Hypertrophic Cardiomyopathy
Do We Have the Algorithm for Life and Death?

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The molecular genetic basis for familial hypertrophic cardiomyopathy (FHC) is being unraveled, but this project is still not complete. All mutations identified thus far affect the function of sarcomeric proteins, and mutations in 8 different genes have been recognized. The mutated genes code for proteins positioned in the thick filament, including the $\beta$-myosin heavy chain ($\beta$-MHC) and essential and regulatory myosin light chains, and in the thin filament, actin, troponin T, troponin I, and $\alpha$-tropomyosin mutations have been identified. In many families, myosin binding protein C, which connects the thick filaments in the A-band, holds the genetic defect.1,2 It seems likely that in the next decade, most (if not all) mutations will be known, and the mystery regarding the origin of the disease will be solved.

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Ever since the molecular cause of FHC was recognized, studies have attempted to understand the pathophysiology of the disease and discover how the various mutations in functionally different domains of the 8 contractile protein genes lead to myocyte hypertrophy and changes in the architecture of the hypertrophic tissue. This is an arduous task, despite recent advances in molecular biology and physiology. The effect of mutations can be analyzed in vitro by visualizing or measuring the myosin-actin interaction or ex vivo by studying muscle strips from human hearts or skeletal muscle preparations.3,4 More recently, interesting mouse models became available; these models carry human-like mutations in mouse genes or true human proteins and develop marked asymmetric cardiac hypertrophy. These mouse models even mimic the typical hemodynamic changes of the disease by showing impaired relaxation, which is the hallmark of left ventricular dysfunction in humans.5 Still, it is unclear why morphological phenotypes are comparable, although some mutations lead to an increase in function and others show a loss of function. Obviously, the effect of individual mutations must be analyzed in detail to understand the altered contractile function of myocytes and the morphological changes they induce in order to find a common denominator.

In patients, a wide variation is observed in clinical symptoms, including the age at onset of symptoms and prognosis, depending on the genotype. Thus far, it has been difficult to determine a definitive relationship between the localization and severity of the hypertrophy to guide genotyping. However, some clinical parameters can be used, especially when the disease is diagnosed when the patient is at a young age. In the rare families with myosin light-chain mutations, hypertrophy is most evident in the midventricular region. This localized hypertrophy leads to systolic midcavity obstruction, which gives the impression of a ballet dancer’s foot on the left ventriculogram.6 Mutations in the $\beta$-MHC gene are more common, and they account for $\approx30\%$ of the cases of the disease. Mutations in this gene were the first to be recognized and, therefore, more information is available for these mutations with respect to phenotype, penetrance, and prognosis.7

Previous reports demonstrated marked variation within one family with respect to the severity and location of the hypertrophy. Penetrance was incomplete and depended on both age and sex; men were affected more often than women.3,8 Apparently, the disease can be modified by other genes or the development of severe hypertrophy depends on nongenomic factors. Clearly, despite current molecular knowledge, the clinical course and morphological phenotype that will emerge in a given patient are hard to predict.

With respect to arrhythmias and sudden death, which is the presenting symptom in 10% of cases, the situation is worse. Overall annual mortality in adults with FHC is estimated as 1%. A relationship seems to exist between some mutations that predispose patients to arrhythmias, but adjacent mutations in the same gene do not necessarily influence life expectancy. Some mutations in the $\beta$-MHC gene and all mutations in the troponin-T gene are associated with sudden death in up to 50% of genotype-positive individuals.9

Thus far, basic studies have not focused on the pro-arrhythogenic nature of the sarcomeric mutations. It is tempting to consider altered contraction mechanics and changes in intracellular calcium handling as the key players. Although several mutations that have been identified influence calcium handling by the cardiomyocyte, it has not been shown that these changes induce pro-arrhythogenic mechanisms. Furthermore, some mutations have an influence on calcium handling without influencing prognosis.

Obviously, an important issue is the risk stratification of patients with FHC. Genotyping will eventually be one of the most important diagnostic approaches to confirm the origin of the disease, and it can be used to estimate the risk of sudden death in a given patient. To improve the power of this
approach, an accurate registration of families and their genetic background that includes the natural history of the disease is essential. Efforts to initiate and maintain a database file are ongoing within the European Society of Cardiology. It is important to realize that identical mutations in different genetic backgrounds can have a variable effect on prognosis. Therefore, other approaches to determine risk factors should be explored. Potential useful parameters can be obtained from the ECG, including the QT segment. However, every clinician is aware of the difficulties involved in the accurate measurement of the duration of the QT segment. The problem can be solved only partially by designing computer algorithms.

Initial studies focused on spatial differences in the QT segment. The spatial differences indicated by QT dispersion are derived from 12 simultaneously recorded leads and are defined as the difference between the longest and shortest QT segment, as measured by a digitizer or calipers. However, many different techniques have been used to determine the end of the QT interval. The end of the T wave has been marked by either the return or by extrapolating the slope of the T wave to the isoelectric line. Others used the nadir of the T wave and even the following U wave to detect variation in repolarization. The outcome of QT segment measurement also depends on the number of leads available for analysis. If the amplitude of the T wave is too small, it is impossible to correctly judge the QT segment. To standardize the outcome of the QT dispersion measurement, some investigators provide the QTc-derived dispersion in which the QT interval is corrected for differences in heart rate using Bazett’s formula. QTc = QT divided by the square root of the preceding RR(s), before calculating QT dispersion. Hypertrophy in FHC is eccentric and shows considerable variation in predilection sites, leading to increased QT dispersion. In some studies, QT dispersion decreased with antiarrhythmic treatment. Although QT dispersion measurements might be valuable, they have never been implemented as standard techniques in the clinical assessment of FHC patients. This is probably due to the difficulty of establishing normal values and proving the value for diagnosis and/or prognosis.

In this issue of Circulation, an algorithm is proposed that determines temporal variations in QT dispersion. Atiga et al. developed a new approach, and they determined the correction that is required to match consecutive QT measurements to an operator-defined QT segment in one selected lead. The QT variability is related to heart rate variability to obtain the QT variability index. This algorithm was previously tested in patients with dilated cardiomyopathy, and the QT variability index was shown to be higher in patients with the disease compared with healthy subjects. In the present study, the same algorithm was used in 36 genotyped FHC patients. All patients had mutations in the β-MHC gene, but these mutations were in 7 different positions. Only 9 patients proved to have a “malignant” mutation at amino acid position 403. At this position, one base difference at the DNA level leads to the substitution of arginine by glutamine (Arg403Gln). In families with this mutant allele, a high incidence of sudden death is reported: up to 50% before the age of 40. In FHC patients, a slight increase was found in QT variability; this finding was concomitant with a decrease in heart rate variability, which resulted in a significant change in the QT variability index. The differences were significant for the whole group and especially for patients with the Arg403Gln mutation.

Unfortunately, some concerns exist with respect to the size and characteristics of the control group. The young, healthy volunteers had an average QRS duration of 112 ± 19 ms. These figures are markedly different from those published by MacFarlane and Lawrie for comparable age groups. Furthermore, the number of patients included is very small, and no prospective data are available to indicate the predictive power of this algorithm for arrhythmias and sudden death within the group of FHC patients. Because high-risk patients can be protected with an implantable device, a predictive assay would be a clinical treasure. Although the findings of Atiga et al. are promising, it is too early to modify our electrocardiographic systems to include this new approach.

What does this study tell us about the basic mechanisms that lead to arrhythmias in FHC? The authors hypothesize that the uncoupling of heart rate variation from changes in repolarization duration may be related to hypertrophy-related ischemia. If so, it would be reasonable to suggest a direct relationship between the extent of the ischemia and myocardial thickness. However, this proposal is not supported by the morphological data presented here or by findings in patients with troponin-T mutations in whom sudden death is frequent, despite mild or absent myocardial hypertrophy. To unravel the pathophysiology of FHC-related arrhythmias, cellular and in vivo electrophysiological studies in man and in mouse models of hypertrophic cardiomyopathy are needed to provide the answers to these crucial questions.

References

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