Hypertrophic cardiomyopathy: towards an optimal strategy
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Summary

Hypertrophic cardiomyopathy is a relatively common hereditary disease affecting at least 1 in 500 persons in the general population worldwide. The clinical diagnosis can be made when there is left ventricular hypertrophy on echocardiography in the absence of other cardiac or systemic diseases that may cause cardiac hypertrophy, such as aortic valve stenosis and arterial hypertension. Patients can be completely asymptomatic, but HCM can also give rise to heart failure, syncope, and even sudden cardiac death (SCD). SCD can effectively be prevented by implanting an internal cardioverter defibrillator.

Diagnostic genetic testing can reveal a pathogenic mutation in more than half of the HCM patients. This implies the opportunity of screening in relatives by means of predictive DNA testing. Predictive genetic testing in asymptomatic relatives is offered because relatives are assumed to be at risk of (developing) manifest disease (i.e. left ventricular hypertrophy) and associated SCD, and because SCD can be prevented effectively. Mutation carrying relatives are referred for regular cardiological evaluations assessing the presence of manifest disease and the risk of SCD.

However, much is still unknown about the risk of developing manifest disease and the risk of SCD for asymptomatic mutation carrying relatives. Therefore it is difficult to determine how often cardiological evaluations should be performed and which cardiological diagnostic tests should be done. In the ESCAPE-HCM (Evaluation of SCreening of Asymptomatic PatiEnts with Hypertrophic CardioMyopathy) study we set out to gain more knowledge on the risk of developing manifest disease and risk factors for SCD, and the risk of SCD. Possibly, risk stratification could identify which asymptomatic mutation carriers have an increased risk of cardiac events and which mutation carriers are expected to have a more favourable prognosis. This could help to develop more evidence-based guidelines on cardiological evaluations in asymptomatic mutation carrying relatives.

Chapter 1 of this thesis is a general introduction on HCM, which describes the clinical features of HCM, therapeutic and preventive options, risk stratification for SCD, and the possibilities of genetic testing in probands and relatives. It also sets the stage for the other chapters in this thesis and explains how they are related.

Chapter 2 describes the study design of the ESCAPE-HCM study as well as its main results. The study showed that disease penetrance in mutation carrying relatives is age dependent and the development of manifest disease seemed to be decreased in carriers under the age of 40 years. Risk factors for SCD were frequently present both in carriers with and without manifest disease. The SCD rate was very low; two carriers, both with manifest HCM, died suddenly during follow-up. Based on these data we suggested an ECG and echocardiography in all mutation carriers to detect manifest disease. When manifest disease is present risk stratification for SCD can be performed by expanding the evaluation with 24h Holter recording and an exercise test. In carriers without manifest disease younger than 40 years cardiological evaluation can probably be decreased to once every two years instead of on a yearly basis. A cost-effectiveness analysis showed cardiological evaluations to be necessary to prevent SCD. The most cost-effective cardiological screening strategy in asymptomatic mutation carriers involved yearly risk stratification for SCD in carriers with manifest HCM and ECG and echocardiography every two years in carriers without manifest HCM of all ages.

Chapter 3 is all about risk stratification. We started by performing a systematic review of literature on established and possible clinical risk factors for SCD, which provided sound evidence for the use of the established risk factors in risk stratification for SCD in HCM.
patients (i.e. with manifest HCM). These established risk factors were frequently present at first cardiological evaluation of asymptomatic mutation carrying relatives with a mutation in the MYBPC3 gene. In some mutation carrying relatives not all risk factors for SCD had been evaluated. We therefore set out a questionnaire to assess the knowledge of Dutch cardiologists on risk stratification for SCD and the present guidelines on this subject. Although their knowledge was mediocre, cardiologists frequently indicated to consult an expert which might bring patient care to an adequate level. This chapter also contains a case report on two patients with a HCM causing mutation who were resuscitated from a cardiac arrest before hypertrophy was present. This demonstrates that mutation carriers without manifest HCM might be at risk for SCD, although the risk is probably very small. Finally, we also found polymorphisms in the renin-angiotensin-aldosteron system to be involved in the extent of hypertrophy in HCM mutation carriers and in extreme left ventricular hypertrophy, which is a risk factor for SCD.

Chapter 4 describes the studies on cardiogenetic care in HCM mutation carriers. First, we evaluated the proportion of relatives that attended our cardiogenetics outpatient clinic for genetic counselling and DNA testing. This so called uptake was 40% in the first year after the detection of a pathogenic mutation in the proband. We also assessed quality of life and psychological distress in probands and relatives with a HCM causing mutation. Quality of life was lower in carriers with manifest disease before DNA testing (i.e. probands) but higher in carriers who had been predictively tested compared to the general Dutch population. Illness and risk perception related variables were major determinants of quality of life and distress. Predictively tested mutation carriers also gave their opinion on genetic counselling and cardiological evaluations, which were valued positively by almost all carriers. We also describe the experiences of mutation carriers in obtaining insurance. Problems almost exclusively occurred in carriers who already had manifest HCM at the time of application, which makes the risk assessment of insurance companies largely justified.

Finally, the general discussion in chapter 5 describes the clinical and research perspectives in HCM with respect to the identification of relatives at risk for HCM, the cardiological evaluation of HCM mutation carriers, the role of the cardiologist and clinical geneticist in cardiogenetic care, and genetic counselling before predictive DNA testing.