Hypertrophic cardiomyopathy: towards an optimal strategy

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General discussion: clinical and research perspectives
Identification of relatives at risk for hypertrophic cardiomyopathy

Worldwide 1 in 500 persons has hypertrophic cardiomyopathy (HCM), but due to the hereditary nature and the incomplete penetrance of the disease the actual prevalence of people at risk for HCM must be higher. Especially relatives of HCM patients are at risk of developing or having hitherto unnoticed manifest disease. The morbidity and disease related mortality (death due to heart failure and thrombo-embolic complications and sudden cardiac death (SCD)) suggests detection of these relatives at risk is worthwhile, assuming valid treatment/prevention options and acceptable characteristics of the detection (screening) program (Wilson and Jungner criteria). As implantation of an internal cardioverter defibrillator (ICD) is an effective prevention option in selected patients at high risk for SCD, the principal is how to identify these relatives at risk, and among those how to identify candidates for an ICD.

Identification of relatives can be achieved in two ways, and starts in first degree relatives of a patient with manifest HCM, the index patient or proband. In first the degree relatives the probability of a ‘hit’ is high, and, usually, these relatives are readily accessible through the known proband. Echocardiography can detect non-invasively left ventricular hypertrophy, the hallmark of HCM. However, given the age related penetrance of HCM, in relatives who do not show hypertrophy this test has to be repeated every several years. In this strategy no DNA testing is carried out. Another way of identifying relatives is through DNA testing. This option is only possible in families in which a pathogenic mutation has been identified. Relatives can be tested for carriership of the familial mutation starting with the first degree relatives and subsequently more distant relatives can be tested (cascade screening). Non-carriers and their offspring can be discharged from further cardiological evaluations. Carriers, who are at risk of developing HCM, are offered regular cardiological evaluations for testing the presence of hypertrophy and risk factors for SCD. Carriers who do not have hypertrophy yet probably have a low risk of SCD and cardiological evaluations can be planned less frequently.

In terms of costs only, currently the best way to detect relatives is probably by echocardiography. However, because of the age related penetrance of the disease and large phenotypic variability not all relatives at risk will be detected this way, and consequently not all disease associated death will be prevented. Therefore the best way in terms of effectiveness is probably to start with DNA diagnostics in the proband of the family (Figure 1). Following this approach, in about half of the families a disease causing mutation will detected, which enables predictive DNA testing in relatives as described above. To be more cost-effective predictive DNA testing could be preceded by echocardiography. In relatives with overt hypertrophy DNA testing may then be omitted. If DNA diagnostics cannot detect a disease causing mutation in a HCM patient, first degree relatives can then be offered echocardiography at regular intervals and more distant relatives only on clinical grounds (heart complaints, SCD in the connecting relative, detection of manifest HCM in the connecting relative).

The approach described above is currently common practice in all Dutch cardiogenetic outpatient clinics. In some clinics echocardiography precedes predictive DNA testing. The main difference between clinics is in the cardiological evaluation. Some clinics advise carriers to undergo cardiological testing in a local hospital in the proximity of their home, other clinics do all cardiological evaluations in their own university hospital. This difference seems to be based mainly on the number of identified mutation carriers and the distance to the university hospital, and possibly on the capacity of the university hospital. It is known that not all mutation carriers attend for genetic counselling and testing. Our research showed
that quality of life is not affected in identified mutation carriers, and that cardiogenetic care is generally appreciated. Since we did not evaluate the opinion of non-attending relatives, reasons for non-attendance can only be speculated on. It would probably be worthwhile to evaluate reasons for non-attendance since this could help to identify more relatives at risk for HCM and SCD.

**Cardiological evaluation of HCM mutation carriers**

In the former paragraph I describe the optimal way to identify relatives at risk of developing HCM. The detection of relatives is justified by the evidence that the disease associated risk of SCD can effectively be prevented by means of an ICD in patients who are at high risk of SCD. Several major risk factors for SCD (previous cardiac arrest or ventricular tachycardia, non-sustained ventricular tachycardia on 24 hour Holter recording, unexplained syncope, extreme left ventricular hypertrophy, abnormal blood pressure response during exercise, and family history for SCD) have been identified in patients with manifest HCM. Although the presence of one or more of these clinical risk factors is associated with an increased risk of SCD, their positive predictive value is low. Besides, there are several other limitations to the use of these risk factors in clinical practice. Existing evidence on the relevance of risk factors often uses different definitions, e.g. a family history can be defined as positive for SCD if one relative has died suddenly at any age or if two first degree relatives have died suddenly before the age of 40 years. A general issue is the incomparability of study cohorts with respect to both prognostic factors and unrelated factors, which can only be adjusted for to the extent these...
factors are known and measured. Some risk factors like extreme hypertrophy can vary during follow-up and it is unclear if the risk is still increased when the risk factor is no longer present. Finally, the risk of SCD associated with the presence of risk factors sometimes seems to be age-related. For some risk factors the risk of SCD is higher in younger patients.

All studies on risk factors for SCD have been performed in patients with manifest disease. The relatives at risk for HCM who are identified as mutation carrier often do not have manifest disease (left ventricular hypertrophy) yet. As the pathophysiological mechanism for the ventricular arrhythmias causing SCD is still unknown, it is also unknown if manifest disease is prerequisite to be at risk for SCD and if risk factors for SCD are also associated with an increased risk of SCD in mutation carriers without manifest HCM. There are several case reports of relatives from HCM families, and one of HCM mutation carriers (this thesis) who died suddenly or were resuscitated from ventricular fibrillation in the absence of hypertrophy. Mutation carrying relatives can therefore be at risk for SCD even when manifest disease is absent. However, the small number of cases in literature and the absence of SCD in mutation carriers without hypertrophy during follow-up (this thesis) suggest that the risk of SCD in this group is likely to be very small. Consequently, it will be difficult to identify risk factors for SCD specific for this group. Because of the small risk of SCD, risk stratification can possibly be omitted in relatives and mutation carriers without manifest disease (Figure 1), although for research purposes it would be useful to regularly perform a complete cardiological evaluation including risk stratification as this allows to derive better prognostic significance of risk factors for SCD and other clinical variables in this group. Until now, the only studies on this subject originate from the Netherlands. In relatives or mutation carriers with manifest disease risk stratification should be performed regularly. Considering the high negative predictive value of risk factors, even in mutation carriers with manifest disease the risk of SCD is extremely low when risk factors for SCD are absent.

Cardiologists’ and clinical geneticists’ responsibilities

In the Netherlands DNA diagnostics for cardiogenetic conditions in probands and relatives can only be requested by a clinical geneticist by law. However, cardiologists increasingly request (predictive) DNA diagnostics. Once a mutation carrier is detected by a cardiologist, this carrier is often referred to a clinical geneticist, a different pattern of utilisation of genetic expertise. Clearly a transition is apparent in the application of genetic expertise and tools, possibly with a slight change in presentation of the results to the patient. Cardiologists are often not fully aware of or educated in the possible psychosocial and insurance consequences of DNA testing, especially when testing occurs in a predictive setting. They do not always discuss the consequences of genetic testing for relatives of the patient. Cardiologists are often not fully aware of or educated in the possible psychosocial and insurance consequences of DNA testing, especially when testing occurs in a predictive setting. They do not always discuss the consequences of genetic testing for relatives of the patient. Cardiologists often experience difficulties in interpreting DNA test results. On the other hand it is the cardiologist (and not the clinical geneticist) who maintains regular contacts with mutation carriers. When sufficiently aware of the familial situation, regular contacts can stimulate the detection of other relatives at risk of HCM by cascade screening thereby increasing the uptake of DNA testing. Regular contacts can also provide insight in the long term findings in mutation carriers, e.g. the risk to develop manifest HCM for mutation carriers and the prognostic significance of risk factors for SCD.

The clinical geneticist, on the other hand, is professionally trained in dealing with the family, signalling possible psychosocial problems, discussing the consequences of predictive DNA testing, and interpreting DNA test results. However, clinical geneticists’ last contact with
carriers and non-carriers is often when the DNA test result is discussed. Therefore it can be difficult to stimulate ongoing cascade screening of relatives. Besides, the clinical geneticist is not always informed about the results of cardiological evaluations and possible long term complications.

The strengths of both professions are already joint in specialised cardiogenetics outpatient clinics. Here, multidisciplinary teams of a clinical geneticist, a cardiologist and a psychosocial worker bear joint responsibility for the intake, genetic counselling and follow-up of relatives. Interpretation of DNA test results can also be discussed by the multidisciplinary team of caregivers. Cardiological evaluation and follow-up should ideally take place in the same outpatient clinic. It is important to have a case-manager appointed to monitor the planning of follow-up visits and the process of informing relatives and of cascade screening in the patient's family, a 'cardiogenetic nurse' for instance.

Besides, as genetic knowledge will probably become more easily available in the near future and used not only in monogenetic disorders, it can be expected that the role of the clinical geneticist will change. We should expand our knowledge by joining in multidisciplinary clinics and be readily available for consultation.

**Counselling before predictive DNA testing**

In clinical genetic practice, counselling before predictive DNA testing is always guided by a protocol. The first counselling protocol was developed for Huntington's disease, a progressive incurable neurological disease. This protocol consisted of several counselling sessions by a clinical geneticist and a psychosocial worker to guarantee that the counselee was well informed not only of the clinical consequences of DNA testing but also of the psychosocial consequences. As Huntington's disease is incurable and cannot be prevented, the protocol has been developed to make the patient aware of all the possible drawbacks of knowing that he/she is a mutation carrier and that DNA testing does not provide any clinical benefits, and it has not been developed to 'stimulate' predictive DNA testing.

The Huntington protocol has been adapted for counselling in other late onset hereditary diseases, like hereditary breast cancer and cardiogenetic diseases. In many of these diseases some form of therapy or prevention is available, implying that predictive genetic testing can be (partially) beneficial for the counselee's health state. In these diseases the original Huntington protocol is theoretically too strict and if applied in its original form counselees might unduly decide not to pursue in predictive DNA testing, not only individually but also from a public health point of view.

In HCM symptoms of the disease can be treated and SCD can be prevented. Counselees often express anxiety as the disease is associated with a risk of SCD. Chapter 4.2 shows that health related quality of life is probably not affected in mutation carriers identified by predictive DNA testing (this thesis). Besides, counselees in later stages of their life only occasionally regret being tested (this thesis). These findings support a more lenient predictive counselling protocol in 'treatable' late onset hereditary disease like HCM. In HCM we already implemented such a protocol and, as Chapter 4.3 shows, carriers appreciated this (this thesis).

It seems that genetic counselling in HCM following a more lenient adapted protocol has no overt negative consequences. Although in our experience psychosocial problems related to DNA testing for HCM are minimal, attention for possible psychosocial problems before and after predictive testing should not be slackening. We believe that psychosocial
consequences of DNA testing should always be discussed during genetic counselling and preferably the DNA test result should be explained in person by telephone or at the outpatient clinic. Predictive DNA testing in children should always involve psychosocial consultation. During follow-up -preferably at the same centre- possible psychosocial consequences in mutation carriers can again be addressed.

**Future care for HCM mutation carriers**

As the prevalence of HCM patients and mutation carriers is probably much higher than 1 in 500 persons, the number of people in the Netherlands needing regular cardiological evaluations probably exceeds 33,000. Although many of these people still have to be identified by clinical geneticists and cardiologists, one should not disregard this number in the planning of health care capacity. The ESCAPE-HCM study described in this thesis was developed with this capacity problem in mind. The main goal of this study was to optimise the cardiological screening frequency for mutation carrying relatives based on their risk of SCD, in order to reduce the considerable caseload of 33,000 cardiological evaluations each year. Our study results show that the risk of SCD is very low in predictively tested mutation carrying relatives (0.13% per person-year) and in the subgroup of mutation carrying relatives without manifest disease no SCD has occurred during an average follow-up of 3.5 years (this thesis). As the SCD risk appears very low in mutation carriers without manifest disease, the frequency of cardiological evaluations can be decreased and risk stratification for SCD can probably be safely omitted. In this subgroup cardiological evaluations every 2 years should only include ECG and echocardiography as long as hypertrophy is absent. In families without a detected pathogenic mutation it is probably also safe to perform regular echocardiography and ECG in non-manifesting relatives at risk and perform risk stratification only when hypertrophy is present.

The ESCAPE-HCM study also showed that a considerable portion of mutation carrying relatives (30%) already had manifest disease at first cardiological evaluation or developed manifest HCM during follow-up. As international guidelines advise yearly cardiological evaluation including risk stratification for SCD for this subgroup, a capacity problem might still lie ahead of us. A possible solution for this is to centralise care for HCM patients and mutation carriers in specialised regional centres. Not only will the presence of expert-professionals optimise the quality of care, but specialisation may also increase cost-effectiveness due to economies of scale increased quality of care.

As indicated many subjects related to the care for HCM mutation carriers are still under evaluation and discussion. Ongoing research in the still increasing number of HCM mutation carriers will hopefully make care more evidence-based. To facilitate further research in HCM patients and mutation carriers they should be registered in a national database. Such a database already exists for all cardiogenetic diseases, the GENCOR database, and data of all HCM mutation carriers involved in the studies described in this thesis have been entered into this database. I hope this will continue to facilitate further research.