Hypertrophic cardiomyopathy: towards an optimal strategy
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Citation for published version (APA):
Christiaans, I. (2010). Hypertrophic cardiomyopathy: towards an optimal strategy

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Risk stratification in hypertrophic cardiomyopathy

3.4 Ventricular fibrillation in MYH7-related hypertrophic cardiomyopathy before onset of ventricular hypertrophy.

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Heart Rhythm 2009;6:1366-9
Risk stratification in hypertrophic cardiomyopathy

Introduction
Hypertrophic cardiomyopathy (HCM) is one of the most frequent genetic diseases, affecting approximately 1 in 500 persons. Many patients have familial disease, inherited as an autosomal dominant trait and most often associated with a mutation in one of the genes encoding for sarcomeric proteins. The clinical diagnosis is made when an hypertrophied, nondilated left ventricle (maximal left ventricular wall thickness ≥ 15 mm) is seen by echocardiography or magnetic resonance imaging in the absence of loading conditions sufficient to cause the observed abnormality, such as aortic valve stenosis and hypertension. HCM can present at any age and is clinically and genetically heterogeneous.

The anatomic changes in HCM can be a substrate for arrhythmias, which may lead to palpitations, syncope, and sudden cardiac death (SCD). The annual mortality rate of SCD is approximately 1%. SCD can be prevented by means of an implantable cardioverter-defibrillator (ICD) in high-risk patients with left ventricular hypertrophy identified by the evaluation of six known major risk factors for SCD.

We describe two patients resuscitated from a cardiac arrest caused by ventricular fibrillation (VF). In one patient, left ventricular hypertrophy was noted only years after the cardiac arrest. The other patient still has no hypertrophy, but her mother is diagnosed with HCM. Molecular genetic testing revealed a missense mutation in the beta-myosin heavy chain (MYH7) gene in both patients.

Methods
Study design
Both patients provided informed consent for molecular genetic testing. Only clinical relevant investigations were performed.

Case 1
Patient 1 is a 43-year-old woman, who originally was admitted to our hospital at age 31 years. She had collapsed on the street near a health center, and resuscitation had been started by a general practitioner. When the ambulance arrived, VF was present. After receiving two shocks, the patient was back in sinus rhythm. Resuscitation-related abnormalities were present on the initial ECGs (Figure 1A). Follow-up ECGs showed only abnormal q waves in the inferior leads. Echocardiography showed no abnormalities, in particular, no evidence of structural heart disease or segmental movement abnormalities. Creatine kinase level was 27,600 units/L, and creatine kinase-MB level was 552 units/L. No intoxications were found. Exercise test, methoxyisobutyl isonitrite (MIBI) stress scintigraphy, and cardiac catheterization showed no abnormalities. Medical and family histories were unremarkable.

No arrhythmias were inducible during electrophysiologic study, and the patient received an ICD. Almost 9 months after ICD placement, she received two inappropriate shocks because of sinus tachycardia. Seven years later, a malsensing lead caused another set of inappropriate shocks, and the ICD and lead were replaced. Significant hypertrophy of the left ventricle was identified on echocardiography (Figure 2) 5.6 years after the cardiac arrest. Since then, ECG has shown repolarization abnormalities but no other signs of left ventricular hypertrophy. A diagnosis of HCM could be made, and molecular genetic testing was performed. No mutations were found in the troponin T2 (TNNT2) and myosin-binding protein C3 (MYBPC3) genes. In the MYH7 gene, the c.1550T>G (p.Leu517Arg) mutation was identified.
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(Figure 3A). This mutation is located in the myosin head motor region of the protein. Leu517 is well conserved between species (up to *C. elegans*) and different isoforms (skeletal and smooth muscle). This mutation has not been found in 110 Dutch control alleles or 800 alleles from cardiology patients. The physicochemical difference between Leu and Arg is considered to be moderate, with a Grantham distance of 102 (range 1-215). The PolyPhen (Polymorphism Phenotyping) tool (available at http://genetics.bwh.harvard.edu/pph/) considers this amino acid change to be probably damaging.

**Case 2**

Patient 2 is a 37-year-old woman. At age 28 years, she had collapsed while walking her dog and
had been resuscitated from VF. Upon admission, she could be extubated, and she regained consciousness the next day. Neurologic recovery was excellent. The presenting ECG showed sinus rhythm with left ventricular hypertrophy and secondary repolarization disturbances (Figure 1B), which did not change during follow-up. Echocardiography of the heart showed no left ventricular hypertrophy (Figure 2) and normal left ventricular function. The left atrium was mildly enlarged. Coronary angiography showed normal coronary arteries. No intoxications were found. The patient had a history of hyperventilation. Her family history revealed that a brother and sister of her mother had died suddenly when they were in their early 20s.

Electrophysiologic study showed easily inducible VF, and an ICD was placed. Two months after the cardiac arrest, the patient’s mother was admitted to our hospital with heart failure. Echocardiography performed on the mother showed a hypertrophied left ventricle with left ventricular maximal wall thickness of 17 mm. Three years after ICD placement, patient 2 received an appropriate shock. Besides the ECG, cardiologic evaluations remained unremarkable. Seven years after the cardiac arrest, maximum left ventricular wall thickness on echocardiography was only 10 mm, not enough for a clinical diagnosis of HCM even in a familial setting (Figure 2).

Molecular genetic testing did not show mutations in the TNNT2 and MYBPC3 genes. In the MYH7 gene, the c.2573G>T (p.Arg858Leu) mutation was found (Figure 3B). Arg858 is not located in a known functional domain of the protein and is moderately conserved between species (not in C. elegans) and different isoforms (conserved in MYH6, MYH7, and MYH13, but not in MYH1, MYH2, MYH3, MYH4, MYH5, and MYH11). This mutation has not been found
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in 110 Dutch control alleles or 800 alleles from cardiology patients. The physicochemical difference between Arg and Leu is considered to be moderate, with a Grantham distance of 102 (range 1-215). Polyphen considers the amino acid change to be benign. The patient’s mother, who was diagnosed with HCM, also carried the mutation.

Discussion

We report two patients with a cardiac arrest caused by VF, in whom a clinical diagnosis of HCM could not be made at the time of the event. One patient fulfilled the criteria for a clinical diagnosis of HCM only years later; the other patient still has no hypertrophy of the heart, although her mother does. VF is known to occur in patients with sarcomeric mutations as well as in nongenotyped or genotype-negative HCM patients. However, SCD occurs almost always in patients with ventricular hypertrophy and risk factors for SCD. A few cases of SCD in patients with HCM but normal ventricular mass have been reported in literature. These patients all showed disorganized cardiac muscle cells, also known as myocardial disarray, which is believed to be associated to ventricular arrhythmias (not assessed in our patients). Indeed, with the exception of TNNT2 gene-related HCM patients, VF is unlikely to occur in patients without discernable hypertrophy.

Neither of our patients harbored a mutation in the TNNT2 gene, and the extent of hypertrophy found during follow-up in patient 1 is uncommon for a TNNT2 mutation. In both patients (and the mother of patient 2), a missense mutation in the MYH7 gene was identified. Almost all mutations in this gene are missense mutations, and the majority are unique for the individual family. Initially, mutations in the MYH7 gene were reported to cause HCM with a more severe phenotype with younger age at onset, more severe left ventricular hypertrophy, and a greater incidence of sudden death. However, more recent larger studies and pooled data show no direct genotype-phenotype correlations with respect to the extent of hypertrophy and incidence of SCD.

The MYH7 mutations identified in our patients likely are pathogenic. The p.Leu517Arg mutation in patient 1 has not been reported in literature. Nanni et al. described a mutation in the same codon resulting in a methionine (p.Leu517Met). This mutation was found in a female Italian patient diagnosed with HCM at age 20 years, who showed progression to left ventricular dilatation with New York Heart Association class III symptoms. Her father had died suddenly. Nanni et al. did not find this mutation in 100 normal control subjects and qualified the mutation as malignant. Codon 517 is located close to the helix connecting two reactive cysteine residues required for ATPase activity. Mutations at this level might alter the nature and timing of conformational changes during the contractile cycle.

The p.Arg858Leu mutation found in patient 2 and her affected mother is also a novel mutation. Two groups have described a different mutation in the same codon in their HCM patient population. The p.Arg858Cys mutation was found once in 389 unrelated North American HCM patients and not in 200 normal control subjects. The p.Arg858His mutation was found once in a population of 100 unrelated Chinese HCM patients as a novel mutation, was not found in 120 control subjects, and co-segregated with affected family members.

The finding of VF in the absence of manifest HCM in our patients who carried sarcomeric mutations that likely are pathogenic has two major implications. First, in (young) patients with VF, a diagnosis of HCM should be reconsidered even in the absence of hypertrophy on echocardiography or a positive family history. Follow-up of patients with idiopathic VF should therefore include an echocardiogram at regular intervals. Second, family members and
mutation carriers from HCM families who do not have cardiac hypertrophy might be at risk for SCD. Although it is unclear whether risk factors for SCD are also of prognostic significance for HCM mutation carriers without manifest disease, we suggest regular risk stratification for SCD in these carriers, as advised in international guidelines.\textsuperscript{5}
References


