examining the flow in the cardiovascular system.

An important contribution of **Paper II** was the generation of valuable reference data concerning the location and intensity of turbulence in the aorta. As 4D Flow MRI-based turbulence examinations have only recently gained traction against invasive catheter-based measurements or computational studies, this data is unique. While our cohorts were modest in size, the data here lays a foundation for future work that could examine subjects against population-

normal values and draw physiological conclusions. Future studies must of course include women in their cohorts, something not done in this work. As women are less likely to have thoracic or abdominal aortic aneurysms, it would be worthwhile to examine the presentation of turbulence in cohorts of similar age and compare the results to the data generated here. This may help elucidate the role of turbulence in vascular diseases.

Focusing on vascular diseases implies a focus on the vascular wall as well, and therefore, understanding the impact of turbulence on the wall was the focus of **Paper III**. Turbulent flow near the vessel wall has been associated with vessel remodeling and is thought to damage the vessel wall [2, 67, 93–97]. To examine these potential effects, a method that represents the stresses that are generated by the chaotic velocity fluctuations is necessary. We found it was not feasible to estimate tWSS using current 4D Flow MRI spatial resolution, and therefore developed and presented nwTKE as a surrogate measure of tWSS that was possible to measure in vivo.

The most important contribution from **Paper III** was therefore the development of nwTKE as a surrogate parameter for tWSS. Using nwTKE as a surrogate measure for tWSS was also investigated by Andersson et al using CFD, and their results appear to echo our findings [98]. While adding another hemodynamic wall stress parameter to the already innumerable list makes selecting parameters for investigations difficult, nwTKE enables in vivo MRI-based investigations of the effects of turbulence on the vascular wall which were studied previously using in vitro methods (e.g. [94]) or animal models (e.g. [97]). Moreover, nwTKE reflects the intensity of chaotic fluctuations in WSS, and this feature is not well represented in contemporarily popular flow parameters such as OSI, the WSS gradient, or transWSS. OSI, for instance, reflects the laminar oscillations in WSS and is best used as a measure of WSS vector inversion [87]; the WSS gradient describes the local spatial changes in WSS [99]; and transWSS describes the multi-directionality of the WSS vector [100]. In addition, the time-resolved nature of nwTKE presents opportunities that whole-cycle parameters do not. Therefore, the use of nwTKE in future investigations appears merited.

We deployed the nwTKE analysis method in **Paper V**, alongside other hemodynamic wall stress parameters like WSS and OSI, to examine the carotid bifurcation. The primary goal of **Paper V** was to examine the relationship between carotid bifurcation geometry and the stresses acting on the vessel wall, though a secondary goal of **Paper V** was to understand the relationships, if any, among these hemodynamic wall stress parameters.

In examining the relationship between carotid bifurcation geometry and the stresses acting on the vessel wall, we quantified several basic parameters describing the bifurcation. The bifurcation angle, the branch diameters as well as the ratios between upstream and downstream branches, and vessel tortuosity were quantified. These are parameters that are immediately understandable and commonly used by clinicians. Vessel geometry has been implicated as a driver of atherosclerosis, given the focal nature of that disease [101–103], and numerous investigations have therefore taken place, with a variety of findings. Markl et al [104], using 2D PC-MRI planes to estimate WSS and combining those results with geometric measures, found a relationship linking the bifurcation angle to WSS and OSI. Lee et al [105] used CFD simulations to study this problem, and found that the surface area exposed to low WSS could be predicted by the

area ratio and tortuosity. Our results, however, did not replicate the findings from either of these studies. In our cohort of 191 subjects, we only found weak correlations at best. These findings are similar to the study by Van Ooij et al [106] that used the same methodology as **Paper V**, and found weak correlations among these parameters in their cohort of 20 elderly subjects. Gallo et al [107] used CFD simulations to estimate WSS in 41 cases, and did not find correlations between their more specialized geometric parameters like flare and curvature and low or oscillatory shear stress.

The results in **Paper V** must be tempered by an acknowledgement of the limitations inherent to in vivo WSS measurements using 4D Flow MRI. The estimation of WSS and derived quantities is limited by spatial and temporal resolution, artifacts like noise and background phase-offsets, as well as segmentation errors [85, 108], all of which could impact our results. Therefore, **Paper V** cannot conclusively determine relationships (or the lack thereof). That being said, our study included a cohort an order of magnitude larger than previous studies in this area, and deliberately used measures of geometry that are intuitive and routinely discussed as having impact on hemodynamics and subsequent atherosclerotic development. In addition we employed best-practice techniques for data acquisition, and estimating hemodynamic wall stresses.

Echoing Lee et al [109], we sought to examine interrelationships among hemodynamic wall parameters. In that study, Lee et al found many strong correlations among their roster of hemodynamic wall parameters, and concluded from this that many of these parameters characterize similar information from the flow, and therefore some can be considered redundant. For example, they found that relative residence time (RRT) had an extremely strong correlation to the TAWSS, which given the mathematical definition of RRT was not entirely surprising¹. It was in this spirit we examined nwTKE against WSS in both time-resolved as well as whole-cycle quantities, as well as OSI and the relative surface area metric described in [105]. Our analyses indicated moderate correlations between time-resolved nwTKE and WSS, and interestingly, no strong correlations between either the time-averaged nwTKE and OSI or nwTKE and SA80. This finding indicates that nwTKE, as proposed in **Paper III**, provides information not currently presented using common wall stress parameters.

6.3 Quantifying Vessel Wall Composition

With the ability to quantify vessel geometry and hemodynamics, the composition of the vessel wall demands examination in order to examine the interplay among these factors in both diseased and healthy individuals. The main contribution of **Paper IV** is a semi-automatic method for quantifying the composition of the vessel wall using the FF and R_2^* signal generated through a Dixon method MRI acquisition.

Paper IV built upon the work of Koppal et al [63], where they used a four-point Dixon sequence to quantify FF and R_2^* signal in atherosclerotic plaques of the carotid artery and validated these signals against histological findings. This work was limited in scope by the need for manual segmentation of the plaque boundaries. Manual segmentation is not only a time-consuming and non-trivial

¹RRT was defined in that study as: $RRT = 1/((1 - 2 \times OSI) \times TAWSS)$.

task, even for experienced observers, but it also introduces inter- and intra-observer variability to future analyses [110–112]. Therefore, our introduction of a support vector machine segmentation and automated definition of the vessel wall region contributed a new way to reduce the manual work needed to generate compositional data for the vessel wall.

In this work, we did not seek to segment and quantify the composition of only the plaque, but instead we examined the vessel wall region, a region we defined as having a maximum distance from the boundary of the vessel lumen. This simplification enabled the use of bright-blood CEMRA images for lumen segmentation. Moreover, this decision allows the proposed method to examine changes in composition across a larger region, instead of solely the plaque. This presents opportunities for longitudinal studies as the region being studied is consistent across subjects, and simplifies analyses in vessels where plaque boundaries are difficult to discern. **Paper IV** therefore contributed a key method towards the development of a more comprehensive non-invasive MRI-based examination for vascular disease.

6.4 Future Work

Future work to build upon this thesis could take a variety of forms. To drive further research and clinical use, development is likely to be focused on a two broad areas: increasing automation of the data processing and analyses; and, generating context and visualizations for analysis results.

Increased automation of data processing and analyses will drive more research and clinical users towards tools like 4D Flow MRI that generate very large datasets which are impossible to lightly peruse in search of a quick result. As discussed in Section 4.3.2, 4D Flow MRI acquisitions generate a three-dimensional time-resolved vector field representing blood flow, in addition to the magnitude image representing magnitude and any turbulence data. To extract meaningful data, the vessel or region of interest needs to be segmented or identified. Automated methods for placing flow-analysis planes [113] or segmenting the data [114] are crucial given the time-consuming nature of manual segmentation² and will drive large-scale analyses of these datasets. Accurate segmentations are also a prerequisite for analyses considering the vessel wall. For example, WSS analyses depend on this boundary to calculate the gradient of velocity at the wall [85]³. In regions with large wall motion, time-resolved segmentations are likely necessary. Moreover, methods that are reasonably robust to input image quality are desirable. For example, using the bright-blood CEMRA images for automated lumen segmentation and vessel identification becomes difficult with acquisition timing errors like those discussed in Section 4.4. With respect to vessel wall and plaque composition analyses, building upon the technique presented in **Paper IV** to more accurately define the outer boundary of the vessel wall and subsequently identify plaques would be a valuable development. Methods using Deep Learning (e.g. CNN’s) present possible solutions for these tasks as well, though training-data is required.

²Time-resolved segmentations are even more time-consuming to perform manually, and as a result, rarely used.

³Though, “segmentation-free” techniques are being presented[115].

Generating context for the numerous hemodynamic, geometric, or compositional parameters discussed is challenging, and without this context the information generated cannot be understood. To drive clinical use of these techniques, reference values for a variety of patient cohorts is necessary to contextualize a given parameter. Therefore, future work necessarily must include studies similar in nature to **Paper II**, where we examined the extent and degree of turbulence in the aorta. The large-cohort studies necessary to generate reference data rely on the automated methods described in this work and elsewhere. Innovative techniques like hemodynamic atlases [116] and cohort-average parameter maps [117] are valuable for contextualizing the results from a given subject against a given cohort and visualizing the result. Comparing a given subject against reference values also increases the value of a given assessment, as it can therefore be used for risk-stratification or determining the best course of treatment. It is not enough to generate a number while presenting results. Generating descriptive visualizations and contextual information during each hemodynamic, geometric, or compositional assessment will also help engage clinicians in research work. Engaged collaboration between engineering staff and clinical staff is crucial for advancing the techniques described in this thesis.

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