Visualising the invisible

SCIENTIFIC AND SOCIETAL IMPACT

What is scientific and societal impact?

"The demonstrable contribution that excellent research makes to the society and economy"

Cardiovascular diseases (CVDs) have a major impact on people's everyday life. Not only have CVDs been the leading cause of death globally in both men and women for numerous decades now, the corresponding financial and social impact is tremendous. The associated healthcare costs for CVDs alone are already exceeding 11% of the total healthcare costs in the Netherlands, with even more shocking numbers in other parts of the Western world. And even though CVD related mortality is falling, an increasing number of patients with non-fatal CVDs must live with chronic disabilities and impaired quality of life. Due to the increasing prevalence of known risk factors, including obesity, diabetes, high blood pressure, and inactivity, the incidence of CVDs is increasing rapidly.

Among CVDs, coronary artery disease (CAD) ranks as the most prevalent, responsible for 16% of the world's total deaths. For many patients, myocardial infarction (MI) is the first symptom of CAD. Already over a decade ago, it was first demonstrated that even small regions of MI were associated with large increases in major future adverse cardiac events, and that regional functional recovery of the myocardium following revascularization was highly dependent on the transmural extent of the infarct. More recently, there is an increasing interest in the localization and assessment of fibrotic substrate for the work-up and treatment of cardiac arrhythmias. Clearly, the detection and accurate assessment of infarcted areas in terms of size, location, extent, and transmurality are an essential requisite for patient management decisions and selection of the optimal therapeutic approach.

This thesis focuses on the development, validation, evaluation, and various clinical applications of a novel late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) method to improve the detection and assessment of areas of MI. One of the main conclusions from this work is that the novel dark-blood LGE MRI method showed to be superior in both the detection and assessment of MI compared to the current in-vivo reference standard. The widespread and direct availability, combined with its simplicity and ease-of-use, already led to the implementation of this novel method into the clinical routine settings of various medical centers across the globe, including our own. Ever since publication, our findings have been evaluated and confirmed by other research groups, advancing and strengthening the translation into the clinic.

Novel dark-blood LGE MRI may bring clear benefits to the patients. Due to superior detection and assessment of (subendocardial) myocardial scar, patients may be reclassified below or above a threshold in clinical practice to guide revascularization therapy. The patient may either be saved from treatment that lacks effectiveness in the patient's situation, or may be offered treatment which was not deemed to be effective before. Additionally, the increased scar-to-blood contrast and high spatial resolution of the 3D variant paves the way for myocardial scar assessment in thin-walled structures, such as the atria and right ventricle, which is highly challenging using conventional methods. This additional information may support the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) and may guide the work-up and ablation therapy in patients with atrial arrythmias.

The high potential of such advanced cardiovascular imaging techniques has recently been acknowledged by major research funders, including Stichting de Weijerhorst and the Dutch Heart Foundation, both funding multimillion projects related to this topic. Stichting de Weijerhorst recently funded the 'Cardiovasculaire beeldvorming' project, focusing on various aspects of advanced cardiovascular imaging, including novel imaging techniques and methods, their translation into the clinic, image interpretation, increased insights in the development and progression of cardiovascular diseases, improved diagnostics, and the potential replacement of invasive imaging methods. This multidisciplinary project, including radiologists, cardiologists, nuclear medicine specialists, and medical physicists of the Maastricht University Medical Centre, led to various new insights in the diagnosis, prognosis, and treatment of cardiovascular disease patients, including the results of this thesis. More recently, the Dutch Heart Foundation funded the VIGILANCE study, focusing on individuals with ventricular fibrillation (VF) without a demonstrable cause (idiopathic VF or iVF). In this CVON (Cardiovasculair Onderzoek Nederland) project, in which all academic and various large general hospitals in the Netherlands collaborate, advanced imaging is used to unravel which electrical substrate and triggers are potentially causing iVF. This may include small myocardial scar substrates of earlier MI that remained undetected using conventional imaging techniques, however, may now be detected using the novel high-resolution 3D dark-blood LGE technique presented in this thesis. Although the study is still in full swing, some promising results already led to a different work-up and treatment in a handful of patients.

In the past 20 years, LGE imaging is increasingly used in clinical trials with infarct size as a surrogate endpoint. Due to the reduced variability of dark-blood LGE compared to conventional LGE, dark-blood LGE is expected to play an important role in future clinical trials using infarct size as endpoint. More recently, LGE imaging is used more frequently in the work-up and treatment of patients with (supra)ventricular arrhythmias, mainly for assessing the location, degree, and extent of areas of potential scar and/or fibrotic tissue. Interesting avenues that are currently being investigated, include the role of LGE imaging in predicting whether patients will develop life-threatening ventricular arrhythmias, and therefore may benefit from an implantable cardioverter-defibrillator (ICD) implantation. Since only a minor portion of patients with ICDs currently show life-threatening arrhythmias for which the ICD needs to come into action, the question remains whether they really benefited from the ICD implantation with the associated implantation risks and social-economic consequences.

From a cost-effective point of view, the novel dark-blood LGE method presented in this thesis was not developed as an additional imaging method, but rather as a replacement method for conventional LGE. Novel dark-blood LGE therefore does not prolong existing scan duration or lead to additional examinations for the patient. Instead, dark-blood LGE imaging can be performed with superior sensitivity for MI (less false negatives) and enables improved scar assessment compared to conventional LGE methods. Consequently, dark-blood LGE increased the diagnostic value within the same scan duration which may result in less downstream testing.

Additionally, novel free-breathing LGE methods enable patients to breathe freely during acquisition instead of repetitive breath-holding. This not only increases patient comfort, but also enables the high-quality LGE acquisitions in patients that are unable to hold their breath at all or for a sufficiently long period of time. Furthermore, the improved patient comfort contributes to consistent high image quality and reduces the chance on non-diagnostic examinations.

The results in this thesis are relevant to all MI patients, regardless of whether the cause was arrhythmogenic, structural, or coronary artery related. The novel dark-blood LGE method described in this thesis may lead to reclassification of patients resulting in an alternative treatment strategy, potentially impacting quality of life and anxiety levels.