In silico mechanistic assessment of imaging-based measures of cardiac (patho) physiology

Valorisation

Personalising medicine using cardiovascular computer modelling

Cardiovascular disease (CVD) remains the most common cause of death worldwide. Each year CVD causes over 4 million deaths in Europe representing 47% of all deaths in the whole continent. Active research is therefore required to improve diagnosis and therapies of cardiovascular conditions. Clinical guideline recommendations and management strategies on CVD are often based on findings from large clinical trials. Unfortunately, not all patients respond favourably to a specific therapy because of the existing differences between patients treated under the same therapy. These differences arise from cardiac and vascular properties and components specific for each individual. To treat each single patient under the optimal therapy or clinical intervention, it is crucial to capture these patient-specific cardiovascular properties to evaluate the response and the risk of a particular CVD in the individual patient. Personalised medicine is therefore needed to select specific and accurate treatment for the patient and their genetic profile, thereby providing better diagnoses with earlier intervention and more efficient drug developments and therapies.

Personalised medicine aiming comprehensive understanding of a patient's underlying pathophysiology requires a number of changes in the current healthcare system with respect to industrial and medical regulatory policies and commercialization therapies. Furthermore, acquisition of diagnostic data represents a challenge whereby the interdisciplinary cooperation of scientists from different fields, such as medicine, biology, pharmacology and engineering, is key. Research on better predicting a patient's risk for a particular CVD is practically very challenging using clinical studies. Alternatively, animal experiments offer a controlled environment in which to test hypotheses within variation of cardiovascular properties, but practical, cost and ethical issues limit the interventions on animals. Academic and industrial sectors have been focused on developing alternative approaches to minimise the use of animals. The *principles of the 3Rs* (replacement, reduction and refinement) represent a framework for humane animal research that supports the development and uptake of new technologies and approaches to minimise the use of animals in clinical research. As suggested by the 3Rs, methods that avoid or replace the use of animals on research include mathematical and computer models among others. Computer models do offer a relatively easy manipula-

tion of cardiac and vascular properties as well as an isolated and controlled variation of these properties. Computer models are therefore a suitable approach to gain insight into personalised medicine. Over the last years, computational models of human physiology have begun to be capable of patient-specific simulation, allowing prediction of response to treatments tailored to the patient. The findings presented in this thesis clearly demonstrate that computer models can help to personalize medicine without necessarily requiring the construction of a personalized model.

Opportunities for the CircAdapt model

The mechanisms described in this thesis provide explanation of both normal and abnormal findings from echocardiography and cardiac magnetic resonance imaging. Our findings therefore establish the strength of the CircAdapt model on providing mechanistic insight on imaging-based findings of the heart and circulation. The described mechanisms using the CircAdapt model can improve the interpretation of hemodynamic and mechanical interactions in the heart of an individual patient, thereby contributing on personalising the assessment of cardiac (patho)physiology.

The department of Biomedical Engineering together with an industrial partner has translated the research version of the CircAdapt model into a friendly education tool called CircAdapt Simulator. This tool is available as a free download from www.circadapt.org. CircAdapt Simulator is fully integrated into the medical curriculum at Maastricht University for the teaching of hemodynamics and cardiac mechanics in healthy physiology, in valvulopathies, and in congenital heart diseases. It is also currently being used to train medical and biomedical engineering students at Nijmegen University, TU Eindhoven, and the University of Utah. Additionally, the findings provided in this thesis also demonstrated the importance of *in silico* research into human physiology using the CircAdapt model as they can aid interpretation of cardiovascular system function. The representation of mechanics and hemodynamics of the adult heart and circulation simulated by the CircAdapt model are therefore of significant value in both education and clinical research. Moreover, further research on cardiovascular (patho)physiology can be developed using CircAdapt. The high value of this computational model offers a wide range of potential for collaborations with industrial companies that are exploring and developing new strategies for assessment of valvular diseases and optimization of ventricular pump function.

Application of our mechanistic insights

To contribute on personalising medicine, understanding the mechanisms underlying imaging-based observations is key for proper personalization of clinical decision-

making. In line with this, the physiological mechanisms unravelled in this thesis have direct clinical benefits. Our results on assessment of aortic regurgitation severity described in chapter 3 present important considerations for clinicians and cardiologists treating patients with this valvular disease. The possible inconsistencies in grading aortic regurgitation severity in presence of abnormal cardiac or aortic wall properties demonstrated in chapter 3 facilitates the difficult tasks of aortic regurgitation severity assessment and treatment.

Clinical indices contributing to the improved detection of right ventricular dysfunction in patients with pulmonary arterial hypertension is crucial since this dysfunction is often detected at late stages of the disease when the right ventricle is already failing. Our mechanism explaining the disappearance or appearance of rapid leftward septal motion at early diastole in chapter 4 provides better understanding of the process underlying right ventricular dysfunction in pulmonary arterial hypertension. Pulmonary hypertension arising from left-sided failure synchronizes contractile function in both left and right ventricle, thereby explaining why the abnormal septal motion is not apparent in such a subgroup of patients with pulmonary arterial hypertension. Rapid leftward septal motion at early diastole can be therefore considered as an index reflecting the right ventricle-to-left ventricle dyssynchrony in relaxation, thereby helping to detect right ventricular failure in patients with pulmonary hypertension.

The findings in chapter 5, focused on the complex integration of circulatory physiology during intense exercise, are of direct use for cardiologists and physiologists because they provide insights into early-warning signs for right ventricular dysfunction during exercise. Participation in intense endurance events like marathons or ultra-triathlons is increasing in western society. Despite all the unquestionable benefits of practicing sport, the high prevalence of exercise-induced ventricular arrhythmias and atrial fibrillation in a subpopulation of endurance athletes has led to a debate among scientists and clinicians. Our novel hypothesis on the vicious cycle of right ventricular dysfunction induced by extreme intensity exercise presented in chapter 6 has direct clinical implications. It offers an explanation for the interaction between genetic and exercise-related factors in the development of adverse right ventricular pathological remodelling in a number of CVD, such as arrhythmogenic right-ventricular cardiomyopathy and pulmonary arterial hypertension among others.