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**Title:** Three-dimensional in-vivo intra-cardiac vortex flow from 4D Flow MRI: quantification, automatic identification and association with energy loss

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Chapter 8

Summary, Discussion and Future Perspectives
8.1. **Summary**

The methods presented in this thesis enable quantitative characterization, evaluation and automatic identification of in-vivo 3D intra-cardiac vortex flow patterns in the human heart, specifically through utilization of in-vivo 4D Flow MRI. These methods show the feasibility and expand the potential of 4D Flow MRI towards objective in-vivo evaluation of 3D intra-cardiac vortex flow, noninvasive assessment of intra-cardiac viscous energy loss and of their association in healthy subjects and patients with altered intra-cardiac flow. Different aspects of in-vivo 3D intra-cardiac vortex flow analysis, from 4D Flow MRI, in healthy subjects and cardiac patients were addressed in this thesis.

In **Chapter 2**, a semi-automatic workflow was introduced for identification of 3D left ventricular (LV) vortex ring flow from 4D Flow MRI during diastole. This workflow is based on instantaneous Eulerian 3D vortex core identification using a fluid dynamics-based method called the Lambda2 method. The developed workflow was then used to characterize the 3D vortex ring flow and its evolution during early and late diastolic filling in twenty-four healthy human volunteers who all underwent 4D flow MRI. Reported results revealed the formation of two distinct 3D vortex rings during LV diastole: an early filling vortex ring and a late filling vortex ring. Standardized quantitative parameters were derived to quantitatively characterize vortex ring shape and location (3D position and orientation) relative to the LV geometry at the moments of peak early filling (E-vortex) and peak late filling (A-vortex). We provided quantitative normal ranges of E- and A- 3D vortex rings from the studied healthy volunteers. Both the E- and A-vortex rings were formed at the basal level, but with E-vortex ring center being significantly closer to the mitral valve annulus compared to the A-vortex ring. E- and A-vortex rings were similarly oriented relative to the LV. E-vortex ring shape was significantly more circular compared to a more elliptical A-vortex ring. A strong correlation was found between vortex ring shape and the inflow shape through the mitral annulus and leaflet tips.

In **Chapter 3**, after characterizing and revealing 3D diastolic LV vortex ring formation in healthy cases, the impact of altered inflow and abnormal mitral valve morphology on 3D LV vortex ring formation was studied in patients who are known to develop altered inflow and mitral valve morphology. The workflow and quantitative characterization developed in **Chapter 2** were applied on thirty healthy controls and thirty-two patients who previously underwent a surgical repair to correct a congenital atrioventricular septal defect. Vortex formation time (VFT) was computed in all studied
subject. Results showed altered 3D LV inflow vortex ring formation in patients compared to healthy controls. This alteration was characterized by a more frequent absence of a (well-formed) ring-shaped vortex (a complex irregular vortex flow was detected instead), more oblique vortex ring orientation and 3D position closer to the lateral wall in the patients who presented a vortex ring compared to healthy controls at moments of peak early and peak late filling. Patients with absent (well-formed) E-vortex ring showed significantly higher VFT compared to healthy controls. Three patients showed a reversed E-vortex ring orientation with the vortex’s lateral side being positioned towards the apex in contrast to healthy controls in which the septal side was the apically positioned side. Detected 3D vortex rings in patients were more elliptical in shape compared to healthy controls which could be a reflection of the restricted inflow area found in patients.

In Chapter 4, the influence of the disturbed 3D inflow vortex ring parameters found in patients (Chapter 3) on LV physiology is studied by means of its association with viscous energy loss levels in the LV during diastole. Using Navier-Stokes energy equations, instantaneous 3D viscous energy loss in the LV was non-invasively evaluated from the 4D Flow MRI derived velocity field over diastole in the previously studied population of thirty volunteers and thirty-two patients (Chapter 2 and 3). Association between viscous energy loss levels and previously derived 3D vortex ring parameters (orientation and 3D position) was assessed during both early and late diastolic filling as well as over complete diastole. Normal ranges of viscous energy loss and 3D vortex parameters were derived from the healthy volunteers as the 95% confidence interval. Patients with vortex ring parameters beyond the normal range showed significant elevation in viscous energy loss compared to healthy volunteers. Highest viscous energy loss was found in patients with absent (well-formed) E-vortex ring, and patients with reversed E-vortex ring orientation (on average more than double the viscous energy loss levels measured in the rest of patients). As such, this was the first in-vivo study to confirm the role of normal 3D vortex ring formation on minimization of viscous energy loss using 4D Flow MRI.

In Chapter 5, systolic Left Atrial (LA) vortex flow is evaluated in healthy volunteers and patients with corrected congenital atrioventricular septum defect (AVSD) with both none-mild and moderate left atrioventricular valve (LAVV) regurgitation. Atrial vortex flow was identified using streamline visualization and 3D vortex core analysis (using the Lambda2-method) around the moment of LV-systole. Backward particle tracing with particles seeded from within the identified 3D vortex core was used to identify the
origin of atrial vortex flow. Accordingly, the atrial vortex flow was decomposed into four components based on origin: 1) flow originating from left pulmonary vein (LPV) 2) flow originating from right pulmonary vein (RPV) 3) residual atrial flow or 4) a regurgitant flow originating from LV. Results show that in both healthy volunteers and patients, the majority of atrial vortex flow originates from the LPV. However, patients showed a significant decrease in LPV vortex flow and significant increase in residual atrial vortex flow. Compared to a single recirculating atrial flow region detected in healthy volunteers, patients showed disturbed atrial vortex flow with multiple regions of recirculating flow structures around the regurgitation jet and with opposed circulating directions.

In Chapter 6, a method is proposed for automatic extraction of 3D LV vortex ring core isosurfaces (by means of Lambda2 vortex cores) of peak E- and peak A-filling phases from whole-heart 4D Flow MRI. The proposed method is based on capturing the intrinsic global shape features of the cardiac vortex ring isosurface using the Laplace-Beltrami (LB) spectral shape signature. The LB signature is defined as the diverging eigenvalues sequence of the Laplace-Beltrami differential operator. This LB sequence encodes the discriminating shape features that are intrinsic to the shape of interest. In this work, an LB reference signature of the LV vortex ring shape is derived from a training set of LV vortex ring isosurfaces of healthy volunteers. In the extraction phase, the trained reference signature is used to iteratively search for the LV vortex ring object (isosurface) among co-existing vortex objects. The target vortex ring object is defined as the isosurface that gives best LB-signature match with the trained reference signature. This method has been evaluated in a dataset of eight healthy volunteers using leave-one-out cross validation yielding a precision of 84%. However, one limitation of this work is that it expects the input to be multiple isolated isosurface objects, among them is the target vortex ring isosurface to be extracted. This requires prior definition of the isovalue that produces such a well-defined vortex ring that is isolated from other co-existing vortex objects. In this work, isovalue selection was done empirically based on manual interaction. Selection of appropriate isovalue may require experience and can be a tedious and subjective process.

In Chapter 7, to overcome the aforementioned limitations of the method in Chapter 6, a new method is proposed for automatic identification of the 3D vortex ring core isosurface from 4D Flow MRI flow field without any presumptions on the isovalue selection. In fact, the proposed method allows simultaneous automatic identification of both the best appropriate isovalue and the object corresponding to the vortex ring isosurface. First, the 4D Flow MRI velocity field is converted into a vortex core scalar field
using the fluid-dynamics-based Lambda2 method. Second, a vortex shape signature is derived from a training set of healthy subjects by means of shape distributions: probability distribution of pairwise Euclidean distances of randomly sampled points on the vortex ring isosurface. This derived shape distribution is used as a reference signature defining the shape of the vortex ring isosurface. Finally, a hierarchical vector quantization algorithm is proposed to simultaneously define the best appropriate isovalue and to identify the vortex ring isosurface among co-existing vortex isosurfaces. The method was evaluated qualitatively and quantitatively in two cohorts: a cohort of twenty-four healthy volunteers and a cohort of twenty-three congenital heart disease patients. Results of performed experiments showed excellent performance and good agreement with blindly generated ground truth as well as generalizability to challenging abnormal vortex rings in patients. As such, the proposed method is a step forward towards allowing objective automatic 3D vortex ring analysis from 4D Flow MRI in clinical practice.

8.2. Discussion and Future perspectives

The aims of this thesis as stated in chapter 1 were accomplished. Nevertheless, this thesis can serve as a ground for further work. In this thesis, we have identified and qualitatively characterized the 3D vortex ring formation and its evolution over complete diastole (Chapter 2). However, 3D vortex ring quantification (Chapter 2, 3, 4) and automatic identification (Chapter 6, 7) were mainly limited to only peak early and peak late filling phases which are considered the moments around full vortex ring development. Nevertheless, as shown in Chapter 2, 3D cardiac vortex flow is a dynamic process that involves development, propagation, interaction with chamber wall and subsequent decay. These dynamics were not fully quantified in this thesis. A potential mechanism of vortex flow in cardiac (dys)function is more likely to be evident in the vortex evolution process. Future work should be aimed at quantifying this evolution and its relation to cardiac (dys)function.

The main focus of this thesis was inflow vortex flow formation in the LV during diastole and LA during systole. In principle, the vortex identification and energy evaluation methods developed in this thesis (Chapter 2, 4, 6, 7) are generally applicable to analysis of other blood flow regions in the cardiovascular system from 4D Flow MRI. An example of this was shown in Chapter 5, where 3D atrial vortex identification was successfully performed using methods and workflow originally developed for LV vortex analysis (Chapter 2). In the future, we plan to employ the 3D vortex and energy methods developed.
in this thesis to expand the analysis into other cardiac chambers (e.g. right ventricle, right atrium), as well as great arteries, such as aorta, and over the complete cardiac cycle. Such comprehensive analysis would provide more insights into the normal physiology of the heart and potential connection or alteration in cardiovascular patients.

Eulerian vortex core analysis using the fluid dynamics-based Lambda2 method was the main method used in this thesis for extracting and identifying instantaneous 3D vortex core regions from 4D Flow MRI. A limitation of instantaneous (Eulerian) vortex core identification methods is that, in practice, they require a threshold (isovalue) to be defined (mainly manually) to identify meaningful vortex core regions. The fact that different thresholds might result in different 3D vortex volumes makes it challenging to derive reliable volumetric measurements (e.g. vortex volume, total strength or total energy) based on such vortex core analysis. This becomes more evident when the input velocity field is typically noisy and with coarse resolution as the case with 4D Flow MRI. That is the main reason why volumetric vortex measurements were largely avoided in this thesis.

A solution to the threshold selection problem was approached in Chapter 7, by automatic identification of appropriate threshold (isovalue). This could be a step forward towards an objective identification of vortex core volume. Further studies are still needed to evaluate the accuracy of such method for vortex volume quantification. On the other hand, Lagrangian vortex identification methods, such as Lagrangian Coherent Structures (LCS), might allow quantification of total vortex ring volume over a period of time, but are generally not meant for instantaneous vortex flow analysis (i.e. not to quantify vortex volumes at specific time points). Therefore, they do not directly aim at analyzing the evolution of instantaneous vortex flow. In the future, different vortex identification methods; including Eulerian and Lagrangian, methods should be investigated in a manner that allows accurate and objective analysis of the evolution of instantaneous 3D vortex flow volumes.

4D Flow MRI is a state-of-the-art in-vivo flow imaging technique and the only modality that allows in-vivo acquisition of 4D flow data of all three velocity components. Nonetheless, 4D Flow MRI has some limitations. Typical long acquisition times (up to 20 minutes) may limit the clinical feasibility. However, applying recent scan acceleration techniques enable more feasible acquisition durations (~10 minutes when no respiratory gating is applied) and this is expected to further improve in the future. Given the slow MR acquisition, 4D Flow MRI is requires acquisition over multiple cardiac cycles. This results in acquiring mainly the average flow field while smoothing out turbulent fluctuations or
potential higher order flow components. This has to be taken in consideration when computing and/or interpreting 4D Flow MRI measurements including vortex flow and energetics. The need to heuristically determine an appropriate velocity sensitivity encoding (VENC) prior to 4D Flow MRI acquisition to avoid potential aliasing artifact can be challenging. The acquired 4D Flow MRI flow field may present errors in the form of eddy current effects, Maxwell terms, signal noise, and/or velocity offsets. These errors should be corrected using appropriate techniques before processing/interpreting flow data. Coarse temporal (~30-50 ms) and spatial resolutions (~3×3×3 mm³) of 4D Flow MRI limits flow analysis to the large scale flow structures with life-span longer than the acquired temporal resolution. All these factors may limit the reliability of 4D Flow MRI-based results and subsequent interpretations.

To allow reliable and correct interpretations of 4D Flow MRI measurements, it is important to evaluate and validate such results. A limiting factor in such validation is the lack of a realistic gold standard (ground-truth) of the in-vivo human cardiovascular flow in general, and vortex flow and energetics in particular. Available phantom techniques are not able to provide such realistic gold standard. One way to tackle this issue in future studies could be to benefit from the advances in computational fluid dynamics (CFD) by building hybrid CFD-4D Flow MRI computational systems that impose realistic in-vivo flow field measurements (not only geometry) from 4D Flow MRI to guide high resolution, more controllable and robust, CFD simulations to reach a realistic high resolution model of human cardiac flow field.

While many studies have speculated on a role of vortex flow formation on optimizing cardiac function and/or a connection with cardiac abnormalities, there is a lack of studies evaluating such assumptions in-vivo using a true and complete flow field. In Chapter 4, using 4D Flow MRI flow fields, we have in-vivo evaluated and confirmed the previously speculated, but unverified, role of vortex flow on minimization of energy loss. More (follow-up) studies of different groups of cardiovascular patients are needed to assess the true association between vortex flow patterns and cardiac (dys)function and to determine whether vortex flow could serve as a biomarker, or whether it is only a byproduct of other factors. In fact, the normal cardiac hemodynamics are largely unexplored and therefore still mostly unknown. While currently underestimated in the community, it is critical to carry out more studies aiming at revealing, at a comprehensive level, the normal hemodynamics of the cardiovascular system before jumping into patient evaluations.
This thesis shows the potential of 3D/4D vortex flow analysis and viscous energy loss measurements from 4D Flow MRI in revealing and evaluating in-vivo intra-cardiac hemodynamics. It is critical to ensure reliability and reproducibility of such measurements and analysis to allow sound clinical interpretations. A sophisticated vortex flow analysis needs to be accessible for clinical personnel with minimal needs of technical background. An important mechanism to achieve this would be to continue working on building automatic reliable systems for identification and quantification of cardiac hemodynamics in general and vortex flow and energetics in particular from 4D Flow MRI.