Evaluation of Flow
Clinical Needs: What Do We Want to See?

Phase contrast MRI (also referred to as velocity-encoded cine MRI) is used in select clinical scenarios to quantify blood velocity and flow in the cardiovascular system. For many patients, it is an adjunct to echocardiography, which is widely available and routinely performed. But echocardiography has weaknesses, including limited acoustic windows and quantitative abilities, and phase contrast MRI has unique advantages. We will discuss how phase contrast MRI is currently used, and how it could be used in the near future to inform the clinical management of patients with cardiovascular disease.

We will focus on the emerging aortic applications of multidimensional MR blood flow imaging (4D Flow). But the techniques and hemodynamic biomarkers that we will discuss can be applied broadly throughout the cardiovascular system. As with the aorta, there are two key issues that must be addressed: 1) clear advantages over ultrasound/echocardiography and 2) matching advanced imaging capabilities with clinical questions that change the management of patients with cardiovascular disease. The goal is to provide a unique understanding of how abnormal flow promotes or exacerbates disease. This understanding, in turn, could allow patients to be risk-stratified based on flow, guide medical therapy, and identify new pathways to target with drug therapy and patients that may benefit from early intervention. A brief list of promising non-aortic applications includes: pre and postsurgical analysis of congenital heart disease; intracardiac flow patterns that are inefficient and/or promote stasis; altered portal venous flow with liver disease; intracranial and renal artery stenosis; and unstable flow patterns in intracranial aneurysms.

Aortic Blood Flow

1. Background

Blood flow imaging with magnetic resonance imaging (MRI) is rapidly evolving. Advances in scanner hardware, pulse sequence design and post-processing of data have allowed the dynamic visualization of flowing blood through large and complex cardiovascular territories (Figure 1), and the quantification of many hemodynamic parameters that influence vascular homeostasis. The aorta has been the focus of many of these developments. It is the largest artery in the body, and subject to extreme hemodynamic forces as it receives and directs the systolic impulse of the left ventricle with each heartbeat.

Introduction to Aortic Imaging

Aortic aneurysmal disease is the 18th most common cause of death, accounting for at least 13,843 deaths annually in the United States (1). Estimating true incidence of disease is challenging. An apparent increase in patients with aneurysms in recent years may largely reflect increased detection with the more frequent use of cross-sectional imaging. Abdominal aortic aneurysms (AAA) are more common than their thoracic counterparts. They are found in up to 5% of men over 65 years-old (2). In addition to male sex and age, other key risk factors are smoking, hypertension and atherosclerosis. Unlike AAAs, thoracic aneurysms are heterogeneous in etiology, patient
demographics and regional progression of disease (3). Like AAAs, however, basic vessel dimensions are the
primary imaging measurement used clinically to risk-stratify patients.

Progression of aortic disease is partially understood. General guidelines exist for managing patients in
various clinical contexts. The commonality is surveillance imaging with elective aortic surgery at a threshold
aortic diameter or interval growth rate (3, 4). Intervention, in other words, is warranted when the risk of not
intervening supersedes procedural risk. For example, elective surgery should be considered for ascending
aortic diameters greater than 5.5 cm, or at smaller dimensions if a growth rate over 0.5 cm/year is found.
However, for both the thoracic and abdominal aorta, a significant percentage of morbidity and mortality is seen
with aortic diameters smaller than intervention thresholds (5-9). The complexity of aortic disease is not fully
revealed by basic anatomic considerations alone.

Current aortic surveillance imaging emphasizes anatomy at the expense of other important and unique
considerations for the progression of aortic disease. Two such considerations are 1) the structural status of the
aortic wall and 2) the effect of hemodynamics. While not the focus of this talk, many new advances have been
made with molecular imaging that allow direct imaging of inflammation within the aortic wall, as well as specific
extracellular matrix proteins and pathologic processes (10, 11). At the same time, recent developments with
MRI allow assessment of dynamic blood flow and a range of associated hemodynamic parameters that may
contribute to understanding and predicting disease progression. Hemodynamics have long been implicated in
the progression of aortic disease. For example, low wall shear stress has been linked to atherosclerosis, aortic
stenosis to aneurysmal disease of the ascending aorta (i.e., post-stenotic dilation), and focal aortic wall stress
to common sites of aortic dissection (5, 12, 13). But until recent advances in MRI blood flow imaging, routine
evaluation of these hemodynamic parameters was not possible. The focus of this talk is the potential clinical
impact of advanced MRI evaluation of hemodynamics.

Current Clinical Applications

MRI blood flow imaging is currently used in select clinical setting. Two-dimensional (2D) phase contrast (PC)
MRI is the most common flow-sensitive cardiac sequence used. A 2D plane is prescribed in the appropriate
orientation for evaluation of a given vessel or heart valve, and during a breath hold, time-resolved phase
contrast data is acquired in a single direction. The technique allows for quantification of cardiac output, valve
regurgitation, severity of vascular and valvular stenosis, pulmonary to systemic flow ratio (i.e., Qp/Qs ratio,
which reflects shunting of blood), differential lung perfusion and coronary flow reserve. We will focus on aortic
valve disease and aortic coarctation.

Aortic Valve Disease

Phase contrast MRI allows precise calculation of aortic regurgitation and reasonable estimation of degree of
valve stenosis (14-17). Echocardiography is the initial imaging modality of choice for assessment of cardiac
valves. It is both cheaper and faster than MRI. But MRI provides quantification of valve regurgitation whereas
echocardiography does not. Instead, echocardiography qualitatively estimates regurgitation based on apparent
size of flow jets, which can be affected by imaging parameters and orientation. The usefulness of MRI for valve
disease is deemed Class 1, which means that it “provides clinically relevant information and is frequently useful;
may be used as first-line imaging technique; usually supported by substantial literature” (18). MRI has the
additional advantage over echocardiography of superior assessment of related left ventricular status, with
accurate and reproducible calculation of ventricular size, function and mass.

For assessment of aortic regurgitation, an imaging plane perpendicular to the aorta is prescribed,
typically 2 to 3 cm above the aortic valve at the vertical, tubular portion of the ascending aorta. The aortic lumen
is segmented at each time point for calculation of flow volumes. Regurgitant fraction is the ratio of retrograde to
antegrade flow. If there is concomitant aortic stenosis, a higher velocity encoding value (VENC) is needed to
avoid aliasing. In some cases, a dual velocity window may be used to obtain optimum flow sensitivity with a high systolic and relatively lower diastolic VENC.

The degree of aortic valve stenosis is estimated by using the modified Bernoulli equation \( \Delta P = 4v^2 \), where \( \Delta P \) is the peak pressure gradient in millimeters of mercury and \( v \) is the peak blood flow velocity in meters per second. This technique is also used routinely for Doppler ultrasound. Good accuracy compared to Doppler echocardiography for aortic stenosis has been demonstrated (19). Unlike flow quantification, images may be prescribed in a parallel or perpendicular orientation to the aorta to capture the peak systolic velocities within the vena contracta downstream of the stenotic valve. A theoretical advantage of a volumetric MRI flow sequence is better 3D localization of the vena contracta. A disadvantage of MRI, however, for pressure gradient estimations compared to echocardiography is its lower temporal resolution.

**Aortic Coarctation**

MRI has become the imaging modality of choice for evaluation of aortic coarctation. Coarctation refers to a narrowing of the distal aortic arch in the region of the ligamentum arteriosum that restricts forward flow. MRI is useful for assessment of both anatomy and hemodynamics. Aortic dimensions are measured with high-resolution, 3D MRA sequences. Blood flow imaging can be used in at least 3 ways for assessment of relevant hemodynamics: 1) pressure gradient estimation can be performed using velocity data and the modified Bernoulli equation as discussed above; 2) quantification of collateral flow; and 3) evaluation of flow versus time profiles in the descending aorta.

Collateral flow occurs with the altered pressure dynamics seen in aortic coarctation. Blood bypasses the region of narrowing through lower pressure intercostal vessels to reach the descending thoracic aorta and beyond. The presence of collateral flow indicates a hemodynamically significant lesion that may require intervention. MRI evaluation is performed with perpendicular planes to the aorta just distal to the coarctation and at the diaphragm. Normal blood flow will drop by approximately 7% over this interval (20). With a hemodynamically significant coarctation, however, flow will increase rather than decrease over the interval through collateral pathways. The percentage increase in flow gives a quantitative measure of the degree of collateralization (20-22). When performing this analysis, images must be carefully reviewed for aliasing. The presence of aliasing can simulate a coarctation. Blood flow at the proximal plane will be underestimated and, consequently, flow at the distal plane may be incorrectly interpreted as increased.

Flow profile analysis in the descending aorta is another straightforward imaging means of indentifying the adverse hemodynamic consequences of an aortic coarctation (23). Normal arterial flow exhibits a rapid systolic upstroke followed by a swift return to baseline (typically within 300 ms). With the obstruction of flow and collateralization seen in aortic coarctation, both the upstroke and return to baseline are delayed. Significant flow persistence into diastole is found. Evaluating these abnormal features of the aortic flow profile is a simple, fast and reliable means of identifying a hemodynamically significant coarctation. The analysis can be performed at the diaphragm where flow turbulence, aliasing and stent-related artifacts seen more proximally are not present (24).

**Emerging Applications**

Multidimensional MRI blood flow imaging has been increasingly studied (Figure 2) and proposed as a tool for the evaluation of many cardiovascular disease processes including atherosclerosis, aneurysm and dissection. The technique has...
become more widely available and easier to use. Timesaving measures like parallel imaging have been employed to reduce scan time to 15 minutes or less, making the technique clinically feasible. Advantages over other modalities and simpler 2D MRI sequences have been enumerated. The technique substantially improves upon echocardiography by capturing volumetric velocity data rather than single-point, single-direction velocity data. Compared to 2D imaging, benefits include complete temporal and spatial coverage of a cardiovascular territory, continuous breathing, no requirement for prospective placement of 2D planes, and many visualization and quantification options for velocity data that are not otherwise available.

The next hurdle in the evolution of MRI aortic blood flow imaging is the demonstration of clear clinical utility. In this talk we will discuss how current research is approaching this hurdle, and showcase the clinical potential of MRI hemodynamic imaging. Quantification of various hemodynamic parameters may represent the true clinical value of the technique. The goal for patients is risk identification with MRI well before life-threatening aortic complications occur.

2. Quantitative Hemodynamic Biomarkers

Visualization of complex cardiovascular flows is just one aspect of 4D Flow. The comprehensive data can also be used to derive a range of quantitative hemodynamic parameters, or biomarkers. The parameter that is used most frequently in the clinical setting is flow. As discussed above, it is typically measured using 2D cine PC-MRI with through-plane velocity encoding. A unique advantage of 4D Flow is that flow can be retrospectively measured at any location. This can be particularly helpful for congenital heart disease where it is challenging and time-consuming to accurately study multiple vessels of interest with 2D acquisitions (25). For example, good correlation between 4D Flow and conventional 2D data has been demonstrated for the measurements needed for the estimation of collateral flow with aortic coarctation (26).

4D Flow permits applications well beyond the mapping and quantification of blood velocity and flow. A list of quantitative hemodynamic biomarkers that can be assessed includes: pulse wave velocity (PWV), turbulence, relative pressure, flow eccentricity and wall shear stress. Many of these parameters can also be obtained from 2D cine PC-MRI or Fourier velocity encoding MRI. Only with 4D Flow, however, can all of these parameters be obtained retrospectively from a single data set. Here we will focus on wall shear stress.

Wall Shear Stress

Wall shear stress (WSS) is the frictional force that flowing blood exerts on the vessel wall. It can be calculated from near wall velocity gradients (Figure 3). By providing co-registered morphological and velocity images, 4D Flow is an appealing option for WSS estimation. However, the lumen-wall contrast can be poor and velocity measurements near the vessel wall limited by partial volume effects. These limitations have been addressed by combining lumen-wall segmentations with line or plane fitting of velocities in multiple voxels (27-31). Most of these WSS methods are relatively easy to use and are widely applied (32-36).

Estimates of WSS using PC-MRI data underestimate actual WSS values (29, 31, 37). The degree of underestimation appears to be non-linear and dependent on voxel size. This implies that measures of the temporal variation of WSS, such as the oscillatory shear index (OSI), may not reflect the true temporal variation in WSS. Moreover, errors may be greater with non-isotropic data. Nevertheless, evaluation of relative values with 4D Flow can reliably identify regions of abnormally high or low WSS. This allows characterization of gross abnormalities of WSS that may be useful clinically (35, 36).

Figure 3: Wall shear stress (WSS) can be estimated from the near wall velocity gradients captured by 4D Flow. Increased WSS is seen in regions of fast and eccentric blood flow.
Wall shear stress is crucial for maintaining vascular homeostasis. Alterations in WSS affect the endothelial cells that line the arterial lumen in predictable ways. Low and oscillatory WSS promote atherosclerosis through many well-studied pathways (12, 38, 39). Endothelial cells switch to an atherogenic phenotype that, among other things, recruits and activates monocytes, promotes vasoconstriction and platelet activation, and increases apoptosis and cellular turnover. As a consequence, atherosclerosis is found in regions of disturbed, recirculating flow where there is low WSS (<4 dyne/cm²), such as within the aortic arch and at vessel bifurcations (40). Recent work demonstrates good correlation between regions of low WSS, as estimated from 4D Flow datasets, and atherosclerotic plaque throughout the aorta (34). Low WSS has also been linked to the growth of intracranial aneurysms (41). For the aorta, however, WSS evaluation of aneurysms associated with atherosclerosis (typically in the infrarenal abdominal aorta) is confounded by the substantial intraluminal thrombus that is often present (42).

High WSS has been less extensively researched, but is linked to the pathologic remodeling of arteries. One study of arteriovenous fistulas showed that radial arteries with increased flow and WSS dilated to a size at which WSS normalized (43). High WSS can lead to endothelial weakening and injury. This was originally demonstrated in a study that subjected dog aortas to markedly elevated WSS (44), and has more recently been incorporated into a low then high WSS theory for why some atherosclerotic plaques rupture (45). The first insult is low WSS, which drives plaque growth and eventually leads to luminal narrowing. This narrowing results in high WSS at the upstream margin of the lesion, which weakens the vessel and predisposes to rupture through a variety of mechanisms including extracellular matrix degradation and smooth muscle cell apoptosis. Gradients of WSS may be more important than absolute WSS values in determining clinical significance. A recent cell culture study suggests that positive WSS gradients are the principal culprit for driving aneurysm growth (46).

High WSS has been investigated with 4D Flow as a risk factor for progressive thoracic aortic disease. Focally elevated WSS has been correlated with characteristic sites of postoperative aortic aneurysms and aneurysm rupture (47, 48). Valve-related aortic disease is another topic of active investigation. Aortic valve disease is common, especially in the elderly, and is associated with ascending aortic aneurysm. The mechanism of this post-stenotic dilation is presumed to be flow-related. Before 4D Flow, valve-related abnormalities of flow and hemodynamics were not well characterized. Recent studies with the technique, however, reveal remarkably altered systolic flow patterns in the ascending aorta with valve abnormalities (49-51). Many patients with bicuspid aortic valve demonstrate focally elevated systolic WSS at the convexity of the ascending aorta (Figure 4) (36). Intriguingly, the convexity is also the site of asymmetric aneurysm formation with bicuspid aortic valve (52, 53), and where early and asymmetric extracellular matrix changes that are potentially flow-related have been reported in surgical specimen (54). More data is needed to better elucidate the relationship between abnormal flow and valve-related aortic disease. But with the prevalence of aortic valve disease, it represents one of the more promising clinical applications of 4D Flow.

3. References


Figure 4: Panel A exhibits normal blood flow in a healthy volunteer. From left to right, magnetic resonance angiography (MRA), systolic streamlines in the ascending aorta and cross-sectional analysis at the plane depicted in the proximal ascending aorta are provided. The MRA shows normal aortic geometry, the streamlines normal laminar systolic flow, and the cross-sectional analysis central fast flow and an even distribution of wall shear stress around the aortic lumen; the green bars represent the relative magnitude of wall shear stress. Panel B is from a 34 year old woman with BAV, aortic stenosis and dilation of the ascending aorta up to 4.6 cm. Eccentric flow with a right-handed helix of systolic streamlines is demonstrated. Shear stress is focally elevated where flow is marginalized against the aortic wall. (Hope et al. Int J Cardiol 2011)


