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Chapter 1

Introduction
1.1. Cardiac Physiology: Background

The heart is a vital organ in the human body that is responsible for pumping blood into the circularity system through a network of blood vessels. The human heart is decomposed of four chambers (Figure 1.1): left and right atria as well as left and right ventricles. Atria are the upper chambers of the heart and work as reservoir for blood incoming from veins to pass it into the ventricles. Ventricles are the two lower chambers of the heart that are responsible for pumping (ejecting) the blood, incoming from the atria, out of the heart to the body. The left atrium and ventricle are commonly referred to as the left heart whereas right atrium and ventricle are referred to as the right heart. The right heart helps oxygenating the blood: the de-oxygenated blood flows through the right atrium into the right ventricle that pumps blood to the lungs where it gets oxygenated. The left heart pumps this oxygenated blood into the rest of the body: oxygenated blood coming from the lungs flows through the left atrium into the left ventricle (LV) that pumps it to the rest of the body through the aorta.

![Anatomy of the heart](https://commons.wikimedia.org)

**Figure 1.1.** Anatomy of the heart (source: https://commons.wikimedia.org)

A single cardiac cycle (heart beat) consists of two phases: systole and diastole. The systole, or contraction phase, is the part of the cardiac cycle when left and right ventricles contract to eject blood into the aorta and pulmonary artery, respectively. Unidirectional flow out of the ventricles is ensured by the atrioventricular (mitral and tricuspid) valves that close during systole to prevent backflow into the atria. Diastole is the
part of the cardiac cycle when the ventricles relax and refill with blood following the systole. Diastolic filling consists of two main phases: early filling and late (atrial) filling. Early diastolic filling (E-wave), also known as passive filling, is the phase when the ventricle relaxes and its pressure drops below the pressure in the atrium. As a result, the atrioventricular valves open causing the accumulated blood in the atria to flow into the ventricle in a passive manner. Late diastolic filling (A-wave), also known as atrial or active filling, is the phase when the atria contract and push the atrial blood into the ventricle. The duration from the end of E-wave to the start of A-wave is called diastasis and it is inversely proportional to the heart rate. In normal hearts, the passive early diastolic filling accounts for 70-80% of the total ventricular inflow therefore, minimizing the needed atrial contraction (work).

1.2. Cardiac Vortex ring formation: Historical perspective

A vortex can be defined, intuitively, as the swirling motion of a group of particles around a common axis. In more formal terms, a vortex is considered a flow region with a concentrated vorticity. In three-dimensional space, vorticity is a vector quantity that quantifies the local rotation rate of flow particles along the three principal components of the flow field. Vorticity is a fundamental property of the flow and, in case of incompressible flow, allows a complete reconstruction of the velocity field [1]. In mathematical terms, vorticity is defined as the curl of velocity.

Vortex structures in the flow motion are abundant in nature, ranging from destroying vortices of hurricanes and volcano eruptions to smoke rings and vortices in the wake of a jelly fish swimming motion. Interestingly, vortex flow does not only form in our surrounding environment, but also inside the heart and in every single heartbeat. In the cardiac left ventricle, both in-vitro and in-vivo studies have shown that during diastolic filling, a vortex ring (also known as a toroidal vortex) is naturally formed from the shear layer distal to the mitral valve (MV) [2-6]. In a two-dimensional (2D) cross sectional view, a vortex ring is visualized as a pair of counter rotating vortices (Figure 1.2).

Vortex ring formation in the left ventricle was initially reported from in-vitro experiments using LV models [2, 4], suggesting it as a mechanism to help the full closure of the bicuspid mitral valve. However, given that the in-vivo study of vortex flow requires a flow imaging modality, it was not until the rise of color Doppler velocity mapping when Kim et al. have confirmed the vortex formation in-vivo in a pig’s heart using 2D color Doppler recordings [5]. Kim et al. was the first to in-vivo show the presence of vortex flow
in the normal human left ventricle using 3D magnetic resonance (MR) velocity mapping and 2D streamline flow visualization [6]. Kilner et al. have further confirmed the presence of recirculating flow in the LV distal to the MV leaflets from MR velocity mapping. They suggested a role of LV vortex flow formation in efficient redirection of blood inflow towards the aortic outflow tract in an energy efficient manner [3].

![Figure 1.2](image)

**Figure 1.2.** 2D view of an early filling vortex ring flow in the left ventricle (LV) visualized as a pair of counter rotating vortices (left) using streamlines (color coded by velocity magnitude from red to blue) and superimposed on a four chamber MR cardiac view. LV endocardial boundary is delineated in white contours. (RV: Right Ventricle, LA: Left Atrium and RA: Right Atrium).

Moving from investigational studies to more quantitative cardiac vortex flow analysis, Gharib et al. have introduced the vortex formation time (VFT) as a global quantitative and dimensionless index that describes the optimal vortex ring formation and progression during early diastolic LV filling [7]. VFT is essentially the length-to-diameter ratio of an ejected fluid column (VFT=L/D) with length L through an orifice with diameter
D [8]. In the LV, VFT can be computed as \( VFT = \frac{\overline{U(t)} \cdot dt}{\overline{D}} \) with \( \overline{U(t)} \) as time-averaged speed through the opened MV over the early filling period \( dt \) and through the average MV inflow diameter \( \overline{D} \). From in-vitro experiments, optimal VFT is found to consistently take place at a specific VFT of \( \approx 4 \). Optimal VFT in the early LV filling phase of normal human volunteers was found to be consistent with in-vitro experiments (normal VFT range = 3.3-5.5). A significantly different VFT from the optimal range was reported in patients with dilated cardiomyopathy [7], stenotic mitral valves [9, 10], heart failure, elevated LV afterload [11] and even in Alzheimer’s disease patients [12]. Therefore VFT has been suggested as a novel index for diastolic dysfunction and cardiac health [7, 13]. Nevertheless, recent studies [14] have reported that VFT happens in the healthy LV much earlier in diastole (VFT=1.6) compared to previously reported optimal VFT (VFT=4) [7], therefore questioning previously suggested relation between VFT and diastolic function and concluded that VFT might not be related to diastolic function [15].

1.3. Progress in vortex flow analysis

In recent years new advancements in in-vivo flow imaging techniques, such as echo Particle Image Velocimetry (echo-PIV) [16, 17] and phase contrast Magnetic Resonance Imaging (PC-MRI) [18, 19] have enabled more in-depth analysis of LV vortex flow. For instance, echo-PIV was used to reconstruct 2D velocity and vorticity fields to quantitatively characterize 2D LV vortex flow in normal subjects and patients with systolic dysfunction [20], prosthetic mitral valve heart failure [21] and patients with apical thrombus formation [22]. Nevertheless, Echo-PIV requires injection of contrast particles (contrast agent) which are then tracked using so-called particle image velocimetry (PIV) to approximate the velocity field. While promising, Echo-PIV is mainly limited to assessment of 2D velocity field and consequently is a 2D analysis.

Recent developments are not limited to flow imaging techniques. Major progress in computational fluid mechanics (CFD) modeling methods has also been made. This has been driven by the significant growth of available computer processing power and the use of in-vivo-derived boundary conditions. Such progress enabled simulation and analysis of cardiac vortex flow in unprecedented detail. Specifically, 3D modeling of LV flow dynamics has revealed the complex 3D nature of the LV flow field [23-25]. Detailed 3D simulations guided by in-vivo MR boundary conditions of diastolic LV vortical flow, revealed the complex dynamics of cardiac vortex ring formation including vortex twisting,
impingement on the wall and following breakup [26, 27]. These studies emphasize the
three-dimensional nature of LV vortex ring flow, indicating that proper in-vivo analysis of
intra-cardiac vortex flow needs to be three-dimensional and involving the three components
of the velocity field.

While CFD simulations provide high spatial and temporal resolution allowing
detailed physical analysis, it involves numerous simplifications to the cardiac geometry and
dynamics. This can result in a different vortex ring flow dynamics from true human cardiac
flow. Hence, in-vivo analysis of 3D intra-cardiac vortex ring flow is important to
understand its dynamics, mechanism and physiological properties in the human cardiac
(dys)function.

1.4. Four-dimensional Flow Magnetic Resonance Imaging (4D Flow MRI)

4D Flow MRI (also known as three-directional three-dimensional phase contrast
MRI) is an emerging in-vivo flow imaging technique that enables the acquisition of all
three components of the flow field, over the three spatial dimensions and over the cardiac
cycle [18, 19, 28-31]. As opposed to other techniques, e.g. echo-PIV, 4D Flow MRI does
not require the use of a contrast agent for flow imaging. Instead, 4D Flow MRI uses the
intrinsic magnetic properties of blood flow. That is, the property of the flow velocity being
directly related to the phase shift in the MR signal along a magnetic field [19, 31]. The
velocity along a specified encoding direction can be detected by applying suitable bipolar
gradients, where two acquisitions are performed that are identical in all parameters but with
two different velocity-dependent signal phases [18, 19, 29]. The velocity images can then
be calculated by subtracting the two resulting phase images. This approach is also known
as phase contrast MRI (PC-MRI).

A dynamic flow acquisition over a cardiac cycle involves acquiring the data over
multiple ECG-gated cardiac cycles to tackle the slow (up to 20 minutes) MR acquisition
relative to the cardiac dynamics. Acquiring velocity encoded data requires to manually
predefine the velocity sensitivity encoding parameter (VENC). That is the maximum
positive or negative velocity that can be detected without an aliasing error. VENC is mainly
defined empirically and based on prior knowledge of the maximum expected velocity in the
region of interest. 4D Flow MRI acquires dynamic volumetric velocity data over three
velocity encoding directions, requiring long scan times (up to 20 minutes) that can hamper
its clinical use. Therefore, different acceleration techniques have been developed to speed up the scan time [28, 32-34].

The typical output of a reconstructed 4D Flow MRI acquisition is three-dimensional image volumes that encode the three velocity field components (i.e. the two in-plane $U, V$ components and the through-plane $W$ component) (Figure 1.3). The fact that 4D Flow MRI provides the complete velocity field, enables in vivo analysis of LV kinetic energy [35, 36], turbulent flow [37, 38], relative pressure field [39-41] evaluation of different flow components [42] and flow patterns [43] in three-dimensional space as well as their evolution over time.

Töger et al. have used Lagrangian coherent structure (LCS) analysis [44, 45] of 4D Flow MRI to quantify the vortex ring volume in LV diastolic function in healthy human subjects and in patients with dilated cardiomyopathy [46]. While encouraging, LCS provides global vortex flow analysis over a period of time without providing direct information about the instantaneous vortex development. To characterize the details of diastolic vortex ring flow dynamics in the LV and in relation to inflow, 3D instantaneous-based analysis of vortex ring flow evolution over the diastolic LV filling is needed.

Figure 1.3. Example of reconstructed whole-heart 4D Flow MRI volumes of the three velocity components (the in-plane $U,V$ components and the through-plane $W$ component). Grey-scale values encode the velocity magnitude and direction along the direction of interest.
1.5. Thesis objectives and outline

The aim of this thesis is to develop methods that enable in-vivo analysis of 3D vortex flow patterns in the human heart, particularly through analysis of the 3D velocity field from in-vivo 4D Flow MRI. Accordingly, this thesis has the following four objectives:

1. To characterize and quantify in-vivo 3D cardiac vortex flow to reveal the normal 3D vortex flow formation process in healthy human subjects.
2. To determine the impact of unnatural cardiac morphology in human patients, on 3D cardiac vortex flow formation.
3. To assess consequences of altered 3D cardiac vortex flow on cardiac physiology.
4. To enable objective analysis of in-vivo 3D cardiac vortex flow from 4D Flow MRI.

These objectives are addressed throughout the remaining chapters of this thesis as follows:

Chapter 2 introduces an interactive workflow for instantaneous 3D vortex ring identification in the LV during early and late diastolic filling from in-vivo 4D Flow MRI. Standardized quantitative geometric characterization of 3D diastolic vortex ring flow is proposed providing normal ranges in a cohort of healthy subjects. The association of 3D vortex ring shape with MV inflow shape through mitral annulus and leaflet tips are evaluated.

Chapter 3 investigates the effect of abnormal atrioventricular (mitral) valvular inflow on 3D vortex ring formation in a cohort of congenital heart disease patients who are known to develop abnormal atrioventricular (mitral) valvular inflow and morphology. These are patients who underwent an atrioventricular surgical repair due to a congenital septal defect. Quantitative characterization of 3D vortex ring shape, geometry and position relative to LV, introduced in chapter 2, are evaluated and compared to those of healthy subjects. Altered 3D vortex formation in the studied patients is revealed.

Chapter 4 evaluates the consequences of altered vortex ring flow formation on LV physiology through assessment of the association between in-vivo, 4D Flow MRI-derived, viscous energy loss during diastole and inflow 3D vortex ring formation during both early and late filling in both healthy subjects and patients.

Chapter 5 explores 3D systolic left atrial vortex flow in healthy subjects and congenital heart disease patients with various degrees of left atrioventricular valve (LAVV) regurgitation.
Chapter 6 and Chapter 7 address the critical need in clinical practice to ensure objective quantitative results by proposing two novel methods, based on 3D shape signatures, for automatic identification and extraction of 3D vortex ring objects (isosurfaces). The proposed methods are evaluated in healthy subjects (Chapter 6 and Chapter 7) and patients (Chapter 7) showing quite promising and encouraging results.

Chapter 8 summarizes the results of this thesis, and discusses future perspectives.

1.6. References

17. Adrian, R.J. and J. Westerweel, Particle image velocimetry. 2011: Cambridge University Press.