Universiteit Leiden
The Netherlands

4D-Flow MRI of aortic and valvular disease

Juffermans, J.F.

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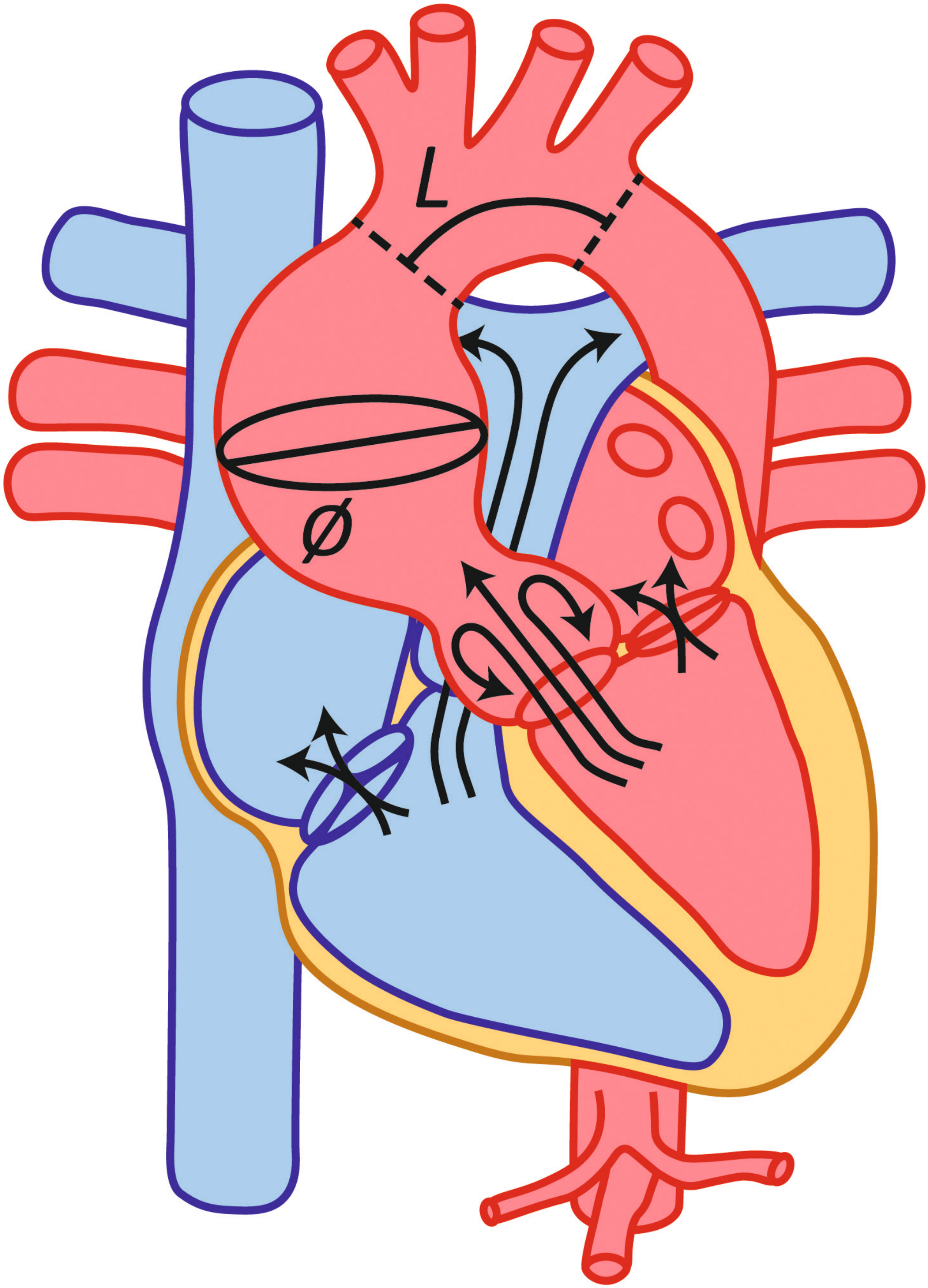
DISCUSSION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CHAPTER 8

General Discussion and Summary

The aims of this thesis were to assess reproducibility and consistency of 4D flow MRI for evaluating aortic hemodynamics and valvular flow, and to explore the clinical potential of aortic hemodynamics for diagnosis and disease progression monitoring in patients with aortic and valvular disease. In **Chapter 1** a general introduction was given thoracic aortic aneurysm, valvular regurgitation, aortic coarctation, and 4D flow MRI. **Part 1 (Chapter 2 – 4)** of this thesis assesses the reproducibility and consistency of 4D flow MRI for evaluation of aortic hemodynamics and valvular flow. **Part 2 (Chapter 5 – 7)** of this thesis explores the clinical potential of aortic hemodynamics for diagnosis and disease progression monitoring in patients with aortic and valvular disease.

Part 1. Reproducibility and Consistency

Reproducibility and consistency of 4D flow MRI for evaluation of aortic hemodynamics and valvular flow was assessed.

Hemodynamic aortic parameters can be derived from 4D flow MRI, but this requires lumen segmentation. These lumen segmentations are mostly (semi-)automatically performed and subsequently manually improved by an observer. In **Chapter 2** the interexamination, interobserver, and intraobserver reproducibility of aortic lumen segmentation on 4D flow MRI was assessed in healthy volunteers. Reproducibility was evaluated by analyzing the morphology of lumen segmentations on volume, surface area, centerline length, maximal diameter and curvature radius in five anatomical segments of the thoracic aorta. Interexamination, interobserver, and intraobserver analysis demonstrated a very good reproducibility for aortic lumen segmentation. Hereby, no major reproducibility limitations were demonstrated for aortic lumen segmentation on 4D flow MRI.

The manual improved segmentations of the aortic lumen are used to derive hemodynamic aortic parameters from the 4D flow MRI. In **Chapter 3** the interobserver and intraobserver reproducibility of hemodynamic parameters was assessed quantitatively in patients with a thoracic aortic aneurysm. The reproducibility was evaluated by quantifying the normalized flow displacement, flow jet angle, wall shear stress, vorticity, and helicity in six anatomical segments of the thoracic aorta. The interobserver and intraobserver analysis demonstrated a very good reproducibility for hemodynamic parameters. Hereby, aortic hemodynamics can precisely be quantified from a 4D flow MRI in patients with thoracic aortic aneurysm.

Automated retrospective valve tracking in 4D flow MRI allows consistent assessment of valvular flow through all intracardiac valves (1). However, due to variance of MRI scanner types and protocols, it remains uncertain if the published consistency hold for other clinical centers. In **Chapter 4** the interobserver agreement and valvular flow variation was determined for automated retrospective valve tracking in 4D flow MRI at multiple sites. Seven sites each contributed data of subjects who underwent a whole heart 4D flow MRI. 4D flow MRI was acquired with locally used MRI scanners and protocols but the image analysis software was identical for all sites. The interobserver analysis demonstrated strong-to-excellent agreement for all sites and valves. In addition, all observers established a low intervalvular variation in their analysis. Hereby, valvular flow quantification can be performed consistently with automated retrospective valve tracking in 4D flow MRI, independently of locally used MRI scanners and protocols.

Part 2. Clinical Potential

The clinical potential of aortic hemodynamics for diagnosis and disease progression monitoring in patients with aortic and valvular disease were explored.

It has been demonstrated that the aortic dilatation rate is influenced by alterations of aortic hemodynamics (2-4). However, the effects of ageing and aortic diameter on aortic hemodynamics have not yet been described. In **Chapter 5** the natural course of the aortic hemodynamics while aging was described in a patient with an ascending aortic aneurysm and a healthy volunteer with long-term follow-up at ten and eight years respectively by 4D flow MRI. The patient and healthy volunteer demonstrated that aortic hemodynamic parameters are marginally affected by ageing and the aortic diameter. Since aortic hemodynamic parameters have been associated with aortic dilation by previous studies (2-4), the outcomes of the two subjects suggest that the aortic dilatation rate will remain constant while individuals are ageing and dilating.

Although certain hemodynamic parameters have been associated with dilatation rate of the aorta (2-4), it is still unknown why some individuals dilate in the aortic root and others in the ascending aorta. Since we hypothesized that patients with aortic root and ascending aorta dilatations have different hemodynamics, the hemodynamic phenotypes of aortic root and ascending aorta dilatations in patients with normal tricuspid aortic valves were determined in **Chapter 6**. These hemodynamic phenotypes were compared with healthy volunteers. Patients with aortic root dilatation showed significantly higher net forward volume and WSS angle in the aortic root compared to healthy volunteers. Patients with ascending aorta aneurysm showed significantly higher normalized flow displacement, flow jet angle and WSS angle in the ascending aorta compared to healthy volunteers. Hereby, two distinct hemodynamic phenotypes were demonstrated for patients with an aortic root or ascending aorta dilation, as compared to healthy volunteers. The hemodynamic phenotypes can potentially explain the presence of aortic root and ascending aorta dilation.

Coarctation patients before curative reconstruction are exposed to abnormal flow patterns which potentially could cause wall deterioration (5). In **Chapter 7** the effect of age at curative reconstruction on the aortic wall stiffness expressed as pulse wave velocity and hemodynamics load on the arterial wall expressed as peak wall shear stress was evaluated in adolescent patients with corrected coarctation. Furthermore, effects of aortic valve morphology and presence of reobstruction were also evaluated. Patients with tricuspid aortic valve showed a significant correlation between the age at correction and descending aorta pulse wave velocity. Besides, significant differences were found between patients without and with reobstruction for peak wall shear stress in the aortic arch and descending aorta. Hereby, a prolonged period of abnormal hemodynamic exposure may result in increased aortic wall stiffening. The increased peak WSS as a result of a reobstruction possibly promotes different disease progression, which endorses longitudinal follow-up examination of corrected coarctation patients.

Considerations

Results presented in this thesis have several methodological limitations. The following considerations should be taking into account when the results are interpreted.

Reproducibility of aortic lumen segmentation and quantification of hemodynamic parameters on 4D flow MRI was evaluated in relatively small populations of healthy volunteers and patients with thoracic aortic aneurysm in **Chapter 2** and **Chapter 3**, respectively. However, robustness of these studies was improved by including multiple observers, analyzing five systolic phases, and dividing the thoracic aorta into five or six anatomical segments. Since only healthy volunteers and patients with thoracic aortic aneurysm were included in these studies, reproducibility of aortic lumen segmentation and quantification of hemodynamic parameters in patients with other aortic pathologies remains unknown.

The interobserver agreement and valvular flow variation for automated retrospective valve tracking was not evaluated in patients with intra- and extracardiac shunts or congenital heart diseases of great complexity (as defined by the American Heart Association (6)). These patients were excluded in **Chapter 4** to allow consistency analysis based on the intervalvular variation among all four cardiac valves. In addition, this study only included adult subjects and no children. Furthermore, none of the sites used an intravascular contrast agent, which eliminated the possibility to study its effect on the intervalvular variation.

The natural course of the aortic hemodynamics while aging was described in a patient with an ascending aortic aneurysm and a healthy volunteer in **Chapter 5**. The unlikely negative dilatation rates between some MRI acquisitions of the patient and healthy volunteer demonstrate the measurement uncertainty of aortic diameters. Like all parameters assessed by an imaging modality, the precision and accuracy of the quantification of the maximal vessel diameter is affected, among other factors, by the imaging modality, acquisition, quantification method, and observer variability .

In **Chapter 6** the hemodynamic phenotypes of patients with root dilation, ascending dilation and healthy volunteers were determined. The cross-sectional study design could not indicate if the aortic hemodynamic characteristics are either the cause or outcome of dilation due to the lack of longitudinal data. The retrospective inclusion of patients resulted into various numbers of patients among aneurysm cohorts. Aortic hemodynamic parameters were quantified only at peak systole. Consequently, temporal information of 4D flow MRI was not analyzed. Besides, patients with degenerative aneurysms are likely to use medication. Influence of medication on the aortic hemodynamics was not assessed in this study.

The effect of age at curative reconstruction on the aortic wall stiffness and hemodynamics load on the arterial wall was evaluated in limited number of adolescent patients with corrected coarctation. The small populations size in **Chapter 7** limited the statistical power which made the comparison of subgroups based on multiple patient characteristics difficult. Besides, the study only incorporated patients and no healthy controls, excluding the possibility to compare results with reference values. Furthermore, the single-center design limited the patient diversity, resulting in a relatively small variation of age at coarctation correction.

Future Perspectives

4D flow MRI allows assessment of the entire three-dimensional velocity vector field over the cardiac cycle. Thanks to ongoing research on sequence optimization and image processing of 4D flow MRI, it is expected that the acquisition time will be reduced, image processing will be automated, and new hemodynamic parameters will be introduced in the future (7). While this thesis demonstrated no major reproducibility limitations for 4D flow MRI to assess the hemodynamics of the cardiovascular system, researchers must monitor the robustness of 4D flow MRI when technical advances will be introduced in the future.

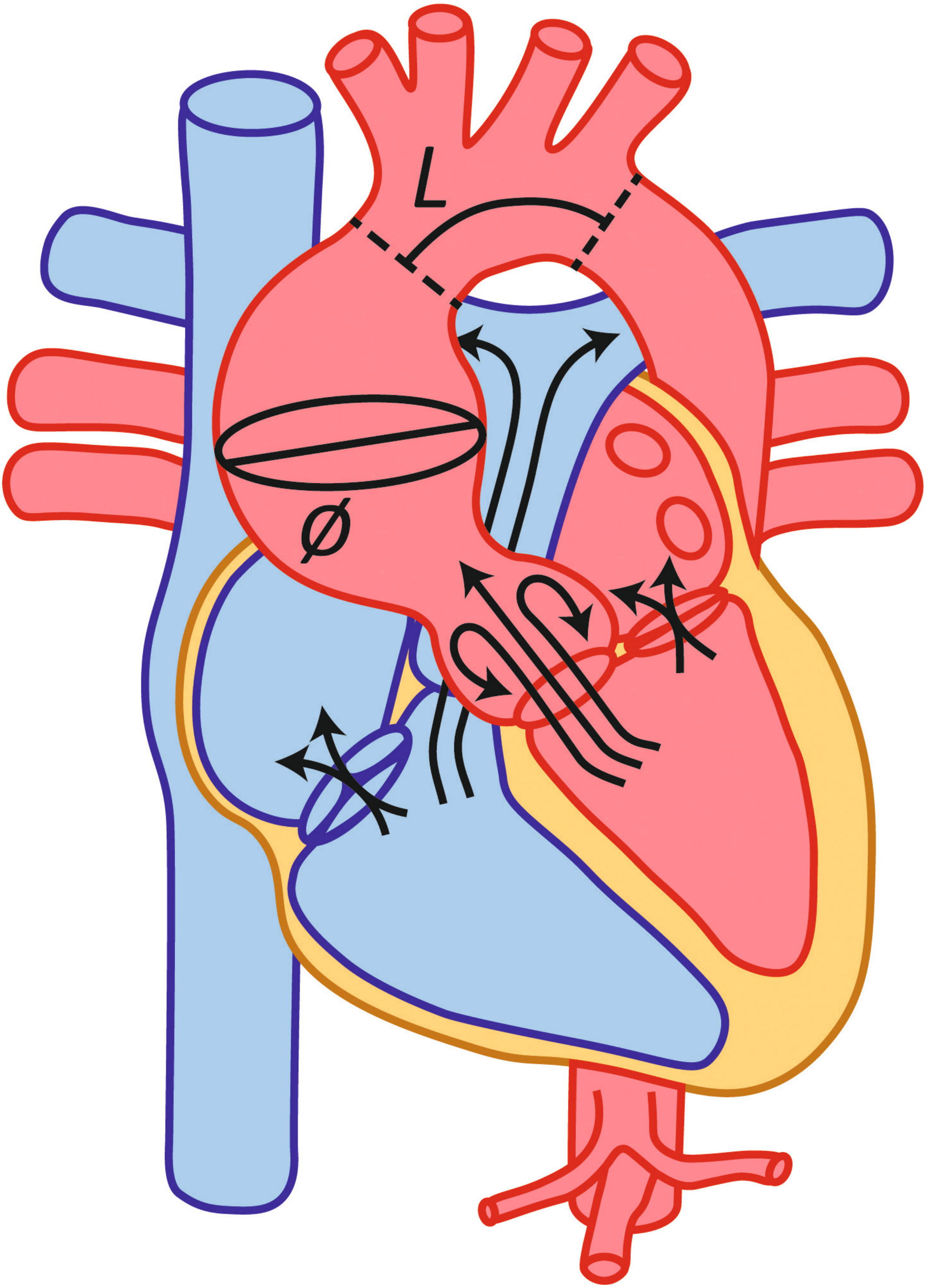
Using velocity vector fields based on 4D flow MRI, recent studies demonstrated associations between the hemodynamics and the aortic dilatation rate (8, 9). While these studies demonstrate the potential of 4D flow MRI to predict disease progression of aortic aneurysm, no studies have been published which assess the influence of aortic hemodynamics on adverse aortic events, such as aortic dissection, rupture, or death. Presumably the prognostic value of these 4D flow MRI-derived hemodynamic parameters on clinical outcomes of patients with aortic and valvular disease need to be assessed by larger prospective and multi-center studies in the future. When coupling between hemodynamics and clinical outcomes has been demonstrated, hemodynamic parameters eventually could be adopted by clinical guidelines to improve the risk stratification of patients what presumably results in a wide clinical implementation of 4D flow MRI. Therefore, research should be conducted to overcome current information overload paradox of 4D flow MRI; while drowning in information of the hemodynamics, we are starving for knowledge on patients with aortic and valvular disease.

Conclusions

This thesis assesses reproducibility and consistency of 4D flow MRI for evaluation of aortic hemodynamics and valvular flow. It is demonstrated that aortic lumen segmentation and quantification of aortic hemodynamics and valvular flow using 4D flow MRI is performed with excellent reproducibility and consistency. With no significant limitations observed regarding reproducibility and consistency, 4D flow MRI allows precise assessment of aortic hemodynamics and valvular flow in patients with aortic and valvular disease. Furthermore, this thesis explores the clinical potential of aortic hemodynamics for diagnosis and disease progression monitoring in patients with aortic and valvular disease. It is demonstrated that aortic hemodynamic parameters remain relatively stable with aging and aortic diameter, suggesting a constant aortic dilatation rate over time for individuals. In addition, distinct hemodynamic phenotypes were identified for patients with root dilation, ascending dilation and healthy volunteers, which could potentially explain the presence of dilation. Besides, it is demonstrated that an older age at curative reconstruction in patients with corrected coarctation is correlated with increased aortic wall stiffening, and presence of reobstruction is associated with increased wall shear stress. Hemodynamic alterations of the aorta in corrected coarctation patients possibly promote different disease progression.

REFERENCES

1. Kamphuis VP, Roest AA, Ajmone Marsan N, van den Boogaard PJ, Kroft LJ, Aben J-P, et al. Automated cardiac valve tracking for flow quantification with Four-dimensional Flow MRI. *Radiology*. 2019;**290**(1):70-8.
2. Korpela T, Kauhanen SP, Kariniemi E, Saari P, Liimatainen T, Jaakkola P, et al. Flow displacement and decreased wall shear stress might be associated with the growth rate of an ascending aortic dilatation. *European Journal of Cardio-Thoracic Surgery*. 2022;**61**(2):395-402.
3. Minderhoud S, Roos-Hesselink J, Chelu R, Bons L, Van Den Hoven A, Korteland S, et al. Wall shear stress angle determines aortic growth in patients with bicuspid aortic valves. *European Heart Journal-Cardiovascular Imaging*. 2021;**22**(Supplement_2):jeab090. 120.
4. Hope MD, Sigovan M, Wrenn SJ, Saloner D, Dyverfeldt P. MRI hemodynamic markers of progressive bicuspid aortic valve-related aortic disease. *Journal of Magnetic Resonance Imaging*. 2014;**40**(1):140-5.
5. Nigro G, Russo V, Rago A, Papa AA, Della Cioppa N, Di Meo F, et al. Heterogeneity of ventricular repolarization in newborns with severe aortic coarctation. *Pediatric cardiology*. 2012;**33**(2):302-6.
6. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, et al. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2016;**133**(8):770-801.
7. Soulat G, McCarthy P, Markl M. 4D Flow with MRI. *Annual Review of Biomedical Engineering*. 2020;**22**:103-26.
8. Soulat G, Scott MB, Allen BD, Avery R, Bonow RO, Malaisrie SC, et al. Association of regional wall shear stress and progressive ascending aorta dilation in bicuspid aortic valve. *JACC: Cardiovascular Imaging*. 2022;**15**(1):33-42.
9. van Hout M, Juffermans J, Lamb H, Kröner E, van den Boogaard P, Schalij M, et al. Ascending aorta curvature and flow displacement are associated with accelerated aortic growth at long-term follow-up: A MRI study in Marfan and thoracic aortic aneurysm patients. *IJC Heart & Vasculature*. 2022;**38**:100926.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