Atrioventricular imaging to predict outcome in dilated cardiomyopathy

Summary

Dilated cardiomyopathy (DCM) is a multifactorial disease characterized by the presence of left ventricular (LV) systolic dysfunction and LV dilation, in the absence of significant coronary artery disease and abnormal loading conditions, such as valvular and hypertensive heart disease. Non-invasive imaging techniques such as echocardiography and cardiac magnetic resonance imaging (CMR) are already implemented in current clinical care of DCM patients. However, the focus has always been on the LV function, using conventional parameters such as LV ejection fraction (EF) and LV reverse remodeling (RR). Since these measures are only based on volumetric LV changes and do not completely visualize the complexity of DCM as heterogeneous disease, novel non-invasive imaging techniques have been developed to provide additional information regarding myocardial function and structure. In this thesis, different non-invasive imaging techniques are applied and combined with multilevel parameters, aiming to improve disease classification and risk prediction of DCM patients.

Part I of this thesis discusses the incremental value of global longitudinal strain (GLS), a novel non-invasive imaging technique that measures myocardial deformation, with a focus on the LV. In 28% of the patients, echocardiographic LVEF recovered upon optimal medical therapy, but 50% of these patients had impaired echocardiographic GLS values, indicating that 'recovered LVEF' doesn't imply full myocardial recovery. In line, GLS had independent value to predict adverse clinical outcomes in optimally treated DCM patients and exceeded the prognostic value of LVEF (**chapter 2**). Myocardial deformation can also be measured on CMR, using feature tracking. In patients with acute myocarditis, which can be a precursor of DCM, not only GLS, but also global circumferential and radial strain were of independent value in predicting major adverse cardiovascular events and overruled not only other clinical predictors, but also LVEF and the presence of late gadolinium enhancement (focal fibrosis, LGE) (**chapter 3**).

Part II discusses the importance of the left atrium (LA) for cardiac function and prognosis. By applying the CMR feature tracking technique on the LA, LA phasic function during the cardiac cycle was measured. LA conduit strain, which reflects the passive filling of the LV, was the strongest LA strain parameter and was independently associated with sudden or cardiac death, heart failure hospitalization and life-threatening arrhythmias. It exceeded the prognostic value of LVEF, LA volume index and LV-GLS, and had, together with LGE presence, incremental prognostic value (**chapter 4**). In a subpopulation of DCM patients without known atrial fibrillation (AF), 10% developed new-onset AF during follow-up. LA booster strain, reflecting the active LV filling, was associated with new-onset AF and an increased risk for ischemic cerebrovascular accidents (**chapter 5**). Besides the ability of LA strain to predict adverse clinical outcomes, it can also be used to discriminate between DCM patients with a genetic truncating titin variant (TTNtv) and DCM patients without this genetic variant. TTNtv patients had worse LA function parameters compared to patients without TTNtv, which could not be completely explained by LV dysfunction alone. This suggests that the intrinsic LA myopathy – which seems to be present in all DCM patients – is more severe in DCM patients with TTNtv compared to DCM patients without TTNtv (**chapter 6**). However, a causal relationship between LV- and LA-myopathy and whether LV-myopathy precedes LA-myopathy or vice versa remains to be determined in future studies. In addition to LA phasic

function, LARR (defined as a significant reduction in LA volume after one year follow-up) has also prognostic relevance on top of LVRR (**chapter 7**).

Part III focuses on the introduction of multilevel approaches to get a more complete capture of DCM as multifactorial disease. Accurate phenotyping is needed in order to optimize disease classification, risk stratification and enables more personalized therapeutic approaches. Myocardial fibrosis is one of the determinants of disease progression in DCM patients and can be detected by a great variety of techniques. Although the gold standard to assess myocardial fibrosis is the measurement of collagen volume fraction (CVF) on invasive endomyocardial biopsy (EMB), novel techniques have been developed to assess myocardial fibrosis non-invasively. CMR LGE represents focal fibrosis and is an important non-invasive prognostic measure in DCM patients. The combination of LGE and carboxy-terminal propeptide of procollagen type I (PICP) – a circulating biomarker of collagen deposition and turnover – provide a more complete capture of the fibrotic burden and improve risk prediction (**chapter 8**). In addition to CMR LGE, CMR parametric mapping enables non-invasive tissue characterization by measuring T1 relaxation time and extracellular volume (ECV). Where LGE reflects focal fibrosis, T1 and ECV are measures of diffuse interstitial fibrosis. Both focal and diffuse fibrosis may be observed in parallel and T1, ECV and LGE should be used complementary to synergize the detection and distinction of myocardial fibrosis in DCM (**chapter 9**). Besides collagen deposition, collagen cross-linking also influences the impact of myocardial fibrosis. Collagen type I C-terminal telopeptide (CITP) to matrix metalloproteinase-1 (MMP-1) ratio is a validated biomarker of collagen cross-linking and myocardial fibrosis. A low CITP:MMP-1 ratio is correlated with impaired GLS, probably resulting from impaired signal transmission, shortening of the end-diastolic muscle fibers and a reduced longitudinal contraction. In addition, MMP-1 has incremental prognostic value, especially when combined with PICP (**chapter 10**).

This thesis describes different non-invasive functional and structural imaging techniques that can be implemented in daily clinical care to optimize disease classification, personalize patient management and to improve risk prediction in DCM patients. We can conclude that there is not one 'holy-grail' that explains it all, but that we need to create a strong combination of parameters for optimal results: atrioventricular non-invasive imaging, towards a multimodality approach!