UNIVERSITY OF CAMBRIDGE
Department of Engineering

Assimilation of 4D Flow MRI Data into a Digital Twin

Sanadi Ilandaridewa

Supervised by Professor Matthew Juniper

Trinity College

I hereby declare that, except where specifically indicated, the work submitted herin is my own original work.

Signed :

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Abstract

4D Flow Magnetic Resonance Imaging (MRI) is an advanced imaging technique that captures time-resolved, three-dimensional velocity fields of blood flow, offering a detailed and non-invasive assessment of cardiovascular health. Its capability in visualising flow through the heart and blood vessels, quantify volumetric flow rates and assess pressure gradients makes it a valuable tool in diagnosis and management of cardiovascular diseases. Its disadvantage is that it requires long acquisition times as well as its limited spatial and temporal resolution. These limitations could be improved by combining flow MRI data with physics-inferred machine learning which reconstructs the flow to a higher degree of accuracy, reduces scan times and provides more actionable diagnostic parameters. This could make 4D Flow MRI a strong tool in routine clinical use. This project explores the possible applications and viability of integration of 4D Flow MRI into clinical workflows in order to diagnose cardiovascular diseases more effectively. Firstly three widely used flow imaging modalities (MRI, Doppler Ultrasound and CT Angiography) were explored to evaluate their methodologies and roles in diagnosing various cardiovascular diseases and limitations. A subsequent investigation explored how physics-informed 4D Flow MRI can address these limitations. A core component of the investigation involved observing clinical workflows and engaging with cardiologists and radiologists to identify the challenges they face in current diagnostic practices. This was achieved through direct observation of collaboration between cardiologists and radiologists during the acquisition of cardiac MRI scans, subsequent image analysis, and diagnostic discussions conducted in reporting sessions. This was further supported by interviews and meetings with a range of clinicians, during which Flow MRI images were presented to evaluate their perceived clinical value and to gather insights on desired improvements given faster scan speeds and diagnostic precision. A subsequent investigation explored the feasibility and utility of a physics-informed 4D Flow MRI in addressing these requirements. Lastly, the future work needed to establish this solver as a valuable tool in improving diagnostic accuracy and efficiency has been outlined. This project found that there is large scope for physics-inferred 4D Flow MRI to improve cardiovascular diagnosis. Firstly, it can be used to more effectively diagnose cardiovascular diseases compared to PC MRI and current 4D flow techniques. This includes eradicating the need for a clinician to trace vessel boundaries, therefore accurately quantify the flow rate through vessels such as the aorta. Furthermore, its accurate flow visualisation allows for abnormalities in the major vessels to be identified, such as aortic dissections, coronary heart disease and stenosis of the carotid artery. Secondly, this technique can be extended to ultrasound which, due to its low cost and high availability, makes its impact potentially wide-reaching. Thirdly, flow MRI can be combined with CT scans, which provide the vessel geometry, to reconstruct the flow more accurately. This approach could advance beyond the current gold standard for coronary heart disease diagnosis, a technique known as HeartFlow. Finally, this technique's ability to provide a single actionable parameter, such as wall shear stress, flow rate and pressure drop, is exceedingly valuable to clinicians. The advantage of this is its simplicity, which facilitates faster clinical decision-making. Overall, its value lies in filling the significant need for precise, accessible and clinically relevant imaging tools, particularly in overburdened healthcare systems. In order for 4D Flow MRI to make maximum impact, it will need to be streamlined for routine use and be validated by clinical studies. Thereby, physics-inferred 4D Flow MRI will become a powerful tool in improving patient outcomes and productivity in cardiovascular medicine.

1 Introduction

4D Flow Magnetic Resonance Imaging has emerged as a powerful tool for comprehensively assessing the flow of blood through the heart and major vessels due to its ability to provide 3D velocity fields in 3D space in opaque environments. This technique enables the visualisation of flow pathways, quantification of velocity and volumetric flow rates and haemodynamic properties. This offers unparalleled insight into the cardiovascular system making 4D Flow MRI an excellent tool to diagnose disease, monitor progression, and follow response to treatment. The current problems with this technique include low temporal and spatial resolution due to high noise in the measured data. This is mitigated by averaging over a large time, leading to lengthy processing times with a typical cardiac scan taking 75 minutes and up to 140 minutes for Congenital Heart diseases. The current spatial resolution is $1.5 \times 1.5 \times 1.5$–$3 \times 3 \times 3$ mm^3 and typical temporal resolution is 30–40 ms. However this can be further improved by combining flow MRI data and physics inferred machine learning to more accurately reconstruct blood flows. By applying a high quality prior of the Navier-Stokes equation and the no slip condition, the Bayesian inverse problem can be solved. This greatly improves the spatial and temporal resolution of flow-MRI.

The most significant improvement of physics-inferred flow MRI compared to current 4D Flow MRI techniques is the reduction of scan times by a factor of 10. This is especially significant due to the rising cost of healthcare in every developed country, driven by an aging population that is living longer but requiring more medical care. While the proportion of ill individuals has remained relatively constant, the absolute number of patients in need of treatment has increased, placing unprecedented strain on healthcare resources. Simultaneously, the number of working-age individuals funding these systems is decreasing, exacerbating economic pressures. This problem is universal across all healthcare models, whether publicly funded, privately insured, or a hybrid system. Whilst alternative funding approaches exist, the frictional cost of transitioning to a new model far outweighs any potential benefit, making systemic reform an impractical solution [30].

Rather than attempting to change healthcare funding systems, which is an overwhelming task, a more viable approach is to focus on increasing productivity within existing systems. The NHS, for example, repeatedly exceeds its operational budget. Making doctors and nurses more productive is the only sustainable way to address this crisis, and investment in capital equipment plays a crucial role in increasing net present value of resources. The key is not just to add value but to make existing processes faster and more cost-effective. Researchers and academics often focus on the diagnostic potential of new technologies, but if a new diagnostic tool leads to expensive treatments and increased demand of resources, it could worsen the financial burden on healthcare systems. By making existing cardiovascular assessments more efficient, 4D Flow MRI has the potential to enhance clinical decision-making while reducing the operational burden on radiologists and cardiologists. Its ability to provide comprehensive haemodynamic data in a single, non-invasive scan may eliminate the need for multiple diagnostic tests, ultimately leading to cost savings across the healthcare system. The following sections will explore the various applications of 4D Flow MRI, emphasizing its role not only as a diagnostic tool but as a means to improve healthcare efficiency. By shifting the focus from adding value to increasing productivity, this technology could play a critical role in making modern healthcare systems more sustainable.

This project aims to determine how the existing package for physics- inferred 4D Flow MRI can be integrated into clinical workflows. The first section will investigate the underlying physics of three common imaging techniques: MRI, Doppler Ultrasound and Computed Tomography Angiography. The subsequent sections will explore the various current applications of 4D Flow MRI and potential applications in the future. Additionally, the feasibility of extending this method to other imaging techniques, such as Doppler Ultrasound and Computed Tomography Angiography, will be assessed. The objectives of this project are to firstly identify how physics-inferred flow MRI can make diagnostic imaging faster, cheaper, and more accurate. Secondly, identify what improvements this technique can make across current applications of Flow-MRI as well as diagnostic processes currently involving other imaging modalities. Thereby determine the significance of the role physics-inferred 4D Flow MRI could play in cardiovascular medicine. Thirdly, identify the impact it will have on making modern healthcare systems more sustainable. Lastly, outline the necessary steps to maximise the adoption and integration of this technique in clinical workflows.

2 Methods

2.1 Introduction

A review of the current flow imaging techniques was conducted in order to fully understand what the most commonly used technologies are and what is considered 'state of the art'. This allows for the complications and limitations of these technologies to be identified so that we can better target the development of our solver to provide solutions to specific problems. This was done by firstly reviewing the literature about state of the art flow imaging. This was then supplemented by interviewing clinicians about how they process and analyse data from various flow imaging technologies in order to isolate areas that can be improved.

2.2 MRI

Flow MRI uses phase contrast velocity mapping images, which is useful for quantifying blood flow in order to diagnose a variety of conditions such as congenital heart disease and stenosis [27]. It is a technique that can reproducibly and non-invasively measure flow velocities with good correlation with invasive measurement techniques. It is the most expensive of the three imaging techniques discussed in this report, with a typical full-body three Tesla machine costing between $1-3 million [13]. It is also the longest process with the typical time allocated to a scan being 75 minutes [8], and up to 140 minutes for scans related to Congenital Heart Disease [6].

MRI works by applying a bipolar gradient pulse to induce a change in the Larmor frequency of the spins, which is the frequency of spin precession, therefore creating a phase difference between the spins. The equation for the Lamor frequency is given below:

$$\omega_0 = \gamma \cdot (B_0 + G_z \cdot z) \tag{1}$$

Where ω_0 is the Lamor frequency, γ is the gyromagnetic ratio, B_0 is the strength of the external static magnetic field (in Tesla) and G_z is the strength gradient pulse (in T/m).

A stationary spin will experience a unit change in phase. If a spin is moving whilst the gradient is being applied, for example in a blood vessel, it will accumulate phase with time. If the spin is moving with constant velocity parallel to a constant gradient, this phase accumulation can be predicted.

$$\varphi = \gamma \int \cdot \omega_0 dz \tag{2}$$

$$\Delta\varphi = \gamma \int_{t=0}^{t=T} G_z \cdot z dt \tag{3}$$

Where φ is the phase change, γ is the gyromagnetic ratio, G_z is the strength gradient pulse and the time interval, T, from the contraction of the cardiac muscle as blood is ejected into the aorta (systole) to it relaxing to allow the chambers to fill up with blood (diastole).

As the bipolar gradient consists of two lobes with equal magnitude but opposite polarity, phase changes in both the clockwise and anticlockwise direction are induced in the spins. The net phase change of the spin indicates the direction in which the fluid flow was traveling. Therefore a velocity vector of the moving fluid can be reconstructed as the magnitude of the phase changes gives information about the velocity of the spin through the slice, and the direction of the phase change tells us the direction in which the velocity was. If bipolar gradients are applied in all three Cartesian axes simultaneously, the magnitude and direction of spins in all directions can be identified. In order to isolate this phase change from background phase contributions, the phase change of the stationary spin is subtracted from that of the moving spin. The result is that areas with large phase changes are represented as bright. Conversely, small phase changes, i.e. stationary spins, are represented as darker areas, allowing the blood flow to be visualised. This data is stored in the 'wavenumber space', known as 'k-space', which can then be transformed into an image using Fourier transforms. This is called Phase Contrast MRI (PC MRI) and the data acquisition and processing strategy is shown in Figure 2 [25].

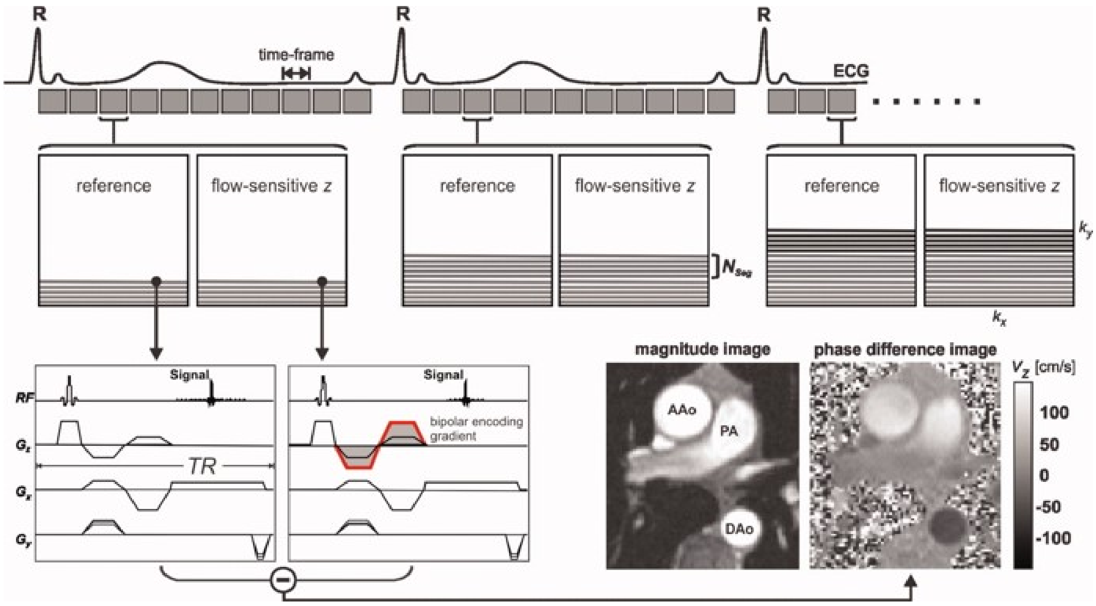


Figure 1: The process of acquiring and processing a 2D CINE PC MRI with out-of-plane velocity encoding in one direction. [25]

There is much scope for improvement because Phase Contrast MRI has a typical absolute signal-to-noise ratio of 10. It has the potential to play a significant role in the guidance of patient therapy so the refinement of PC MRI image analysis could make this technique a more critical part of the diagnosis process. The main complications are detailed in Section 2.1.

Recently, 4D flow MRI has been developed which uses full 3D CINE coverage with velocity encoding in three directions. A schematic of the process is shown in 2.

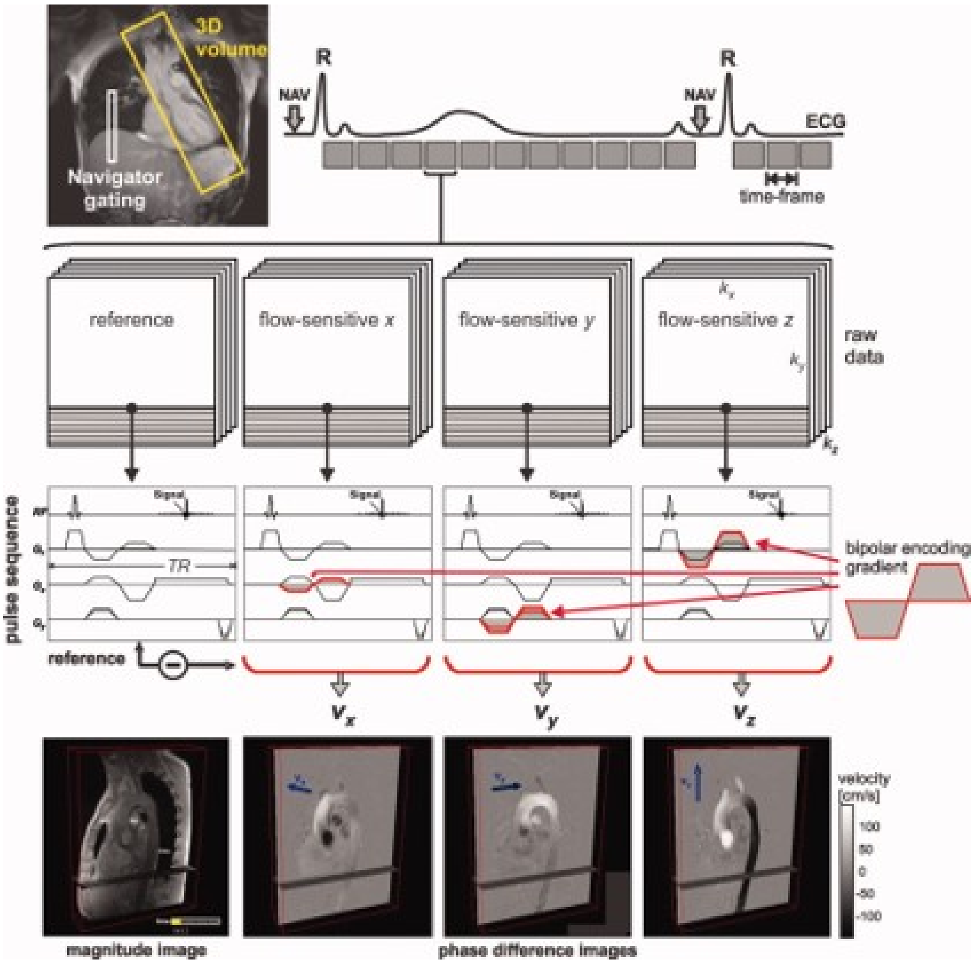


Figure 2: The process of creating 4D flow MRI from a reference scan and 3 velocity encoded acquisitions. [25]

Similar to the method of acquiring PC MRI images that utilised one-directional velocity encoding, data is acquired in all three directions along the phase-encoding line in the k-space. The image is then reconstructed to represent the velocities in all 3 directions. This is repeated over a cardiac cycle to reconstruct the flow over a time series.

2.3 Doppler Ultrasound

Ultrasound is a useful technique because it is a fast and easily accessible method with a mid-range unit costing $15,000 - $25,000. It can be used for a variety of applications from examining blood vessels to cancerous tissues. An ultrasound transducer probe is placed on the body which sends ultrasound waves into the area being examined. At boundaries between different tissues, the waves are either reflected or transmitted further depending on the ratio of impedance between the two tissues [18]. The equation for the acoustic impedance of a medium is given by equation 4.

$$Z = \rho c \tag{4}$$

Where Z is the impedance of the medium, ρ represents the density of the medium and c is the speed of sound through the medium. A tissue-fluid interface has an impedance ratio of approximately 1 and mainly transmits whereas a solid-fluid interface has an impedance ratio of significantly more than 1 and and mainly reflects. A measure of the amount of ultrasound which will be reflected at the interface is given by the ratio of the reflected to the incident intensity which is known as the reflection coefficient. The equation for the reflection coefficient is given by equation 5 below.

$$R = \frac{Z_2 - Z_1}{(Z_2 + Z_1)}^2 \tag{5}$$

Where Z_1 and Z_2 represent the impedance of medium 1 and medium 2 respectively. The transducer receives these reflected waves (also called 'echoes') and builds an image in gray scale with lighter areas showing a lower amount of reflected waves, and dark areas showing denser tissues with a stronger reflection. This image is the B-Mode ultrasound or 'brightness mode' which is the most widely used ultrasound imaging technique. The main limitation is the low resolution of the images that are produced making diagnosis difficult. Axial resolution (pixels along the length of the ultrasound beam) depends on the pulse length and ranges from 0.5 to 1mm.

Doppler ultrasound employs the Doppler effect to detect the velocities of blood flow through vessels. Doppler effect is the shift in sound frequency as the target moves with respect to the source. It is used in conjunction with Pulse Wave Doppler to determine blood flow velocities in a specific area of interest within the body. The clinician sets the location of interest called a 'gate' and the transducer sends out short ultrasound pulses. As the speed of these pulses in soft tissue is known, the transducer can adjust the period during which it 'listens' for the reflected echoes depending on the expected time waves would take to travel back from the specified location. Thereby the frequency shift associated with the blood flow in the specified area can be isolated and used to calculated the flow velocity [36]. This frequency shift is called the Doppler shift which can be used to calculate the velocity of the red blood cells. The governing equation for these measurements is (Gill 1985 [16]):

$$f_D = \Delta f = \left(2\frac{V}{C_0}cos\theta\right).f_0 \tag{6}$$

where f_D= Doppler shift, C_0 = Speed of sound in intervening medium, V = Speed of object, θ = angle between ultrasound beam and direction of motion and f_0 = Frequency of measuring signal. θ is determined using the B-Mode ultrasound image which can give the angle between the blood vessel and the transducer head. The mean frequency is calculated from N received samples using an auto-correlation based method. The mean velocity is found by (Ali et al 2008 [4]):

$$\bar{v} = \frac{\bar{w}}{w_0} \cdot \frac{C}{2\cos\theta} \tag{7}$$

Where w_0 is the carrier frequency, C is the velocity of sound, θ is the angle between sound beam and blood flow, and $\bar{w}$ is the mean angular frequency of the power spectrum of the received signal. Typically, the flow direction is obtained from the polarity of the Doppler frequency shift. [24]

There are multiple sources of error in Doppler ultrasound that effect that bias and noise characteristics of the processed signals. [26]

- The echo received from the red blood cells includes low frequency components due to the motion of blood vessels walls which is filtered out using different methods depending on the ultrasound machine, for example, a simple high pass filter or correlation based algorithms.
- Significant aliasing occurs when the Doppler shift of moving red blood cells is higher than half the Nyquist frequency.
- As Doppler Ultrasound measures the velocity in the direction of the ultrasound beam, high out of plane velocity will be underestimated.
- Poor positioning of probe along the primary flow direction.

When Doppler ultrasound is used to examine the heart in particular, this is called Echo-cardiography. The ultrasound beam used is a quadrilateral pyramid with resolution in 3 dimensions; axial (resolution along the beam), lateral (resolution horizontally across the 2D image) and elevational (resolution across the slice thickness). Usually, Echo-cardiography has a slice thickness of 3-10mm. Axial resolution is in the range of 0.2 to 0.5mm and is equal to half the spatial pulse length which is dependent on the wavelength of the beam. Therefore axial resolution can be improved by using smaller wavelengths, however this leads to increased attenuation so there is a tradeoff between resolution beam penetration. The most reliable data is acquired when the beam is perpendicular to the area being examined. Lateral resolution depends on the focusing of the beam on the area of interest and is typically 1-2mm. For a given 2D image, structures at larger depths have lower resolution due to beam divergence, causing many artifacts in the Echo-cardiogram.

2.4 CT Angiography

Computed Tomography Angiography is a flow imaging technique whereby contrast dye is administered to a patient through an IV line which enhances the blood vessels so that they can be seen more easily on the X-Ray image. It is a widely used technique because it is non-invasive and has a pixel sizes of 0.5 - 0.6mm. The International Atomic Energy Agency recommends that cumulative radiation exposure is limited to 50mSv in a single year [2] which is equivalent to 3-5 CT Scans per year [14].

The setup of a CT scanner is shown below, depicting how X-rays are produced, passed through the body, and the resulting waves are detected at the other end. The X-ray source and detector are mounted on a rotating gantry, allowing for many projections to be taken of the same area at different incidence angles.

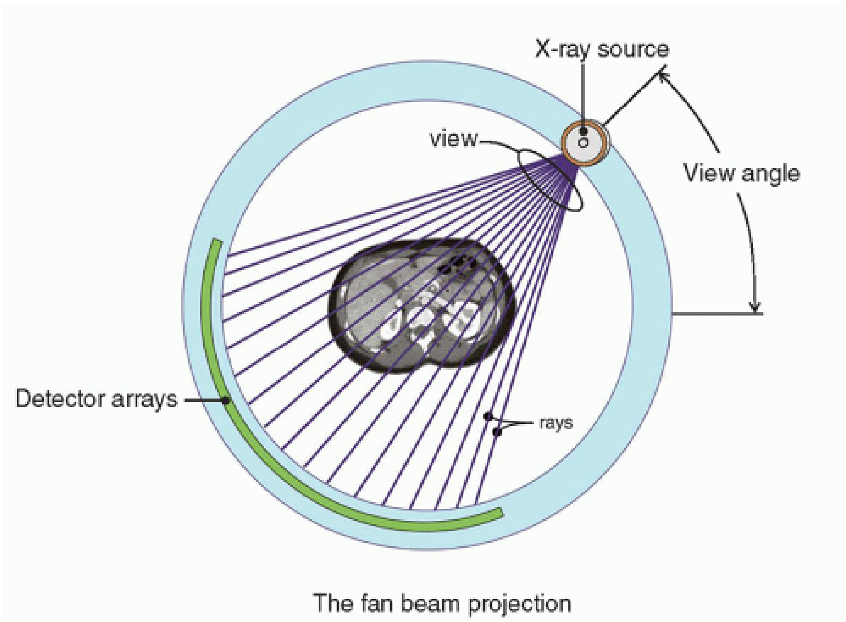


Figure 3: The general configuration of a CT scanner in cross section. [Radiology Key 2021]

The CT Scan obtains a sequence of 2D X-Ray images of an area of interest from many different views. These 2D images are then reconstructed to form a stack of cross-sectional slices which provides a digital 3D greyscale representation or tomogram of this area. To create each 2D slice, X-Rays are passed through the body, and differentially attenuated depending on tissue characteristics. The attenuation measured by the detector, N, is given by the following equation:

$$N = N_0 e^{-\mu x} \tag{8}$$

where N_0 is the strength of the X-ray emitted by the source, μ is the local attenuation coefficient of the tissue, which can then be used to reconstruct the global distribution of $\mu(x, y, z)$ from the images. The detector contains a high pass filter, which increases the average energy of the X-rays incident on the detector which allows for sharper images to be produced. The attenuation values of the detected X-rays are measured and plotted against distance along detector, which produces an image called a sinogram.

The first step of image reconstruction from the sinogram is a process called back projection. By dividing the 2D slice into a grid of pixels, we can imagine that each pixel represents a different tissue in the body and therefore experiences varying attenuation. The sum of attenuation through all the pixels in a row is given by the sinogram which is divided by the number of pixels in the row to give the average attenuation in each pixel. In this case we assume parallel beam projections and thus the back-projection operation simply spreads the detector value back along the directions that the rays were measured in. The gantry is rotated and a new singoram is produced at a different projection angle and the process is repeated. This allows for an initial approximation of the image, which is significantly blurred. The back projected image can be further improved by a method called iterative reconstruction. The overall process of this is shown in the figure below.

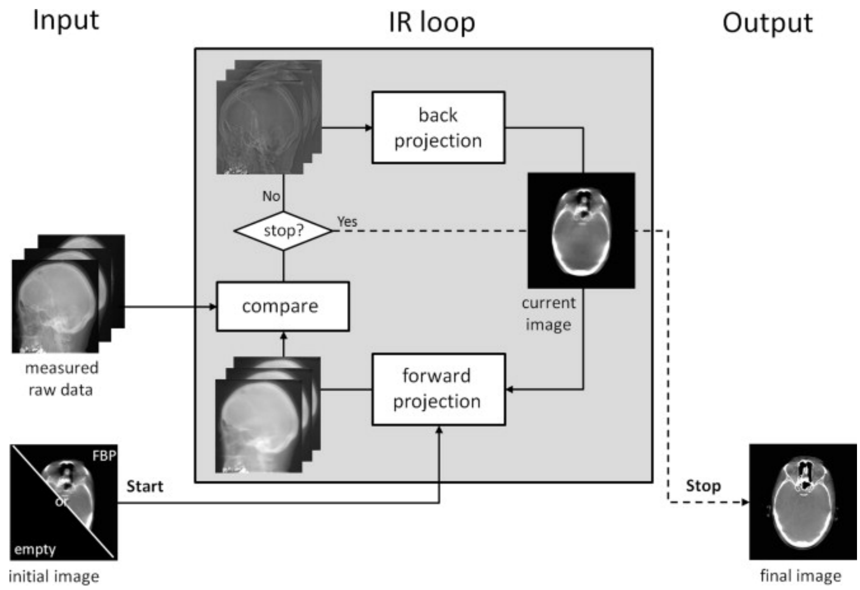


Figure 4: The process of iterative reconstruction methods in X-ray CT. [M Beister etal 2012]

Here, the forward projection is the opposite process of the backward projection where the attenuation in each pixel is summed to give the total attenuation along a row (or column) of pixels in the 2D slice grid. The forward projection of the back projection from the sinogram, gives artificial raw data. This can be compared to the real measured raw data to give an error term. The error term is back projected again and the iteration repeats. The process is considered to have converged when the update for the current iteration is below a predetermined tolerance.

Image reconstruction from the sinogram produces the 2D slice in grayscale with the colour of each pixel corresponding to values of CT numbers or Hounsfield units. This is a unit that measures attenuation, standardised against the attenuation of water, i.e. materials have a positive Hounsfield unit if they attenuate more than water, and a negative unit if they attenuate less than water. Thereby, CT scans allow tissues and blood vessels in the body to be visualised however it does not provide any velocity information about blood flow unlike Doppler Ultrasound and PC MRI.

3 Applications

3.1 MRI

To gain insight into the current clinical applications of MRI and its usage, I utilised a range of research methods. Firstly, I conducted a literature review to identify the most widely documented applications of MRI, providing a foundation for further inquiries with cardiologists and MRI specialists. Secondly, I visited the MRI department of the Heart and Lung Hospital, Harefield [1] where I observed cardiologists using state-of-the-art software called CV142 [20]. This allowed me to understand the process of acquiring, post processing and analysing MRI images. Most importantly, it allowed me to indentify the short-comings of the current 'gold standard' and therefore how it can be improved. Lastly, speaking to MRI specialists, in both cardiology and stroke medicine, helped establish the future applications of the 4D Flow MRI solver being developed by the Cambridge University Engineering Department. The research showed that MRI images are currently used to diagnose a variety of diseases, which will be detailed in the sections below.

Through the observation of cardiologists' workflow when using cardiac MRI images, the following process of image analysis and subsequent patient diagnosis was identified. A cardiologist begins by specifying 3 points on the cardiac wall in the long axis magnitude MRI, which allows the software to segment the 4 chambers of the heart in both the long and short axis. The result is shown in figure 5. It was observed that the automatic segmentation carried out by the software is often inaccurate and has to be manually adjusted by the cardiologist. This is because it incorrectly detects darker areas (representing backwards flow) as cardiac muscle. This effect is exacerbated when the patient's chambers are distorted due to infection or cardiac abnormalities such as leaky valves. The software then calculates the volume in each chamber using the Simpson method, which sums the cross-sectional slices through the chamber.

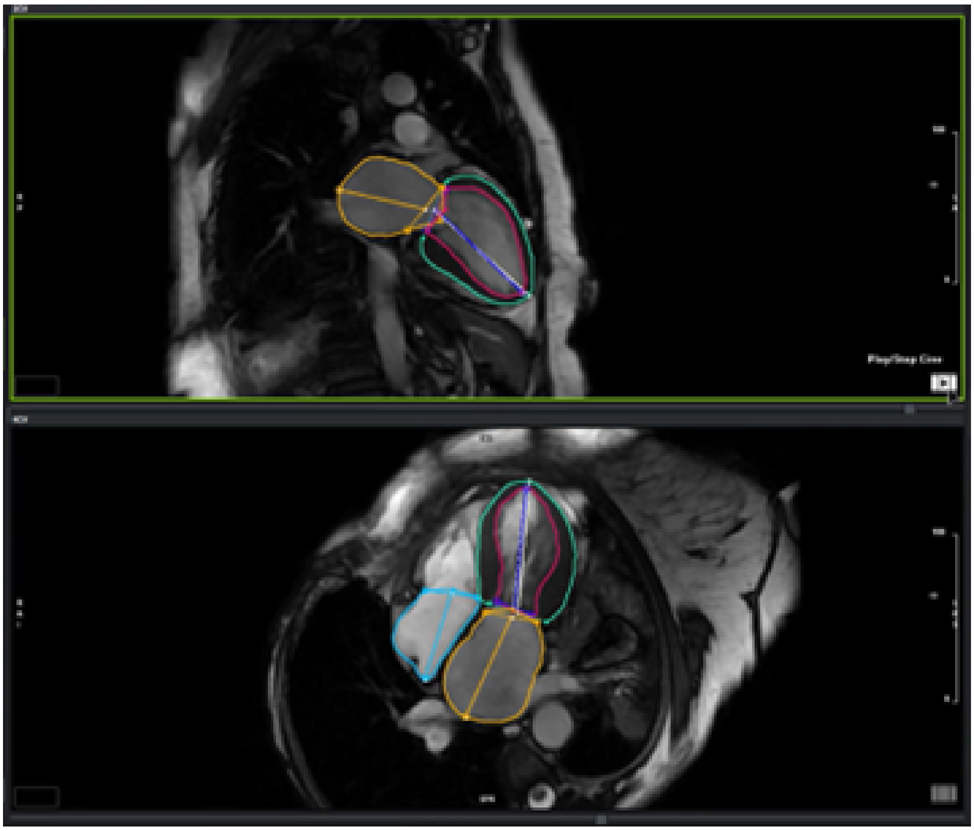


Figure 5: Segmentation of cardiac chambers in CV142.

The magnitude MRI is also used to measure the diameter of the aorta. A cardiologist will draw 3 lines at each of the 3 sinuses in the aortic roof and measure the length of these lines, as shown in 6 below.

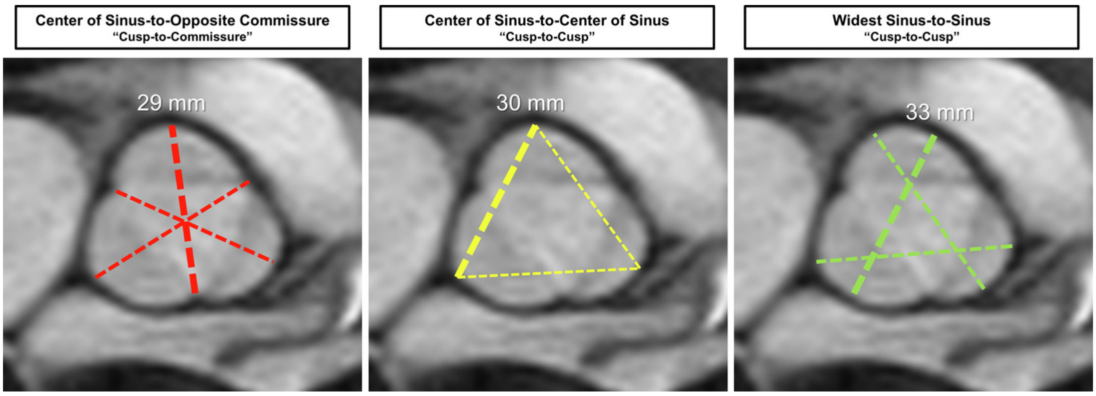


Figure 6: Different techniques used to measure the diameter of the aorta. [38]

Firstly, a slice is taken perpendicular to the ascending aorta in order to quantify the flow through it. The boundary of the aorta is identified by eye and drawn by the cardiologist using the computer mouse on the magnitude image. The Phase Contrast image displays forward flow as bright areas and backward flow as dark areas within this boundary. From the PC MRI, the velocity of the flow is multiplied by the cross sectional area of the hand-drawn vessel to give the flow rate in ml/s. A graph is produced of flow rate of blood against time from the contraction of the cardiac muscle as blood is ejected into the aorta (systole) to it relaxing to allow the chambers to fill up with blood (diastole). For a healthy heart, this graph looks like a normal distribution representing the high forward flow rate in the systole and a small amount of backwards flow in the diastole due to the elasticity of the aortic valve. The area under this graph is integrated to give a value for the forward and backward flow rate in order for the cardiologist to compare it to the standard value.

Estimation of the vessel boundary through visual inspection and hand drawings is crude and produces inaccurate values for the blood flow rate. This can be improved by solving the Bayesian inverse problem for Navier-stokes to infer the vessel boundary. This method utilises prior knowledge we have of fluid flow behaviour such as conservation laws of mass and momentum and no-slip at the boundary. This results in higher spatial and temporal resolution of flow-MRI images.

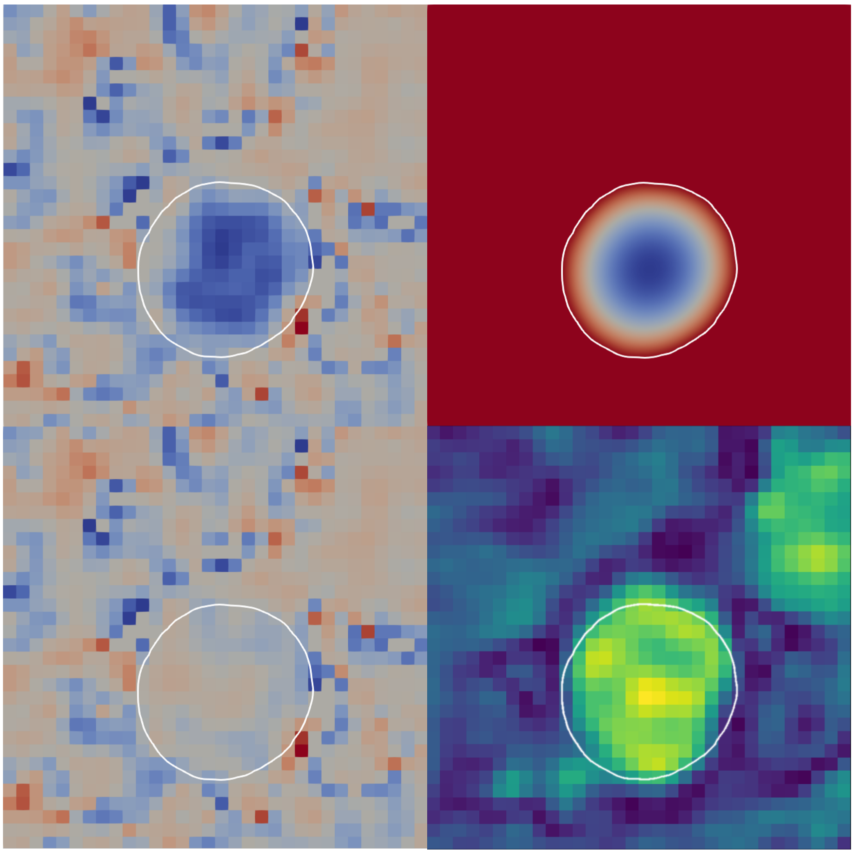


Figure 7: Figure showing how the vessel boundary can be inferred from flow MRI data. Original velocity data from MRI scan (top left) is assimilated to produce the final inferred velocity field (top right). The model-data discrepancy is shown (bottom left) and the density data for each pixel to validate (bottom right). The inferred boundary is shown in white in all four images.

Although 4D Flow MRI is a feature of this state-of-the-art software, it is not widely used in clinical practice due to its inaccuracies. However, research has identified several valuable applications where it could be beneficial, which have been detailed in the sections below.

3.1.1 All Vessels

Through observation of the process of an MRI technician analysing PC MRI images, a major limitation was found. Vessels of interest are identified by the technician visually inspecting the phase contrast image and tracing the area they identify to be the boundary of the vessel using a computer cursor. An image produced using this technique is shown in figure 8.

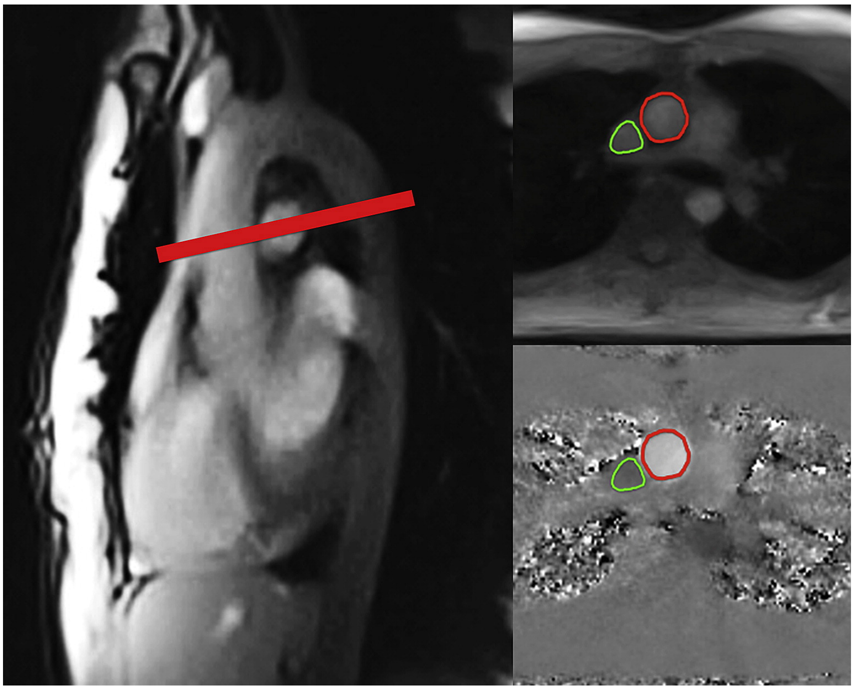


Figure 8: Magnitude image of side view of the heart (left) from which a perpendicular slice has been taken at the root of the ascending aorta to show the cross sectional magnitude image (right, above) and phase contrast image (right,below). [Fasshauer et al 2014]

This is an inaccurate method of detecting the boundary. This could be improved by using an automatic segmentation method. The velocity profile through a 2D slice of the vessel and the assumption of no slip at the wall can be used to find the boundary. This is a significant development as it does not require contrast to be administered to the patient, and this method will locate the boundary more accurately.

The biggest physiological indicator of disease in vessels is stenosis. Stenosis is the narrowing of blood vessels which is often caused by the build up of plaque on the inside of the vessel, called atheroma. An image of this is shown in figure 9 below.

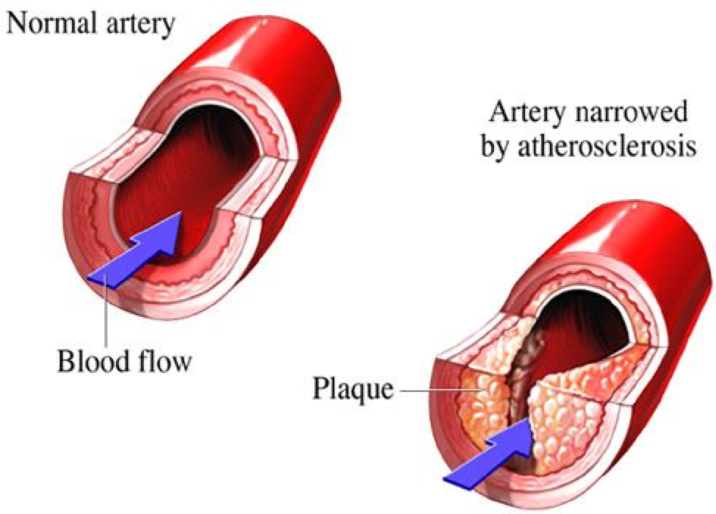


Figure 9: Image showing the effect of plaque build up on the interior of a blood vessel causing stenosis.

The degree of stenosis is graded using the haemodynamic effect: local flow velocity at the level of a plaque or stenosis, pressure drop or reduced flow volume. The threshold for surgical intervention is 70% stenosed, but clinicians find it difficult to make decisions on borderline cases in the 50% to 70% range from current MRIs. These haemodynamic parameters can be more accurately recovered from the Flow MRI solver being developed by the Cambridge University Engineering Department (CUED), therefore allowing clinicians to make better informed decisions.

One of the most clinically relevant applications is the assessment of the mechanical properties of the arterial wall as how stiff or compliant it is effect the blood flow through the vessel. Furthermore, the ability to quantify how much the arterial wall moves in response to pulsatile blood flow is useful for monitoring aneurysm progression, because vascular compliance and blood pressure are closely related in patho-physiology. Stiffer vessels may contribute to hypertension and increase the risk of vascular complications. This is because the lack of elasticity prevents the vessels from expanding and contracting, increasing the force required from the heart to pump blood around the body. This results in higher systolic and diastolic pressure in the blood vessels. On the other hand, excessively compliant vessel walls may be prone to pathological dilation and rupture. Understanding these mechanical properties could also be valuable in clinical trials assessing the effects of pharmacological interventions. By evaluating changes in vessel wall compliance before and after treatment, researchers could determine whether certain medications influence vascular stiffness, potentially guiding the development of targeted therapies for conditions such as hypertension and aneurysmal disease. The compliance of the arterial wall is a parameter that can be more easily determined using the 4D Flow MRI method developed by CUED compared to current techniques.

Another promising area of investigation is inference of the wall shear stress (WSS), the force exerted by flowing blood on the endothelial surface. The current gold standard for Current 4D Flow MRI is not yet optimised for routine WSS measurement as the micro landscape is smaller than the voxel size, but the 4D Flow MRI method developed by CUED can infer this parameter possibly enabling it to become an indicator of vascular pathology. It has been hypothesised that changes in WSS contribute to disease progression, particularly at vessel bifurcations where flow patterns shift abruptly. These regions are thought to be susceptible to plaque formation and vascular remodeling due to changing shear stresses, but the relationship between WSS and disease requires further investigation. Current studies have shown that in patients with coronary artery disease, vessel segments with changes in WSS develop more vulnerable plaques [33]. Further research demonstrated that regions of low WSS within the carotid bifurcation are preferential sites for intimal thickening (thickening of the inner layers of an arterial wall) and atherosclerotic plaque formation [42]. Further research to prove WSS is a direct causative factor in pathology is limited, in part due to the lack of an accessible, reliable, and non-invasive method for measuring it. Current methods are too expensive and not widely available, meaning they are only used in clinical research and inaccessible for use in disease diagnosis. A more efficient and standardised approach for quantifying WSS could help researchers investigate whether medications or lifestyle interventions influence vascular geometry and atherosclerotic plaque development. This is particularly relevant for stroke risk assessment, as plaque stability is the main risk factor for a stroke occurring. This will be expanded in section 3.1.5. Future advancements in 4D Flow MRI could enable more precise WSS analysis, providing a non-invasive means of studying stroke pathophysiology and optimising treatment strategies.

While current 4D Flow MRI provides extensive information about blood flow, it does not currently allow for direct visualisation of micro-structural wall characteristics, such as surface roughness or endothelial dysfunction, because these structures are smaller than an MRI voxel. These fine details are critical in understanding endothelial health and plaque morphology. Currently, such analysis is performed using Optical Coherence Tomography (OCT), an invasive imaging technique that involves inserting a small optical probe into an artery and flushing the vessel with saline to obtain high-resolution images of the vessel wall. OCT offers great detail, revealing microscopic features of the endothelial surface and plaque composition, but its invasive nature limits its widespread use. A non-invasive alternative with similar resolution would allow for routine monitoring of the endothelial wall and plaque evolution without the risks associated with catheter-based procedures.

An emerging non-invasive technique of imaging vessel wall biology is Positron Emission Tomography, a nuclear imaging technique. A radio-labeled molecular tracer is administered, usually radio-isotopes with short half lives, that emit positrons. When a positron encounters and electron, annihilation photons are released that are detected by the PET scanner. 3D reconstruction of tomographic images displays the distribution of the tracer therefore specific radio-isotopes can be chosen depending what needs imaging. F-fluorodeoxyglucose has been proven to be a successful tracer in imaging vascular wall health [37]. The spatial resolution of PET can be further improved by combining MRI or CT scans. Whilst the physics-inferred Flow MRI diagnostic cannot infer wall roughness on its own yet, using it in conjunction with other imaging modalities such as PET or CT could reconstruct the flow on the blood vessel wall in order to infer vessel wall biology [35].

Recent advances in high-field cardiac MRI, particularly with 7 Tesla magnets, have shown promise in enhancing the spatial resolution of cardiac images. It is widely recognised in clinical practice that arterial and carotid wall imaging demands the highest spatial resolution and have received the most benefit from high-field CMR. An investigation into

7 Tesla MRI machines conducted by Niendorf et al [28] compared the signal to noise ratio when imaging cardiovascular morphology using low Tesla and 7 Tesla machines. The results are summarised in figure 10 below.

Application	Imaging Technique	SNR Gain	Note
Carotid vessel wall imaging[27]	2D T_1-weighted black blood prepared fast spin-echo	2.0 (vs 3.0 T)	RF coil designs used for reception were optimized for the 7.0- and 3.0T setup, 3.0- and 7.0T RF coil sensitivity similar at target
Cardiac chamber quantification[12]	2D CINE fast gradient echo	2.1 (vs 1.5 T)	Different RF coil designs used for signal reception at 7.0 and 1. 5 T, RF coil sensitivity in favor of 1.5T setup
Noncontrast-enhanced, time-resolved phase velocity 4D aortic flow imaging[21]	3D free-breathing, navigator-gated, velocity-encoded gradient echo	2.2 (vs 3.0 T) 3.8 (vs 1. 5 T)	Different RF coil designs used for signal reception at 7.0 and 3.0/1.5 T, RF coil sensitivity in favor of 3.0/1.5 T setup
Coronary MRA[10]	3D free-breathing, navigator–gated, and fat-suppressed 3D k-space segmented fast-gradient echo	1.63 (vs 3.0 T)	Different RF coil designs used for signal reception at 7.0 and 3.0 T, RF coil sensitivity in favor of 3.0 T setup
^{31}P spectroscopy of the septum[19]	UTE-CSI	2.6–2.8 (PCr signal; vs 3.0 T)	Same RF coil design used at 7.0 and 3.0 T

Figure 10: Synopsis of Gains in SNR Obtained for Cardiovascular MR Applications at 7.0 T vs Lower Field Strengths [28].

It was found that the SNR doubled when using a 7T machine to image the carotid wall compared to a 3T machine. With these advances, the physics-inferred Flow MRI diagnostic developed by CUED could directly be applied to vessel images with higher spatial resolution to infer the roughness parameter.

It is clear from the section above that there are many applications of improving 4D Flow MRI using physics-inferred machine learning. However many of the parameters that can be found using this method, are not commonly used or even understood in current medicine. Therefore clinical studies would need to be carried out in order to verify the relevance of these metrics as markers for disease, making this method a promising tool for researchers in the meantime.

3.1.2 Aorta

There are many aortic diseases that are diagnosed using MRI and, more importantly, benefit from an improved method of processing Flow MRI data to give 4D models.

Firstly, if the aortic valve is not functioning correctly, the diastole will have a large amount of backwards flow or regurgitant flow back into the left ventricle. Currently this is examined using a 2D PC MRI slice. In order to quantify a regurgitant jet, it is very important that a perpendicular slice is taken at the level of the regurgitance. This provides a visual representation of the backwards flow but also produces a graph of flow rate over a cardiac cycle through the slice. Integrating the reverse flow in this graph, gives the volume of the regurgitant jet. As the flow rate is found by multiplying the average velocity by the approximate area determined by manual segmentation, it is a crude estimate.

The aorta can suffer from congenital conditions such as aortic coarctation. This is when there is narrowing in the aorta, most commonly in the arch. A 4D Flow MRI of a 3.5 year old pediatric patient diagnosed with aortic coarctation can be seen in figure 11 below.

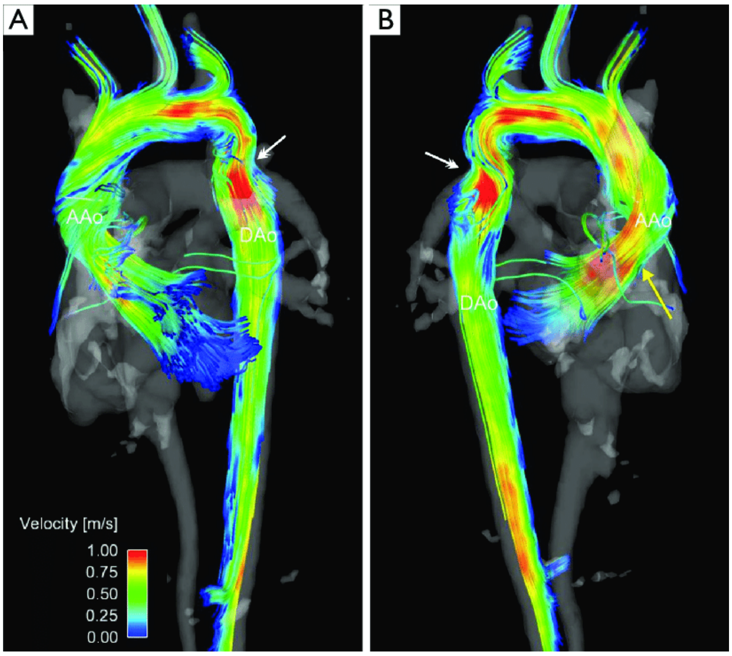


Figure 11: 4D flow MRI in a 3.5-year-old pediatric patient in (A) anterior and (B) posterior views. The area of high velocity in the aortic arch and subsequent helical flow (shown by the white arrow) can be seen.

Figure 11 shows the significance of 4D Flow MRI in diagnosing abnormal physiology such as an aortic coarctation. Analysis of the streamlines and flow velocities is essential for diagnosis compared to simple magnitude images from MRI, CT or Ultrasound.

Another condition is aortic stenosis which is when the flow rate out of the aorta is reduced due to calcification of the aortic valve. It is often difficult to discern from heart failure as this causes weakening of the cardiac muscle that also reduces the volumetric flow rate out of the aorta.

3.1.3 Heart

Another application of phase-contrast MRI (PC MRI) is the diagnosis of cardiac shunts—abnormal cross-flow between the left and right sides of the heart due to septal defects, which reduce cardiac output efficiency. This is typically assessed by plotting flow rate against time in the pulmonary artery and quantifying the forward flow. The ratio of flow in the pulmonary artery to that in the aorta is then calculated; a ratio greater than one indicates the presence of a shunt. This occurs because the higher-pressure flow in the left side of the heart is diverted into the right side, resulting in increased flow rate in the pulmonary artery .

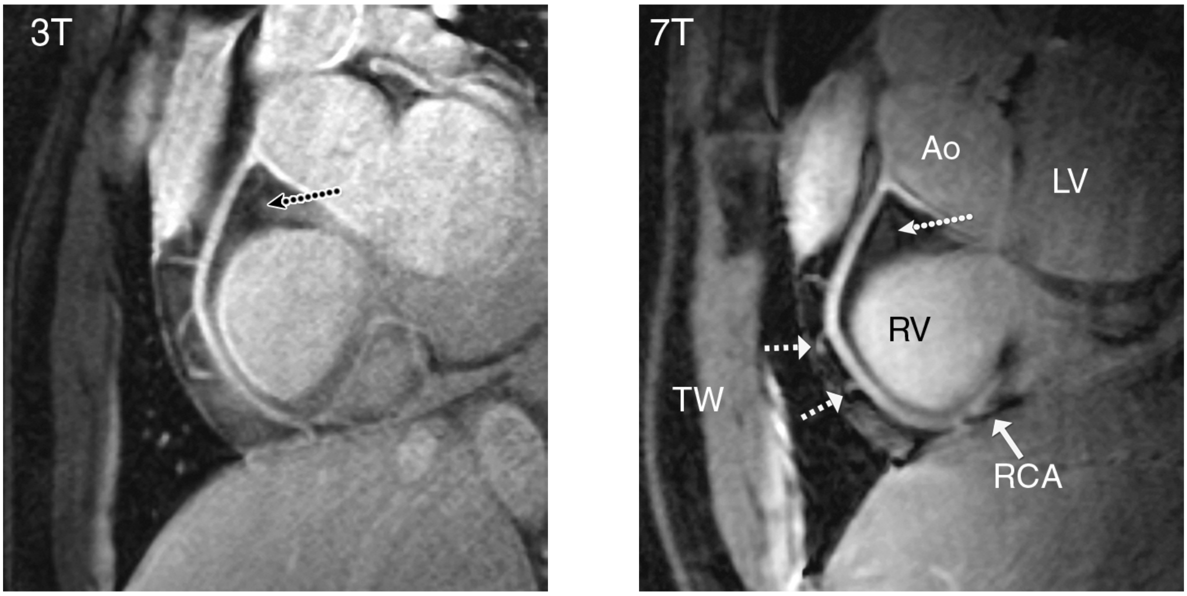
Another common application is to quantify stenotic lesions, which is the narrowing of blood vessels due to blockages caused by build up of plaque on the vessel wall. PC MRI allows the decreased blood flow rate due to the blockage to be quantified and compared to a database to assess the severity of the stenotic lesion.

3.1.4 Coronary Arteries

The British Heart Foundation recognises Coronary Heart Disease as 'the world's biggest killer' with 9 million deaths caused by the disease in 2021. Coronary Heart Disease is caused by stenosis in the coronary arteries which is the narrowing of the vessels due to build up of plaque on the vessel wall. Therefore clinicians are concerned with the objective degree of stenosis in the coronary arteries. It is one of the most significant areas of diagnosis and treatment that 4D Flow MRI can help improve. In current clinical practice, stenosis is identified using Fractional Flow Reserve. Fractional Flow Reserve is the maximum blood flow in a diseased coronary artery and the maximum blood flow in the same vessel with no stenosis, with a theoretical ratio of 1.0. The FFR is calculated as the arterial pressure ratio between the part of the coronary artery closest to the aorta and the distal artery at the stenosis site. Developments in recent years have allowed FRR to be more accurately calculated by incorporating the use of CT, which was pioneered by HeartFlow and is discussed in section 3.4.2 below.

There is great scope for 4D Flow MRI to be applied to imaging the coronary arteries. The perfusion of blood via the coronary arteries, through the myocardium (the middle lining of the cardiac wall that contains majority of the coronary arteries) is analysed for diagnosis as this is essential for healthy functioning of the cardiac muscle. Lack of perfusion, caused by stenosis of the coronary arteries, leads to death of the myocardium due to lack of perfusion, clinically named ischemia. The gold-standard for assessing perfusion is a method called Positron Emission Tomography (also detailed in section 3.1.1), however it is expensive and too expensive to be widely used. The most common method is administering gadolinium to the patient and performing a cardiac MRI scan. By detecting the concentrations of gadolinium in various parts of the myocardium, the flow of blood to these areas can be identified. However, Cardiologist B [5] identified that there is currently no imaging technique that allows clinicians to analyse coronary arteries and the myocardium simultaneously, which can be done by 4D Flow MRI. This would improve the analysis of coronary arteries and the diagnosis of ischemia greatly. This is because it is useful to see what is happening on the inside of the coronary artery that is causing the ischemia; for example stenosis or plaque build up. It is important to determine whether there are enough coronary arteries in the area of the ischemia as this would determine the need for surgical intervention.

Coronary arteries are 3-4mm in diameter which is 3-4 voxels wide in a typical MRI scan meaning very little information is provided about the flow through these arteries. To gain more physiological information about the blood flow in coronary arteries through MRI, its spatial resolution needs to be higher. This can be done with new MRI machines that have higher strength magnets, up to seven Tesla. This can be seen from the results of the investigation conducted by Niendorf et al, summarised in figure 10. It was found that using a 7 Tesla machine to image the coronary arteries using MR Angiography resulted in a gain in SNR of 1.63 compared to a 3 Tesla machine. The improvement in spatial resolution using a 7 Tesla machine allows the coronary arteries to be visualised more accurately and a larger amount of the distal coronary arteries to be visualised as well. The improvement in coronary artery image quality from 3 Tesla to 7 Tesla MRI machines was found by van Elderen et al and is shown in figure 12 below [39].



(a) (b)

Figure 12: Coronary MR angiograms of the RCA obtained at (a) 7 T and (b) 3 T in the same healthy 18-year-old man. At both field strengths, a number of small branching vessels are depicted (short dashed arrows). Also at 7 T, a long portion of the RCA is visible (solid arrow = distal part of RCA). Ao = aortic root, LV = left ventricle, RV = right ventricle, TW = thoracic wall. [39]

This means the physics-inferred Flow MRI diagnostic can be applied to these high-field MRI scans to reveal crucial details about the flow within to coronary arteries.

3.1.5 Carotid

Strokes are considered the second biggest global killer according to the World Health Organisation [29]. The World Stroke Organisation states that 12.2 million new strokes occur every year and of these patients, over half die as a result. This contrasts heavily with patients who suffer from heart attack as according to the NHS, the survival rate is nine in ten for those who seek early hospital treatment for a heart attack. Furthermore, these patients can live a normal life after a heart attack due to the large amounts of research into cardiac diseases. Surviving stroke patients are left with devastating impacts, affecting physical mobility, speech and emotions. These complex needs pose difficult care and financial challenges on caregivers and healthcare systems. Considering the significant effect of this disease, the better diagnosis and management of initial and subsequent stroke risk is paramount. Developments in 4D flow MRI can aid this process by increasing its precision and productivity.

87% of strokes are ischemic strokes which are caused by stenosis of the blood supply to the brain which is provided through the carotid artery. The stenosis is caused by plaque build up on the vessel walls, restricting and even completely blocking blood flow. In clinical practice, doctors are concerned with the degree of stenosis of the carotid artery and the risk of an atheroma or blister rupturing and propagating downstream, causing blockages in smaller vessels. These blisters commonly occur at the bifurcation of an artery. The current gold standard for imaging plaques is using sodium-fluoride PET scans to identify collagen build up on the atheroma and Nuclear Magnetic Resonance to analyse the architecture of the atheroma. However these techniques are only available in a few specialist hospitals and Flow MRI is a more accessible and applicable method, especially because they do not pose a radiation risk to patients. Application of the solver developed by Kontogiannis et al., which takes the Bayesian-inversion of the Navier-Stokes problem, to a flow MRI scan of a healthy adult carotid is shown in figure 13 [3]. It depicts the carotid vessel boundary as it bifurcates and the flow streamlines with the associated velocity gradient. This type of image will clearly display stenosis due to the altered vessel boundary geometry and abnormal streamlines of the flow.

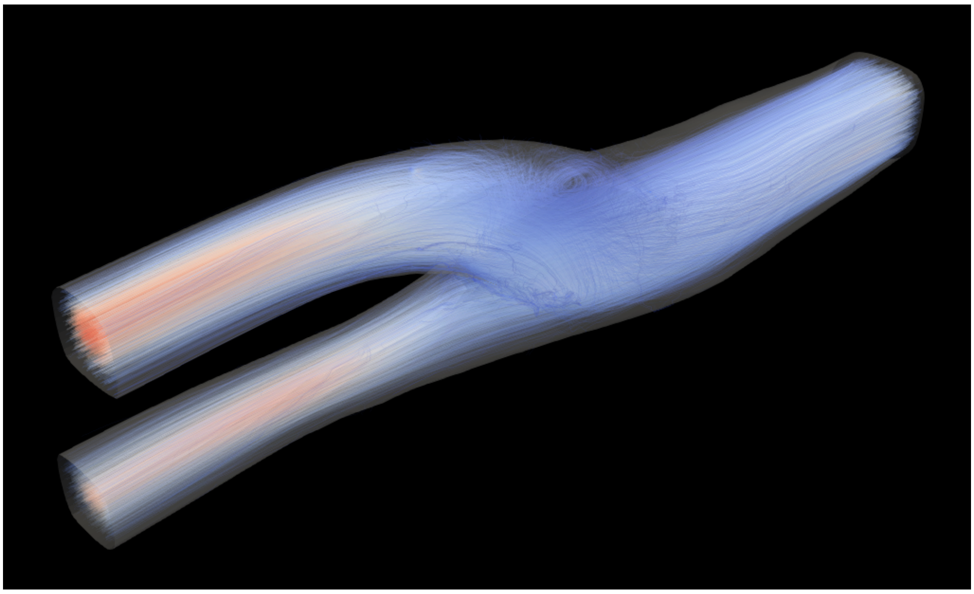


Figure 13: Application of a Bayesian inverse solver of Navier-Stokes to Flow MRI scan data through a healthy adult carotid. A colour gradient has been applied to the streamlines to represnt high velocity (red) and low velocity (blue). The streamlines are contained within the vessel boundary geometry shown in white.

A Consultant Stroke Physician [31] who aided the research for this project, stated that monitoring the shear stresses in the cap of an atheroma will allow clinicians to predict predict when it will rupture and therefore inform decisions regarding surgical intervention.

Carotid stenting is the treatment for a narrowed or blocked carotid artery by inserting a small, expandable mesh tube (stent) to keep the artery open and improve blood flow to reduce the risk of stroke. The risk of stroke for a patient with a carotid stent reduces to 15-17%. Clinicians want to stratify the risk after a stent is put in and ascertain what physiology is most likely to be affected. It is currently not possible to use MRI for imaging stents, because they are made of metal mesh. CT is commonly used to image a stent in the vessel, but it often can cause artifacts in the CT image. Using a CT scan for determining the physical anatomy and reconstructing the flow through the stent. A current CT technique that could be applied here is Heartflow which is described in detail in section 3.3.2. The physics inferred Flow MRI technique developed by CUED could also be applied by using Flow MRI for the blood flow and a CT scan for the geometry, thereby inferring the flow through the stent. This would need to be compared against a gold standard scan for validation.

3.1.6 Parameters

4D Flow MRI provides haemodynamic information, offering a detailed view of cardiovascular flow patterns. However, while this level of detail is invaluable for research, clinical decision-making often benefits from simplified metrics and single numbers that encapsulate key flow characteristics. This makes clinical interpretation and decision-making more efficient which is particularly significant in the context of making healthcare more productive, not just adding value. In contrast, artificial intelligence could handle the full complexity of 4D Flow data and may eventually enable the extraction of more nuanced insights. A promising direction could be the integration of AI-driven models with flow-based metrics to enhance diagnostic precision and productivity.

In two-dimensional slices of blood flow through the aorta, several parameters can be extracted to characterise flow abnormalities. One such measure is flow eccentricity, which quantifies systolic flow displacement by identifying the location of peak velocity and determining how far it deviates from the centre of the vessel. This has relevance in conditions such as aortic valve disease, where asymmetric flow patterns may indicate congenital abnormalities or calcification of the aortic valve. Another key metric is systolic reverse flow, which captures the extent to which blood moves in the opposite direction during systole. By integrating the downstream and upstream velocity fields across the aortic cross-section and analysing these values over time, it becomes possible to track variations in flow reversal, offering simple metrics for conditions such as aortic regurgitation. These quantities can be presented as continuous time-dependent functions or simplified as peak systolic and diastolic values for clinical interpretation.

Beyond two-dimensional analysis, three-dimensional volumetric flow assessments offer more comprehensive insights into cardiovascular haemodynamics. These parameters are commonly seen in fluid mechanics and interestingly have similar interpretations in vascular medicine. One fundamental measure is total kinetic energy, calculated as the integral of velocity squared over the entire aortic volume. By analysing how this fluctuates across systolic and diastolic phases, it becomes possible to assess cardiovascular efficiency and detect energy imbalances linked to vascular disease. Closely related to this is total kinetic energy dissipation, sometimes referred to as viscous energy loss or total heat dissipation by cardiologists, which serves as an indicator of cardiovascular efficiency. Increased dissipation suggests energy loss due to turbulence or inefficient flow patterns, which may occur in aneurysmal disease, atherosclerosis or after surgical interventions. Additional metrics such as total vorticity and helicity further characterise the swirling and rotational nature of blood flow, which may have diagnostic significance in aortic abnormalities, aneurysm formation, or post-surgical reconstructions. Turbulence at the aortic roof is another relevant parameter, as excessive turbulence in this region can disrupt distal perfusion and contribute to ischemic complications.

While these measures provide valuable overall summaries, more localised assessments can refine the analysis further. Instead of considering overall kinetic energy dissipation, it is possible to map local variations in viscous and turbulent energy losses, potentially identifying sites of early vascular dysfunction. This metric is increasingly becoming an important marker for cardiac efficiency and aortic reservoir function. This refers to the aorta's ability to store blood during systole (heart contraction) and release it during diastole (heart relaxation), smoothing out pulsatile blood flow and ensuring a steady supply to the body. Similarly, local vorticity and helicity maps offer spatially resolved data on rotational flow dynamics, providing a more detailed picture of haemodynamic disturbances.

3.2 Doppler Ultrasound

As discussed in Section 1, Doppler ultrasound utilises the Doppler effect, wherein ultrasound waves reflected off moving red blood cells exhibit frequency shifts proportional to their velocity. These shifts are used to calculate and display blood flow dynamics. Color Doppler ultrasound is a specialised imaging modality that enables the visualisation and quantification of blood flow within vessels which represents the velocity data as red for flow moving in the direction of the ultrasound wave (i.e. away from the transducer) and blue for flow moving opposite to the direction of the ultrasound wave (i.e. towards the transducer).

A clinical application of this technology is observed in fetal ultrasound, particularly in the analysis of the umbilical cord. Figure 14 shows blood flow through the cord, with a corresponding velocity trace in centimeters per second at a point in the flow. The analysis of blood flow in the umbilical artery is critical in evaluating fetal health during complicated pregnancies because it indicates the health of the placenta. This guides clinical decisions about the timing of surgical interventions, which requires analysis of the trade off between fetal growth and the risk of still birth. The baby's health requires a high blood flow through the placenta and good mass exchange in the placenta which requires monitoring the health of the placenta. Currently clinicians can only measure the velocity at a point and then crudely multiply it by the visible cross-sectional area. The accuracy of this measurement can be improved by directly measuring the flow rate through the blood vessel.

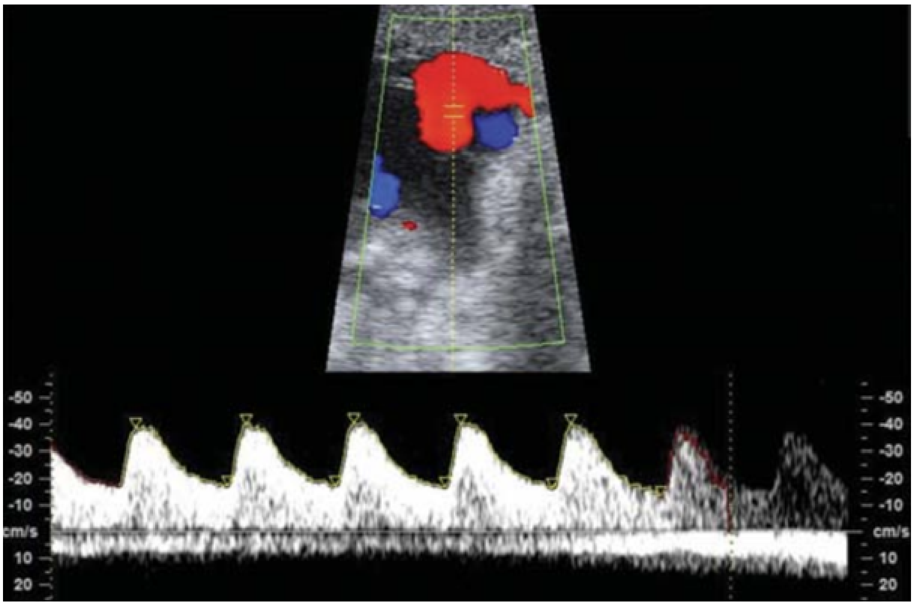


Figure 14: Colour Doppler image of the arteries in the umbilical cord of a foetus, including the trace of flow velocity in cm/s. [Goh and Zalud, 2011]

Despite its utility, color Doppler ultrasound has limitations. Over saturation of colour at vessel edges can obscure structural details, skewing velocity measurements. Furthermore, achieving precise alignment of the transducer probe with the vessel, particularly in dynamic environments such as fetal imaging, is challenging. This issue arises due to fetal movement and the difficulty in maintaining a perpendicular angle to the vessels. These limitations, however, are less pronounced in more accessible and stable regions, such as the carotid arteries, where imaging conditions can be more easily optimised.

Doppler Ultrasound can also be applied to Cardiac Ultrasound, also called Echo- cardiography. Its biggest advantage is its accessibility and high temporal resolution allowing real time assessments to be made for a variety of different physiological conditions. This includes estimation of blood flow velocity, pressure gradients, valvular regurgitant volumes and shunt volumes. However there are several limitations such as the fact that the image quality and accuracy depends on the skill of the operator for probe alignment and angle correction. Furthermore, similar to fetal ultrasound, the regurgitant and shunt flow rates are found by manually multiplying the measured velocity by the visual cross-sectional area. This can be improved if the physics-inferred solver is applied to a 2D slice of Doppler Echo-cardiography to infer the flow rates directly. The biggest disadvantage over 4D Flow MRI and CT is there is no position information associated with each 2D slice. This can be resolved by placing an accelerometer in the transducer so that the position that each 2D Echo-cardiogram was taken in, relative to the body, can be relayed.

The use of color Doppler continues to be a valuable tool in both obstetrics and cardiac clinical settings, providing critical hemodynamic information while highlighting areas for potential technological improvement.

3.3 CT Angiography

3.3.1 General CTA

CT angiography is commonly used to check for stenosis which is the narrowing of or blockages in major arteries such as the carotid and coronary arteries. Clinicians use CT angiography to measure stenosis because this gives a larger field of view compared to Doppler ultrasound so that unknown flow features can be recognised more easily. It is commonly used in hyper acute cases because it is fast and easy to access and provides sufficient information about vessel structure in the short amount of time for the scan to be taken. It is also a popular technique because it can be done at the patient's bed side after an initial stroke to monitor for Transient Ischemic Attacks (TIAs) which commonly happen up to 48 hours after an initial stroke. At this point the patient's condition is not acute which allows for processing to be carried out in a non time-pressured situation. Stenosis measurements are fairly crude and clinicians often look at velocities and flow rates (from Doppler Ultrasound) to back up these measurements. This is commonly done for the carotid to monitor strokes and identify thrombosis (local coagulation of the blood) but can be applied to other areas of the body such as femoral arteries and around the liver. We can greatly improve the time efficiency and accuracy of stenosis measurements using our flow imaging techniques. If we take a 2D slice from the CT Angiography and find flow velocities and flow rates from Flow-MRI or Doppler Ultrasound, it would be a more accurate measurement.

Further motivation for improving CT Angiography measurements is that clinicians would like to incorporate stenosis checks into health check ups for adults to monitor stroke risk. A check for atherosclerosis, which is the build up of fats, cholesterol and other substance on arterial walls, is carried out because this is indicative of stroke risk. With an improved method of measuring stenosis, this can be done more easily and accurately. However, the relationship between blood flow velocities and turbulence caused by atherosclerosis is unknown and would require further investigation. In the future, the ionising radiation of a CT scan can be avoided because the MRI imaging technique being developed can reveal the stenosis and the flow features, providing critical information about stroke risk.

Another area of interest is arterial dissections, which is a tear in the intima (inner layer) of the arterial wall causing blood to build up between this layer and the adventitia (outer layer). This can produce a false lumen which is a chamber in the arterial wall between the intima and adventitia where there is stagnant blood. Dissections are difficult to diagnose as clinicians look for a taper or 'apple core' like feature in the artery. An example of a axial plane cross section (top down view) from a CT Angiography scan is shown in 15.

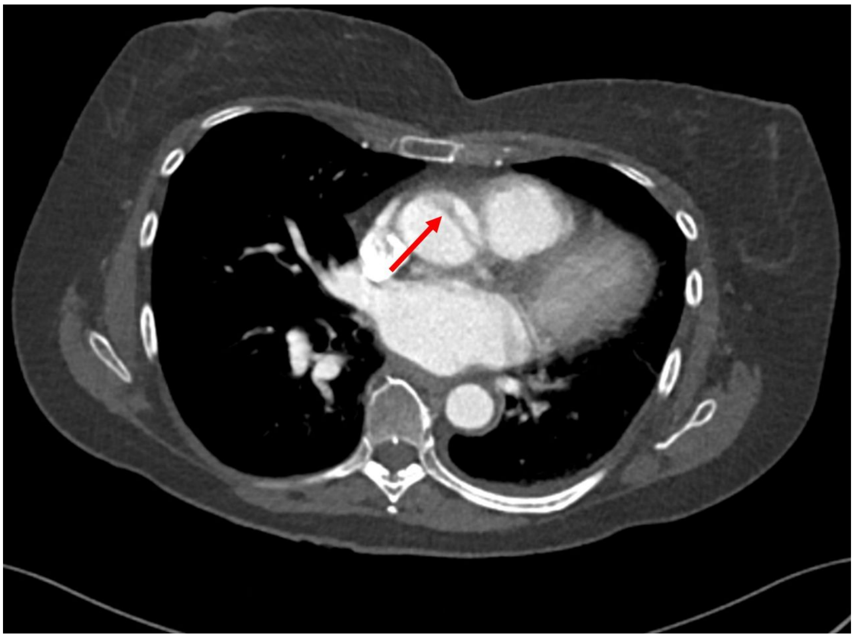


Figure 15: Axial plane CT Angiography scan of a patient with an aortic dissection where the red arrow indicates the separation between the inner and outer layers of the aorta. [19]

It is difficult, however, to identify this when the resolution of images is low. The false lumen is particularly difficult to diagnose because the shape is unclear and irregular and is often difficult to differentiate from stenosis if a clot has formed. Measuring flow velocities may make diagnosis more accurate because the direction of flow would be changed by a dissection and flow would occur through the boundary of the vessel. Studies have confirmed that turbulence is produced at the dissection site and there is correlation between areas of high turbulence and thrombosis formation. A study conducted by Cheng et al in 2013 analysed the flow through aortic dissections in 4 separate patients by creating 3D models of the aorta from CT scans and applying a CFD solver [10]. Figure 16 displays the streamlines of the flow through the 4 different dissections, showing flow entering the false lumen through the tear with high velocity, subsequently impinging upon the inner surface of the false lumen opposite to the tear. Flow in the false lumen is separated, recirculating and turbulent as seen by the streamlines.

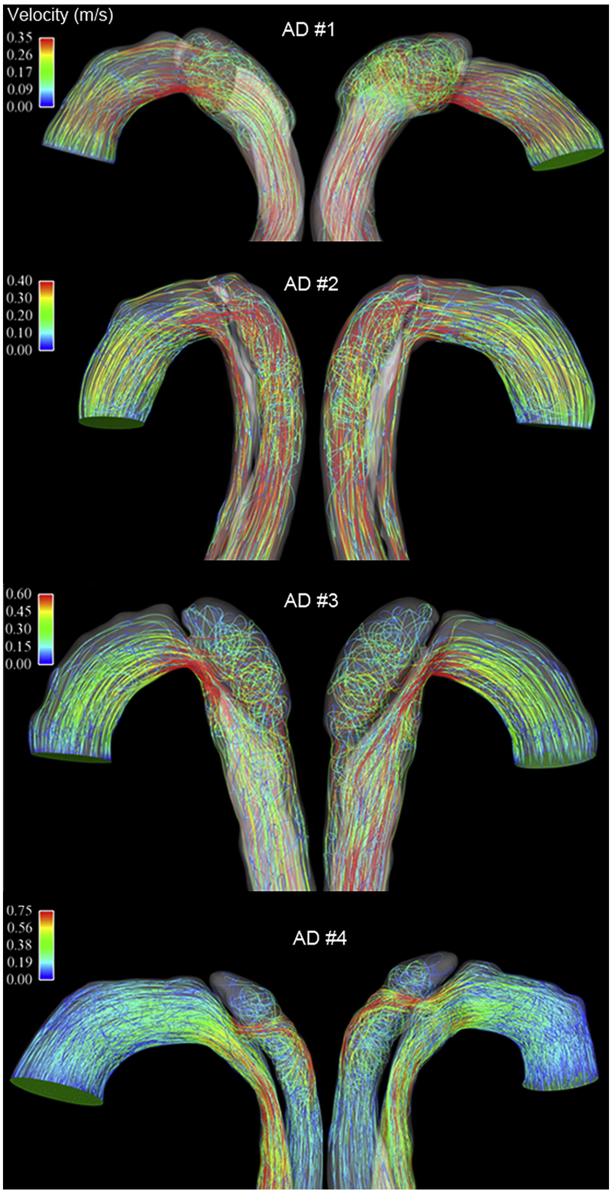


Figure 16: Streamlines of blood flow in each aortic dissection model from both the right-anterior view (left) and left-anterior view (right). Velocity scale is shown with red indicating highest velocity and blue indicating lowest. AD, Aortic dissection. [10]

Visual inspection of figure 16 shows that the highest levels of turbulence occur in the region surrounding the tear. This can be quantitatively confirmed using a parameter called relative residence time (RRT) which is related to the time interval that a particle is in a region of the model. It is an indicator of turbulence because particles spend more time in separated, recirculating flow. The study showed that regions with large RRT values correlated highly with areas that subsequently developed thrombosis. Figure 17 below shows the RRT contours mapped onto the aortic wall and the development of the thrombosis over time to display the correlation.

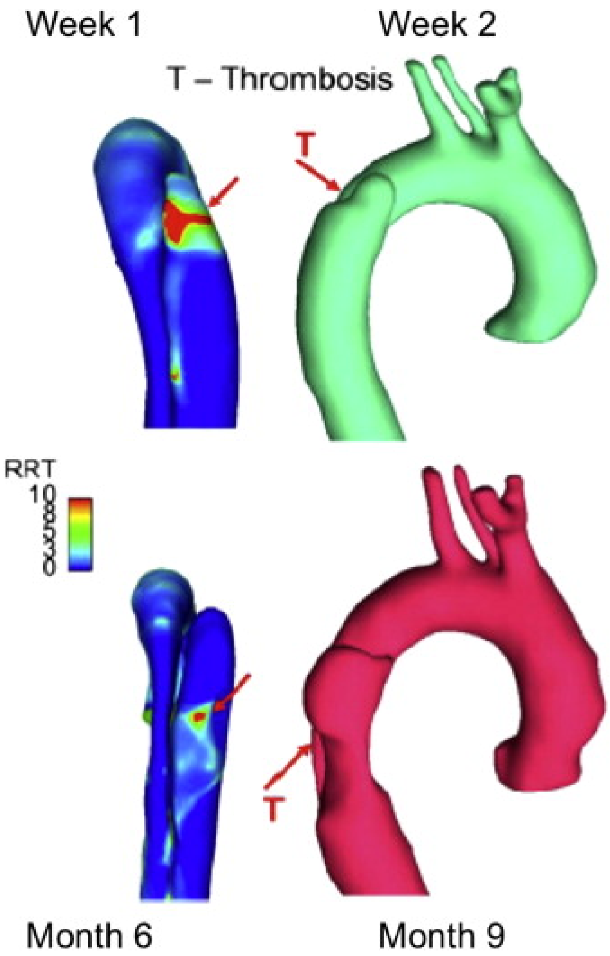


Figure 17: Relative residence time contours across the aortic model (left) with red indicating high RRT (i.e. high turbulence)and blue representing low RRT (i.e. low turbulence). Comparisons with models reconstructed from follow-up scans on the right. [10]

This shows that there is strong evidence for turbulence at the dissection site and in the false lumen before a clot forms. This means the physics-inferred Flow MRI technique developed by CUED could be used to diagnose aortic dissections. By using the Dirichlet boundary condition, the solver will need to check for flow through the boundary of the vessel which would indicate a dissection. If a clot has begun to form, it would be difficult for this technique to detect a dissection as there would be stagnant flow that would provide no velocity information.

3.3.2 HeartFlow

HeartFlow is a recently developed technology that uses CT scans to produce a digital 3D model of the coronary arteries and the flow of blood through these vessels. It is marketed as using 'deep learning' to produce the CT scans to promote sales, however in reality it uses geometry from CT scans to solve standard CFD. It is used for identifying flow limiting lesions that are indicative of Coronary Artery Disease. The pathway of Heartflow begins with sending a 64 slice CT scan to the central processing centre in the US to create the 3D digital model. This model is then refined by HeartFlow analysts before applying

Computational Fluid Dynamics to compute the blood flow through the vessels. This gives the Fractional Flow Reserve of the vessels which is the ratio between the maximum achievable blood flow in a diseased coronary artery and the theoretical maximum flow in a normal coronary artery. The results are compiled in a report and transferred back to the clinician so they can use it to help guide patient therapy. The process takes 48 hours which makes other methods such as invasive pressure measurements more suitable for identifying stenosis in the coronaries. HeartFlow is further limited by its cost of £700 per test. Invasive pressure measurement methods are £1500 which is the current gold standard.

Currently, HeartFlow is not accurate enough when analysing borderline cases of blood flow limiting lesions which is when analysis is most critical [5]x. Furthermore, the technology is only suitable for patients with stable and recent onset chest pain or suspected angina (lack of blood to the cardiac muscle) as it has not been tested on any other patient groups. These groups include patients with an acute coronary syndrome, coronary stent, bypass or heart attack.

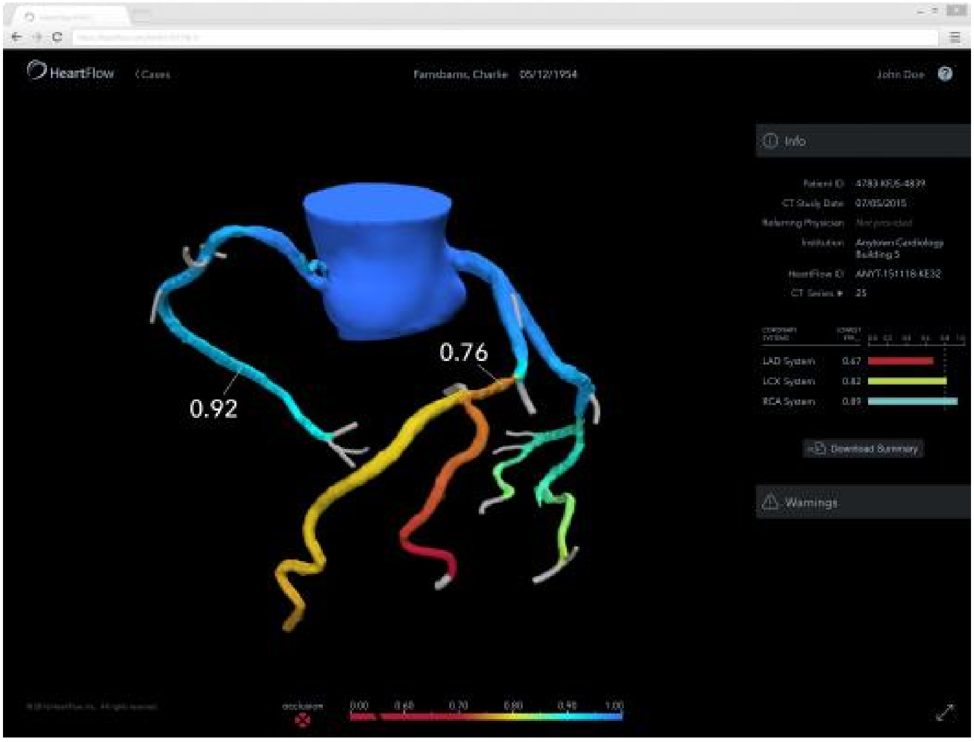


Figure 18: Example of the model a clinician would receive from HeartFlow, detailing the specific value and colour map of the degree of stenosis in the coronary arteries.

4 Conclusion

In conclusion, this project aims to explore the utility and advancements of 4D Flow MRI, Doppler ultrasound, and CT angiography in cardiovascular diagnostics. By systematically analysing each imaging technique, their applications, limitations, and potential improvements have been identified.

I begin by examining Phase Contrast MRI as a commonly used tool by cardiologists to examine 2D flow fields through major vessels. Using Phase Contrast MRI and encoding flow in all three dimensions of space and to the dimension of time, 4D flows can be constructed along the cardiac cycle, to serve as a tool for assessing complex cardiovascular pathologies. This technique provides a detailed, three-dimensional view of blood flow dynamics, making it particularly useful in diagnosing conditions such as aortic abnormalities, carotid artery disease, and coronary artery disease. By integrating advanced flow parameters such as kinetic energy dissipation, vorticity, and helicity, 4D Flow MRI offers a more comprehensive assessment of vascular efficiency and perfusion. Notably, its ability to analyse both the arteries and the muscle of the heart simultaneously marks a significant improvement over conventional methods. However, its clinical adoption is limited by the need for simplified diagnostic metrics that can integrate seamlessly into decision-making workflows.

Doppler ultrasound is then explored for its real-time capabilities and accessibility, particularly in fetal and carotid artery imaging. While Doppler ultrasound remains a valuable tool for assessing blood flow velocity, its reliance on point-based velocity measurements results in crude estimations of flow rate. The challenges associated with probe alignment and color saturation at vessel edges also introduce inaccuracies. Despite these limitations, its widespread availability and non-invasive nature make it a crucial tool in clinical settings.

CT angiography, widely used for stenosis assessment in coronary and carotid arteries, is also reviewed. Its ability to capture vascular anatomy given short scan times, makes it critical for rapid assessment of plaque build up and the need for surgical intervention . However, its reliance on ionising radiation and contrast agents poses risks, particularly in vulnerable patients. The integration of physics-inferred Flow MRI for flow reconstructions is a promising pathway for improving its diagnostic accuracy.

Throughout this research, we have identified key areas where existing techniques could be improved, particularly through the integration of physics-based modeling. A major challenge remains the validation of new imaging biomarkers against histological and clinical outcomes, which requires clinical studies to be conducted for validation. Future research should focus on refining these methods to ensure they provide actionable metrics for clinicians while maintaining accessibility and efficiency in routine practice.

Ultimately, the findings of this study show the significance of the growing need for precise, accessible, and clinically relevant imaging tools. The potential applications of Flow MRI is vast due to high volume of CMR scans that, especially in the United Kingdom, every year. A survey conducted by the British Medical Association based on data from 2018, reported 114,967 clinical CMR scans in that year, marking a significant increase from

100,386 in 2017—a 15% year-on-year rise [22]. Over the decade from 2008 to 2018, the number of CMR scans increased fivefold, highlighting the growing reliance on this diagnostic modality in UK healthcare. Given that physics-inferred Flow-MRI methods can improve scan times by a factor of 10, this technique provides great scope for increasing the productivity of CMR imaging in the UK.

Furthermore, despite the technical difficulties to overcome, the low cost and accessibility of ultrasound machines means that this method would have great impact if extended to echo-cardiography. If the technical challenges of applying physics-inferred 4D Flow methods to ultrasound can be overcome, the applications stretch beyond cardiovascular medicine for example to fetal ultrasound. This makes it a large potential market.

Lastly, CT scans provide accurate information about the boundary geometry of blood vessels therefore combining CT scans with Flow-MRI to examine flow through the coronary arteries or stents is a valuable application. Considering the increase in the prevalence of coronary heart disease and the growing need for CT coronary angiography, the significance of physics-inferred 4D flow method is further proven. Based on analysis published by the British Medical Association [11], an annualised rate of 42 340 CTCA examinations in the UK (66 per 100 000 population, per year) was found. However clinical guidelines set by the National Institute for Health and Care Excellence (NICE) state that CT coronary angiography (CTCA) should be offered as the first-line investigation for patients with stable chest pain. It was estimated that approximately 350 000 CTCA scans (545 per 100 000 population, per year) would be required per year to fully implement the updated NICE guidelines. This shows the growing need for more efficient imaging methods of the coronary arteries which can be done more efficiently through the combination of CT scans and physics-inferred flow methods.

In summary, this project not only highlights the individual strengths and limitations of 4D Flow MRI, Doppler ultrasound, and CT angiography, but also reveals a compelling opportunity: the integration of physics-informed techniques into current imaging modalities could transform cardiovascular diagnostics. The clinical demand for faster, more precise, and actionable imaging is rapidly increasing, as evidenced by the dramatic rise in cardiac MRI and CTCA usage in the UK, creating a crucial need for innovation. More importantly, the potential reach of this approach extends far beyond cardiovascular medicine. If successfully translated to Doppler ultrasound the impact could be revolutionary, bringing advanced flow analysis to point-of-care and low-resource settings. Similarly, the fusion of anatomical data from CT with blood flow insights from Flow MRI could vastly improve the evaluation of the coronary arteries in particular. This convergence of modalities, powered by physics-informed modeling, could lead the way in making healthcare systems more productive and cost-effective. The focus shifts from merely adding value to providing an efficient and sustainable solution to the operational burden clinicians face. It offers the prospect of faster diagnoses, better clinical decision-making, and ultimately, improved patient outcomes. Despite current technical hurdles, the direction is clear: this technology holds immense promise, and with further research and refinement, it is well-positioned to become a cornerstone of future clinical diagnostics.

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5 Appendix

5.1 Risk Assessment

The risk assessment submitted to the Safety Office at the beginning of the project sufficiently covered all the hazards encountered during the course of the project. In retrospect there are no further risks that would require consideration if I were to start the project again.

5.2 Notes from Interviews

The clinicians I conducted interviews with are as follows:

1. Consultant Clinical Scientist
2. Consultant Stroke Physician
3. Consultant in Maternal and Fetal Medicine
4. Registrar Cardiologist
5. Consultant Cardiologist 1
6. Consultant Cardiologist 2
7. Consultant Cardiologist 3

The following sections provide the meeting notes from each interview.

5.2.1 Meeting with Consultant in Maternal and Fetal Medicine

- MR → placenta penetrating uterus in pregnancy, fetal brain → close overlapping tissue

- MR can give 3D geometry and ultrasound gives flow and put the two together

- Problem is flow measurements assume slice is perpendicular but in reality very difficult
- free floating umbilical chord • fetus moves

• If flow between mother and fetus is better analyzed, can better make diagnosis between stillbirth vs baby

- Artery between mother and placenta is FIXED

- Artery between placenta and baby is FREE FLOATING –umbilical cord

- These vessels coil longitudinally, like a helix.

• “Gate”: Window of interest placed perpendicular to angle of incidence on 2D slice to analyze flow.

• Two arteries(thick-walled, elastic) and one vein. • Speed: cm/s.

• Power Doppler picks up ”tricky” vessels and is less saturated.

• Increased pulsatility index in placenta means resistance; baby’s heart is working very hard.

• End-diastolic flow - continuous with pulse.

• Blood flows from baby’s heart → placenta via arteries, and placenta → baby via venous return.

• If placenta is resistant, backward flow may occur due to artery elasticity.

• Flow at end of pulse wave drops.

• Although flow in this vessel is a good indicator, it’s difficult to view using ultrasound.

• Venous flow (in ”smiley face”) goes back to baby.

• Over-saturation at edges of vessel.

• Doppler is a different scale and is less saturated.

• Cine sequence: to show flow in and out of 2D slice.

5.2.2 Meeting with Stroke Physician

• Clinicians use CT angiography to measure stenosis as this gives a larger field of view compared to Doppler ultrasound so is better for looking for unknown flow features. However this is done in a non time-pressured situation and processing takes several days. Stenosis measurements are fairly crude and clinicians often look at velocities and flow rates to back up these measurements. Consultant stroke physician does this for the carotid to monitor strokes and identify thrombosis but can be applied to other areas of the body such as femoral arteries and around the liver. If we take our 2D slice and find flow velocities and flow rates, it would be a more accurate measurement.

• There is some evidence to say that the right carotid is lower down than the left as the left carotid originates directly from the aortic arch whereas the right originates from the brachycephalic artery

• Clinicians would like to incorporate stenosis checks into health check ups for adults to monitor stroke risk. Therefore it would be useful to investigate the relationship between velocities and turbulence caused by atherosclerosis.

• Dissections are difficult to diagnose as they are looking for a taper or ’apple core’ like feature in the artery but it is difficult to differentiate this between artifacts of the image. In aortic dissections, they also look for the false lumen which is difficult to identify. Measuring flow velocities may make diagnosis more accurate. Dissection could cause clot to form which could be difficult to differentiate from stenosis. – davit's dirchlet BC could help look for this on the boundary. Find out exactly how this happens to find out what to tell solver. – is there flow in the false lumen?

5.2.3 Meeting with Registrar Cardiologist

• Carotid: In carotid, clinicians are not concerned with stenosis (narrowing of vessels) but the risk of an atheroma or blister rupturing and propagating downstream, causing blockages in smaller vessels. These blisters commonly occur at the bifurcation of an artery. The shear forces in the cap of the atheroma is monitored to identify the risk of the blister rupturing.

• Coronaries: In the aorta and coronaries, clinicians are concerned with the objective degree of stenosis. Coronaries are currently examined using CT-Fractional Flow Reserve that produces a 3D model of the coronaries from a CT scan. It is currently difficult to determine whether a stenotic lesion is flow limiting, especially in borderline cases, which could be improved by our method especially with the use of 7T MR machines. Measuring the dissipation of energy due to turbulence in the coronaries would also help with the diagnosis of issues in the coronaries.

• Femoral Arteries: In the femoral arteries, there are often multiple stenoses and clinicians need to quantify the collective stenosis rather than each individual one. The current imaging technique is doppler ultrasound which is user dependent and it is difficult to see small arteries due to the muscles and tissues around it.

• Dr Wall stressed that there is currently no imaging technique that can look at the flow in the cardiac muscle (coronaries) and other major blood vessels at the same time. For the flow in the cardiac muscle, disease usually occurs in capillaries of width 0.5-2mm so 2mm is the minimum resolution we would need.

· Aortic Coarctation (congenital condition where there is a narrowing of aorta, most commonly in the arch)

• Aortic stenosis is the reduced flow rate out of the aortic valve due to calcification of the valve. It is difficult to discern from heart failure which means the cardiac muscle is not strong enough to pump the required flow rate of blood out of the aorta. Dr Wall said that he would email us back with more information about this.

• Aortic aneurysm is the bulging of the aorta and it is examined by measuring the diameter of the aneurysm which can be done more accurately using our method. Furthermore, it can be indicated by the compliance of the aortic wall which can be affected by certain diseases making a patient more susceptible (particularly to Thoracic Aortic Aneurysm).

5.2.4 Meeting with Consultant Cardiologist 1

• Ultrasound is quick but low resolution – difficult to recognise structures but our segmentation is much better than theirs. Cancerous tissues are detected by irregular shape with angular/asymmetrical edges.

• Also talked about stenosis and intermittent flow in other areas like legs, near liver like the Consultant Stroke Physician did with carotid. Doppler gives flow profile • Renal – blood flows in vein, flow profiles (given by ultrasound Doppler) , degree of venous congestion, flow is intermittent if there is congestion

• Point of care ultrasound - immediate analysis – estimation of inter-cranial pressure, extra pulmonary water, quantification of fluid in plura in lung, haemodynamic data – velocity time integral across LV, ejection fraction, estimate of cardiac performance – tissue Doppler

• Do we take raw data or phase corrected data? As phantom correction is an issue which is talked about in Consultant Clinical Scientist's presentation and is still an issue as I found in a 2020 paper and greatly varies between CMR machines – chemical engineering data is raw data but medical machine is processed

5.2.5 Meeting with Consultant Cardiologist 2

All arteries/vessels

• our most valuable feature is scan time reduction. Flow MRI scan times would have to be a couple of minutes (rather than current 10+ minutes). The processing time is less important because most people who get MRI have been waiting for weeks to have MRI. It is not used for acute cases.

• automatic segmentation would be very useful, if accurate, particularly without using contrast agents; currently, segmentation is crude and manual (cardiologists will do 160 segmentations himself by hand). (Huang in DAMTP does segmentation.)

• pressure drops across arteries will be clinically useful

• it will be useful to know how stiff/boggy/compliant is the arterial wall and how much the wall is being moved around; useful for aneurysm progression as compliance affects blood pressure. Also useful in drug trials to analyse whether medications influence vessel wall compliance.

• wall shear stress is not currently measured. People hypothesize that it causes pathology, particularly at bifurcation of vessels due to change in wall shear stress, but this has not yet been shown in clinical trials. Quicker, easier and more reliable tool will make it easier to study whether medications can change geometry or effect plaque formation.

• although not possible with Flow-MRI, it is useful to know the micro roughness/smoothness of the wall; this is currently done with OCT (Optical Coherence Tomography), in which a visual probe is inserted into an artery flushed with saline. You can see a lot of detail at the walls but the process is invasive.

• although we could infer the haematocrit with Flow-MRI, this would be an expensive way to infer a quantity that we can obtain in cheaper ways.

• our Flow-MRI method would have high value if combined with other cardio studies, while also scanning more quickly.

• the heart may be too big for us now, but this could plug into the other clinical scans around the heart, ideally with a single acquisition; e.g. better outline of heart.

• turbulence, like wall shear stress, is currently for researchers not clinicians.

• Segmentation from CT or MR is unreliable especially if there is calcification on the boundary so our method is better. Segmentation is a semi-automated method where clinicians gives the centreline, then an automated boundary is formed but the clinician has to manually move the points to fit better.

• Accurate geometry measurements from vessel boundaries without giving contrast is an advantage of our method.

Coronary arteries

• coronaries are a huge market

• at the moment, CT scan of the beating heart wait until the heart is as stationary as possible and then do a very rapid CT scan in one snapshot.

• CT scans have a 0.3–0.6 mm spatial resolution.

• segmentations, degree of stenosis, and pressure drops across coronaries would be hugely useful.

• It would be good to image both coronary flow and the muscle health downstream (i.e. combining Flow-MRI with normal MRI). escimia. One way of detecting a coronary stenosis is to look at the heart muscle downstream.

Aorta

• it would be useful to track flow after surgical shunts (i.e. re-plumbing to correct for birth abnormalities); the flow in these patients must be followed through life, so a low radiation accurate measurement diagnostic would be good.

• it would be useful to look at flow patterns in distorted aortas, to see whether things change over time, and to see which patients get worse.

• it would be useful to track aneurysm dilatation although, currently, we do not know the link between diagnosis and prognosis

• the compliance of the aortic wall and the wall shear stress would be a useful diagnostic, although we don't know the links to diagnosis.

Carotid

• From a magnitude scan, it is difficult to tell whether a lesion is dangerous and could be improved by measuring the pressure drop instead.

Heart

• This could be a really useful alternative method to assess valve disease because ultrasound is very challenging.

• left ventricular outflow tract and aorta would be useful as it is currently difficult to find the maximum velocity in the aorta.

• a diagnostic for valve disease/tears would be useful; this can be seen in ultrasound but is difficult to see.

Heartflow (called CT FFR)

• Heartflow have a good business model.

• HFlow makes CT FFR very easy: on the PAC system you press a button and the data goes to Hflow. It comes back 2 hours later as a pdf report with a map of the coronaries and the pressure drops. If you log in online, you can manipulate the 3D model. Not all clinicans want the extra information (mainly due to lack of trust in HFlow).

• CT FFR costs £1500 and HFlow costs a further £700.

• HFlow ONLY answer the question that the clinician wants answered, and which cannot be answered with standard CT. This is good because clinicians want to make a defensible decision and don't want to consider other information that they may not understand and would have to look up. (Ignorance is bliss because clinical doctors don't want information that may make them liable if they make a bad decision.)

• For example, HFlow could provide the wall shear stress, but there is no clinical need for this now

• HFlow is viewed as a black box, so our method would be easier to sell because it is based on real measurements.

• Chris and Jason use heartflow for patients with a stenosis that is not significant and they use it to back up their decision to not put in a stent.

• They find that Hflow gets things wrong in the borderline cases; some information just muddies the waters.

• Another advantage of our method is that it is more integrated and can plug into many parts of the clinical package compared to HeartFlow.

• Another disadvantage of HeartFlow is that it takes a snapshot of the heart at one time point in the cardiac cycle which is not accurate. It also assumes constant perfusion pressure which is not correct as it varies throughout vessels and in time.

- HeartFlow also doesn't take into account that some of the coronaries actually go into the cardiac muscle so they become stenosed when the heart contracts which is normal.

Flow-MRI now

- Flow-MRI is for specialists at the moment, not general cardiologists

- in some hospitals (e.g. Cambridge), MRI falls under radiology. In other hospitals (e.g. Norwich), MRI falls directly under cardiology (because there is no radiation).

- once papers get published and demonstrate Flow-MRI's reliability, it will become more generalist.

- different OEMs have different sequences and different capabilities; hospitals rely on the particular OEM that they have [we could easily work across different OEMs]

Academic research vs. clinical

- you have to create demand with an academic research tool, get research papers published, run clinical trials, show that a measurement is useful in clinical trials, and then people will pay for it.

5.2.6 Meeting with Consultant Cardiologist 3

Although we can provide detailed 4D flow, there is benefit in providing a single number for clinical decisions. These are simplistic but better for human decision-making. [But not for AI decision-making, which could handle complexity - so maybe we could combine our work with clever AI.]

For example, in 2D slices of flow through the aorta: - Eccentricity: systolic flow displacement (i.e. locate the point with maximum speed and measure how displaced it is from the centre of the vessel) - systolic reverse flow in the aorta (i.e. integrate the downstream velocity field across the slice and (if present) the upstream velocity field across the slice; plot both as a function of time) - These can be plotted as a function of time, or quoted as numbers for systolic (max) and diastolic (min).

For example, in 3D volumes of flow through the aorta: - total kinetic energy in the flow as function of time in relation to cardiac phases (i.e. integrate v^2 over the entire volume for systole and diastole phases) - total kinetic energy dissipation (i.e. integrated over the entire volume) as function of time. This is sometimes called 'total heat dissipation' or 'viscous energy loss' and is a marker for cardiovascular efficiency. - total vorticity as function of time - total helicity as function of time (also in relation to cardiac phases - systole and diastole) - turbulence at aortic roof as this leads to reduced distal flow The above quantities have come from fluids textbooks so we can probably assume that they have the same meanings that we have.

[We could use these as gateway drugs for more discerning measures such as:] - local kinetic energy dissipation in the flow (viscous and turbulent), which we could map - local vorticity map - local helicity map

The problem with wall shear stress is that it is a vector on the wall, so is difficult to represent diagrammatically and with a single number. They are interested in axial and circumferential wall shear stress.

The kinetic energy dissipation (what they call 'viscous energy loss') is becoming an important marker for cardiac efficiency. **AORTIC CONDUIT AND RESERVOIR FUNCTION

Next steps - find and investigate 4D flow MRI papers where they have mapped out vorticity, helicity etc. - see nature cardiology paper