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Phospholamban p.Arg14del cardiomyopathy

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PART V - SUMMARY AND GENERAL DISCUSSION

Summary

CHAPTER 12

In the past decade, the development and implementation of next-generation sequencing techniques have allowed identification of a still-increasing number of variants related to inherited cardiomyopathies. Inherited cardiomyopathies are genetically highly heterogeneous. Moreover, there is important phenotypic heterogeneity: from the initial view that there is a specific set of molecular pathways linked to each cardiomyopathy-subtype, more recently the notion emerged that pathogenic variants within one cardiomyopathy-related gene can lead to several cardiomyopathy subtypes. This thesis focused mainly on the subtype arrhythmogenic cardiomyopathy (ACM), in particular phospholamban (PLN) p.Arg14del cardiomyopathy. However, in several chapters the genetic and clinical overlap between various cardiomyopathy subtypes becomes apparent.

Part I provided a general introduction. **Chapter 2** and **3** described the genetics, pathology, pathogenesis, translational aspects and the clinical utility of genetic testing in ACM. ACM encompasses a broad spectrum of disease that includes the classical right-dominant forms, predominant left-sided involvement and biventricular subtypes. The disease is histopathologically characterized by fibro-fatty replacement of the myocardium which predisposes patients to ventricular arrhythmias (VA) and slowly progressive ventricular dysfunction. Mutations in genes encoding proteins of the cardiac desmosome are found in the majority of cases worldwide however non-desmosomal genes have also been identified. Unravelling the genetic basis of ACM has led to the generation of animal and cellular models, in an attempt to uncover the molecular mechanisms underlying ACM to understand disease development and discover new therapies. These breakthroughs in the genetic underpinnings of the disease, enable genetic screening of the index patients and cascade screening in their families. Close relatives of the index patient who do not carry the familial pathogenic mutation can be dismissed from regular cardiological follow-up, provided that the severity of the phenotype in any family member does not suggest carriership of multiple mutations.

Part II of this thesis focused on the morphological features of phospholamban p.Arg14del cardiomyopathy. **Chapter 4** and **5** showed that phospholamban p.Arg14del cardiomyopathy is characterized by large perinuclear and circumnuclear PLN protein aggregates. These are detectable in complete heart specimens and myocardial tissue samples obtained from the apex of the left ventricle (LV) harvested during left ventricular assist device (LVAD) implantation but rarely in right ventricular endomyocardial biopsy samples. By electron microscopy, we observed the aggregates to be membrane-free and located adjacent to microtubule arrays, consistent with aggresomes. Double immunohistochemical (IHC) staining revealed that these PLN-containing aggresomes contained both p62 and LC3. Moreover, we demonstrated the presence of lysosomes within these aggresomes. These findings support the hypothesis that autophagic degradation of aggregates and aggresomes occur in PLN p.Arg14del cardiomyopathy. The PLN-containing perinuclear aggresomes appeared to be specific for PLN p.Arg14del cardiomyopathy, since they were not encountered in other examined hearts of patients with idiopathic or genetic DCM and genetic ACM. In clinical practise, PLN IHC analysis of LVAD specimens can be of incremental value in the diagnostic workup of this cardiomyopathy, even more so if genetic analysis is not readily available.

In **Chapter 6** and **7** distinct pathological features, i.e. the molecular signature and fibrofatty pattern, of PLN p.Arg14del cardiomyopathy were presented. Morphologically, biventricular presence of fibrofatty replacement, mainly in the RV wall (as in classic ARVC), and interstitial fibrosis, most pronounced in the LV left posterior wall, is typical. Phospholamban p.Arg14del cardiomyopathy is characterized by a distinct molecular signature only partially overlapping with classical ARVC: Firstly, plakoglobin was depressed or absent at the intercalated disks in the majority of cases fulfilling ARVC criteria but was negative in the few cases only fulfilling DCM criteria, confirming that the protein distribution patterns depends on the phenotype. Interestingly, in all cases with diminished plakoglobin signal intensity, another gene variant (pathogenic or VUS) was present. Secondly, SAP97, a protein which was previously shown to be consistently reduced in the ventricular myocardium of ACM-patients independent of the specific causal mutation, only showed an overall diminished signal intensity in one out of eight investigated cases. Thirdly, the same was observed for GSK3β: only one out of eight (the same case) showed junctional redistribution for GSK3β while in another study all (20 out of 20) ACM cases showed abnormal GSK3β at myocyte IDs. This combination of molecular features support the concept of PLN p.Arg14del cardiomyopathy being a distinct biventricular disease entity within the ACM spectrum.

Part III described phenotypical insights into phospholamban p.Arg14del cardiomyopathy using different imaging modalities. In **Chapter 8** the results of a large multicenter cardiac magnetic resonance (CMR) study, consisting of mainly presymptomatic mutation carriers, are described. Myocardial fibrosis was found to be present in a large subgroup. Index patients showed more extensive structural and functional evidence of disease but fibrosis was also seen in many subjects with a preserved LV systolic function, suggesting that the development of myocardial fibrosis occurs as an early phenomenon in PLN p.Arg14del mutation carriers. Electrocardiographically, the presence of low voltage and inverted lateral T-waves were associated with fibrosis. Fibrosis was most abundant in the LV inferolateral wall, where we electrocardiographically observed a high prevalence of negative T-waves. The presence of myocardial fibrosis was independently associated with the occurrence of VA. Moreover, a strong correlation was observed between LV and RV systolic function, supporting the notion of biventricular involvement in PLN p.Arg14del cardiomyopathy. These findings support the use of CMR early in the diagnostic work-up.

Chapter 9 presented a study which investigated cardiac structure and function in a group of presymptomatic PLN p.Arg14del mutation carriers using echocardiography including state-of-the-art tissue deformation imaging techniques. We observed subtle but significant structural remodeling (reduced LV mass) as well as loss of LV diastolic function and RV systolic function, compared to well-matched controls. In clinical practice, these findings may help to recognize early disease development in this ever-growing group of presymptomatic mutation carriers identified by genetic cascade screening. The early observed biventricular abnormalities further supports the concept of biventricular cardiomyopathy in this disease, in line with previous findings (part II and Chapter 8).

In **Chapter 10**, the follow-up results of the CMR cohort (chapter 8) were shown. Our aim was to investigate whether the presence of late gadolinium enhancement on CMR is of incremental prognostic value in early-stage phospholamban p.Arg14del cardiomyopathy.

We did observe a clear trend towards incremental value of LV-LGE in prognostication of PLN p.Arg14del mutation carriers, this is of particular clinical interest in subgroup with a preserved LVEF with LV-LGE. But a longer follow-up period is required in order to show whether LV-LGE is an independent predictor of cardiac events.

Part IV, **Chapter 11,** described the design and rationale of iPHORECAST (intervention in PHOspholamban RElated CArdiomyopathy Study). As discussed, cardiac fibrosis appeared to be an early feature of the disease, occurring in many presymptomatic mutation carriers before onset of overt disease. In line with most monogenetic cardiomyopathies, no proven treatment is available for presymptomatic mutation carriers. We designed and initiated iPHORECAST to demonstrate that pre-emptive treatment of presymptomatic PLN p.Arg14del mutation-carriers, with the mineralocorticoid receptor antagonist eplerenone which has established antifibrotic effects, reduces disease progression and postpones onset of overt disease. The study has a multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) design. A total of 82 participants were included in the 4 participating centers since May 13, 2014. Because of slow recruitment it was decided on April 1, 2017, to stop further inclusion of participants but to continue and complete the study with the included cohort. The primary endpoint is disease progression, defined as a composite endpoint of CMR- and electrocardiographical parameters, signs and/or symptoms related to DCM and ACM and cardiovascular death. The follow-up period is three years.