# Echocardiography: A Requisite Friend of the Cardiac Geneticist

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In this issue of the *Journal of the American Society of Echocardiography*, Mottram *et al.*[1] illustrate the role of echocardiography in the early detection of the expression of a mutation in the protein frataxin known to cause Friedreich's ataxia. It triggers this editorial tribute to echocardiography and the role cardiac echocardiographers have played in our pursuit of genetic cardiac disorders. Echocardiography is well recognized for its noninvasive application. It does not require isotopes, so there is no risk of radiation. It does not require magnetic resonance, so it can be used conveniently and in a patient-friendly manner, even with an in-dwelling device such as a pacemaker. Echocardiography is also portable. The portability lends many advantages, such as for very ill patients who cannot be moved and for screening in the clinic or in the field. Second, it provides both anatomy and function. It also provides comprehensive assessment of all four chambers, the four valves, and the great vessels taking blood to and from the heart. Echocardiography, with its modifications such as Doppler and two-dimensional imaging, has become the standard to detect the phenotypes of inherited cardiac diseases. The inherited cardiac diseases are usually divided into structural and nonstructural groups. It is self-evident that echocardiography is the sine qua non to detect and elucidate structural cardiac disease. However, those with nonstructural disease will require echocardiography to exclude structural disease and/or to assess ventricular and atrial function.

It is estimated there are 6000 rare single-gene disorders.[2] In the past 20 years, >2000 responsible genes have been identified.[3] More than 200 of these genes involve cardiac disease. The bulk of them relate to cardiomyopathies, including hypertrophic cardiomyopathy (HCM),[4] dilated cardiomyopathy,[5] and arrhythmogenic right ventricular cardiomyopathy,[6] while others relate to rhythm disturbances such as long-QT syndrome.[7] The phenotype of cardiomyopathy has traditionally been detected by echocardiography as it still is today. It is true that arrhythmogenic right ventricular cardiomyopathy, once it is detected by echocardiography, is often further assessed using magnetic resonance imaging if available. In patients presenting with symptoms such as syncope or palpitations, echocardiography is an essential tool to exclude structural abnormalities and to assess ventricular function.

The most common cause of sudden cardiac death (SCD) at <35 years of age is an inherited cardiac abnormality.[8] The norm rather than the exception for SCD in this age group is a lack of symptoms preceding the event. HCM is claimed to be the most common cause of SCD in patients aged <35 years.[9] However, in Italy, the most common cause of SCD is arrhythmogenic right ventricular cardiomyopathy.[10] HCM occupies a unique position because it is considered to be the most common inherited disorder and, as indicated previously, the most common cause of SCD in the young. The gene occurs with a frequency of 1 in 500.[11] SCD associated with HCM appears to occur more commonly during combative and competitive sports. This has led to controversy as to whether athletes should be screened before being selected for organized sports. Electrocardiography should be part of the assessment, but the diagnosis of HCM is confirmed by echocardiography on the basis of wall thickness > 1.5 cm. It is now standard practice and recommended by American Heart Association and American College of Cardiology guidelines that if a family member is affected by HCM, his or her offspring should undergo serial echocardiography starting at puberty, followed by intervals of 3 to 5 years.[12] It is worthy to indicate that in a study in Italy, among 22 athletes with HCM detected by electrocardiographic screening, only five (23%) would have been identified by history and physical examination.[10,13] There is some evidence to suggest that if combative sports are avoided, the incidence of sudden death is decreased. In Italy, athletes excluded by screening using electrocardiography showed a sharp decline in mortality rates over the period from 1979 to 2004. In the athletes excluded from national sports, SCD occurred in 55 (1.9 deaths per 100,000), whereas there were 265 deaths in nonathletes who were not screened. This may be interpreted as a decrease in mortality of 89% due to screening.[10] Echocardiography is the definitive tool to exclude HCM and other structural abnormalities in high school students with electrocardiographic abnormalities, particularly if they are being considered for college scholarships to play sports such as football and basketball. Abnormal echocardiographic results in such potential candidates are often a devastating emotional occurrence. On the other hand, the diagnosis of HCM on echocardiography will prompt the recommendation to counsel these patients to undertake activities that will be meaningful but less harmful. Detection of HCM can be a lifesaving procedure in those in whom in-dwelling defibrillators are indicated.

Many other inherited cardiovascular abnormalities, such as Marfan syndrome, Friedreich's ataxia, aortic aneurysms, Ebstein's anomaly, and valvular abnormalities, are routinely detected by echocardiography. It is evident from the application of echocardiography that it has become the diagnostic method of choice for detecting most inherited cardiac phenotypes. Over the past 20 years, the resolution has improved, together with the addition of Doppler and two-dimensional techniques. Furthermore, protocols specifying the particular views and axes to be used have been standardized across centers, countries, and continents. The experience of phenotyping with echocardiography is now in its third decade for detecting inherited cardiac disorders.

In this issue, Mottram *et al.*[1] have described the early cardiac findings of a phenotype characteristic of Friedreich's ataxia. This disorder is inherited as an autosomal recessive trait due to GAA triplet repeats in the *FXN* gene,[14] which encodes for the protein frataxin.[15] In general, this disease is associated with ventricular hypertrophy. The investigators studied a large cohort of individuals who are homozygous for the gene responsible for Friedreich's ataxia but have no symptoms. The purpose was to search for early findings that would precede the more deleterious left ventricular dysfunction. The mutation in

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*FXN* induces ventricular hypertrophy, which often progresses to global left ventricular dysfunction. The ventricular function was assessed in its long axis, and regional impairment was detected in the septal and lateral mitral annular borders. These findings were detected despite the preservation of a normal left ventricular ejection fraction. If these findings are confirmed in other studies, it would have great value in screening for early involvement of the disease in individuals of families carrying the gene for Friedreich's ataxia. There will continue to be increased interest on part of genetic cardiologists in further improvements in the diagnostic sensitivity and specificity of echocardiography. This is particularly emphasized in cardiomyopathies, because multiple genes are involved, with incomplete penetrance. This means individuals may carry, as shown by Mottram *et al.* in this cohort of patients with Friedreich's ataxia, the mutation without expression of the disease for decades or even for a lifetime. Thus, echocardiography remains the tool to follow these individuals in assessing for expression of the gene. It is fortunate for physicians and the families involved that we have a noninvasive and sensitive technique to help in the assessment of inherited diseases, many of which can be lethal.

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