Heartbeat-to-heartbeat cardiac tissue characterization

van den Boomen, Maaike

DOI:
10.33612/diss.128413796

Chapter 1

Introduction

The prevalence of cardiovascular risk has currently increased to 48.0% of all Americans that are 20 years or older (Benjamin et al. 2019). With the potential progression into heart failure or coronary heart disease in 9.0% of the overall population, with or without preserved ejection fraction (Benjamin et al. 2019, Lam et al. 2011), detection of microvascular dysfunction is becoming a pressing topic of interest (Haddad et al. 2015). The microvasculature is expected to have a prominent role in the progression of multiple cardiovascular disease, including hypertension, cardiomyopathies and syndrome X, into heart failure (Cecchi et al. 2009, Ahmed and Creager 2017). However, current clinical diagnostics and imaging methods are unable to determine the onset of these disease, while early detection is key in prevention of major cardiac events.

Aside from the more conventional computed tomography (CT) imaging and echocardiography (Shehata et al. 2008, Prakken et al. 2009) or single photon emission computed tomography (SPECT) and positron emission tomography (PET) (Al Badarin and Malhotra 2019, Juárez-Orozco et al. 2018), cardiac magnetic resonance imaging (MRI) is becoming a more common practice in diagnosis and assessment of cardiovascular diseases. While MRI can offer a wide range of different readouts, clinical cardiac MRI examinations primarily include the assessment of the ejection fraction (EF) by using standard volumetric MRI, myocardial infarct size and tissue viability by using late gadolinium enhancement (LGE) (Noureldin et al. 2012), and sometimes also perfusion defects by using stress induced perfusion MRI (Coelho-Filho et al. 2013).

Nevertheless, quantitative cardiac MRI techniques, such as T_1-, T_2- and T_2^*- mapping approaches, are now slowly finding their way into clinical diagnostics (Messroghli et al. 2017). Each of these techniques have proven to be useful for either

assessment of fibrosis, edema and hemorrhage formation, respectively, but are also known to have their shortcomings. The main disadvantage for early detection of cardiovascular disease is that these mapping techniques only help to identify damaged tissue, which occurs post-onset of the disease. Since microvascular dysfunction is expected to play a prominent role in the early stages of cardiovascular diseases (Olivotto et al. 2006, Galati et al. 2016), other techniques should be developed and investigated to enable clinical assessment of the role of microvascular dysfunction in cardiovascular health.

Other approaches that remain mainly used in experimental and preclinical practice include the assessment of strain using tagging MRI (Pai and Axel 2006) or myocardial feature tracking (Eitel et al. 2018), the assessment of extracellular volume (Neilan et al. 2013) and endothelial function (Leenders et al. 2018) using dynamic contrast enhanced (DCE) MRI, and the assessment of the myofiber orientation in micro-tissue using diffusion tensor imaging (DTI) (Nguyen et al. 2016). Each of these techniques are promising but face different limitations or need further validation and improvement to make it into clinical practice.

Since this interest in the assessment of microvascular function is emerging (Petersen and Pepine 2015), it is intuitive to start looking at oxygenation and vascular structure imaging techniques. MRI based approaches that enable these readouts are already widely used in the brain to estimate oxygenation changes (Ogawa et al. 1990), to perform functional MRI (Belliveau et al. 1991) or to determine revascularization in glioblastomas (Emblem et al. 2013). For the cardiac applicability of these techniques, a high temporal resolution in combination with sufficient spatial resolution is essential to overcome the current limitations of existing cardiac oxygenation and vascular imaging methods (Vohringer et al. 2010, Wacker et al. 1999, Feng et al. 2011).

Even though there are several new and older cardiac MRI techniques that can provide valuable information on myocardial tissue characteristics, it took over a decade to get some of those techniques implemented in clinical practice, such as T_1- and T_2-mapping, while others remain only relevant as research tools, such as tagging MRI or cardiac DTI. It seems that the main reason for the clinical success of an imaging technique is whether it can be easily performed or not, and if the reproducibility of the quality is sufficient for a standardized analysis. Therefore, attention should be given to these requirements for implementation during the development of novel cardiac MRI techniques. However, while this thesis contains a thorough description of the development of some novel cardiac MRI approaches, further clinical validation should still be performed with these implementation limitations in mind.

1.1 Scope

The objectives of this thesis are:

- to determine the reference values of current clinically quantitative myocardial tissue characterization techniques;
- to apply novel myocardial tissue characterization techniques in an animal model;
- to develop and clinically validate a novel dynamic cardiac blood oxygenation level dependent (BOLD) imaging technique;
- to develop and provide an initial proof of concept of a novel cardiac vessel architectural imaging (VAI) method.

This thesis will give an overview of the applicability and limitations of current clinically recommended quantitative cardiac MRI techniques. Furthermore, it will describe the evaluation of several new approaches in a reperfusion injury animal model receiving a regenerative therapy. Eventually, this exploratory work leads to the motivation of the development of two novel quantitative cardiac MRI techniques. The first technique enables the assessment of either normal or impaired oxygenation over the myocardium over the time of a single breath-hold, by using cardiac BOLD imaging. The second technique used the same MRI sequence combined with an contrast-agent injection, which enables the calculation of indices for vascular type, volume, caliber, and density. However, these techniques still need further clinical validation and histological comparison to determine their eventual clinical applicability.

1.2 Outline

In the first part of this contribution, reference values are determined for current clinically applied quantitative cardiac MRI techniques, with Chapter 2 covering the reference values for native (non-contrast enhanced) T_1-mapping and Chapter 3 covering native T_2- and T_2^*-mapping. Furthermore, the cardiovascular diseases that would benefit from using these techniques for early diagnosis are described in addition to the cardiovascular diseases and risk populations that would require another approach.

The second part of this thesis shows the application of translational cardiac MRI techniques for the evaluation of novel therapies in a reperfusion injury animal model. Chapter 4 specifically focusses on the assessment of the myocardial tissue changes due to a regenerative therapy by using MRI based readouts for strain, endothelial function, fibrosis and left ventricular function by using tagging MRI, DCE MRI, T_1-mapping, and standard volumetric MRI, respectively. By correlating these MRI readouts with histology, more insights are provided on the accuracy and sensitivity of these MRI techniques.

The third part of this work contains a detailed description of a new cardiac BOLD MRI technique based on a gradient-echo spin-echo echo-planar-imaging (GESE-EPI) sequence. This sequence has the advantage over other cardiac BOLD imaging approaches by providing dynamic heartbeat-to-heartbeat T_2- and T_2^*-maps that provide a quantitative readout of BOLD changes. Chapter 5 includes the technical development and comparison with a non-quantitative version of the same sequence and also the feasibility and repeatability of detection of breath-hold induced BOLD changes. Furthermore, Chapter 6 covers the clinical validation of the GESE-EPI BOLD approach and shows the difference in BOLD response between healthy and hypertensive volunteers. Lastly, Chapter 7 in this part describes the use of simultaneous multi-slice readouts in the GESE-EPI sequence and the influence of the slice positioning and on the BOLD readouts.

In the last section of this thesis, the development and feasibility of using the GESE-EPI sequence for cardiac VAI are described. Chapter 8 shows the first proof of concept of cardiac VAI in healthy volunteers that were able to hold their breath long enough for a first pass of the contrast agent. This same experiment was repeated in a healthy animal model and validated with immunofluorescent based histological findings.

Since this thesis, in addition to an overview of the current state of clinical cardiac quantitative tissue characterization techniques, mainly describes the first results of newly developed cardiac BOLD and VAI techniques, an extensive General discussion and future perspectives of this work is included. Here, potential future studies including clinical and translational evaluations are described in detail. Furthermore, a brief summary of the covered research is presented in the Summary / Samenvatting.

Part I

Establishment of cardiac quantitative MRI reference values