The tale of the three sisters

J. Liu, M.J. Cramer, G.E. Leenders, J. Zhao, P.A. Doevendans, P.G. Melman

In this article we present the myocardial deformation imaging (MDI) studies of three daughters of a man with hypertrophic cardiomyopathy (HCM) who died suddenly. The daughters had been referred for genetic counselling several months earlier. We demonstrate that, despite the absence of conventional two-dimensional echo characteristics of HCM, MDI accurately and easily demonstrated the presence of the disease in the two daughters with the genetic disorder. (Neth Heart J 2010;18:452-4.)

Keywords: Hypertrophic Cardiomyopathy; Myocardial Deformation Imaging; Genetic Disorder

Three sisters, whose father had died suddenly at the age of 63, were referred to our echo lab for extensive echocardiographic examination. He was known to have a dilated left ventricle with asymmetric septum hypertrophy. A coronary angiogram two years earlier revealed only a non-significant stenosis in the circumflex artery. Furthermore he had chronic atrial fibrillation with a QRS duration of 120 msec.

The three sisters had undergone genetic counselling several months earlier but their genetic profile was unknown to the echocardiographer. Their ECGs were unremarkable. The echocardiographic studies were performed utilising a GE Vivid 7 di-

mension machine (software version 2.2.1., GE Vingmed Ultrasound System, Horten, Norway), and an M3S Matrix 3000 elements 1.5-4.0 Mhz transducer. Comprehensive echo-Doppler demonstrated a slight bulging of the mid-septum in sister A. The further systolic and diastolic parameters were in the normal range in each sister (table 1). The two-dimensional (2D) quality in sister B was poor due to obesity. In addition, tissue Doppler myocardial deformation imaging (MDI) was performed, an advanced echocardiographic technique which enables the objective assessment of regional myocardial deformation by calculation of strain (regional deformation) and strain-rate (deformation rate) from differences in local tissue velocities.¹ MDI revealed a marked mid-systolic region of pathological deformation in sister A (figures 1A and 2A) and B (figures 1B and 2B). Sister C demonstrated a perfectly normal strain and strain-rate distribution of the interventricular septum (figures 1C and 2C).

After the examination, the genetic profile of the three sisters was unveiled. Sisters A and B were found to have a c.2373_2374insG (p.Trp792fsX17) mutation in the myosin binding protein C3 gene, which accounts for one-fourth of the HCM cases in the Netherlands.² Therefore MDI accurately and easily detected pre-clinical HCM in these mourning sisters.

Discussion

Hypertrophic cardiomyopathy is a fairly common genetic disorder, which can be caused by a vast number of gene mutations. Its clinical outcome is diverse, ranging from sudden death in the young individual to virtually no symptoms in advanced adulthood. Furthermore, the phenotypic expression can vary markedly.³ An important issue in this disease is the risk analysis of sudden death. Maron et al. have proposed major and minor criteria for the risk of sudden death. Two of the major criteria are sudden death in the family and genetic evidence of the disease.⁴ It is therefore obvious that once sudden death has occurred in the family, early detection of HCM in directly related family members can be of clinical importance for the management of this disease. Beta-blockers, amiodarone, and calcium antagonists might be considered the most effective pharmacological treatment although the data are

J. Liu

Department of Endocrinology, Provincial Hospital affiliated to Shandong University, Jinan, China, and Department of Cardiology, University Medical Centre Utrecht, Utrecht, the Netherlands

M.J. Cramer

G.E. Leenders

P.A. Doevendans

Department of Cardiology, University Medical Centre Utrecht, Utrecht, the Netherlands

J. Zhao

Department of Endocrinology, Provincial Hospital affiliated to Shandong University, Jinan, China

P.G. Melman

Department of Cardiology, University Medical Centre Utrecht, Utrecht, and Department of Cardiology, St. Elisabeth Hospital Tilburg, the Netherlands

Correspondence to: P.G. Melman

Department of Cardiology, St. Elisabeth Hospital, PO Box 90151, 5000 LC Tilburg, the Netherlands

E-mail: p.melman@elisabeth.nl

Table 1. Systolic and diastolic parameters measured by 2D echo.

	E velocity (cm/s)	A velocity (cm/s)	Deceleration time (ms)	E/A ratio	E/E'
Sister A	91.7	49.8	155	1.84	7.59
Sister B	55.2	48.4	180	1.14	4.65
Sister C	80.9	55.8	211	1.45	6.91

observational and there are no controlled comparative trials available. Besides secondary prophylaxis, an implantable cardioverter defibrillator for primary prevention of sudden death can be considered in patients with one or more major risk factors.⁵

Earlier publications have demonstrated the value of tissue Doppler imaging (TDI) velocities in the detection of pre-clinical HCM.⁶ Although cut-off points were identified, some overlap was seen in the individual patients. Other authors suggest a combination of Ea measurement and EF to be highly sensitive for detection of pre-clinical HCM.⁷ The potential disadvantage of applying TDI velocities is that it represents motion of the mitral annulus due to global longitudinal function, and thus can be insensitive to subtle regional deformation abnormalities in the above lying myocardium. Ger-

mans et al. reported successful diagnosis of HCM by late gadolinium enhancement imaging.⁸ Here we detected underlying familial HCM using the advanced echocardiographic technique of MDI. The strain and strain-rate provide the opportunity of studying small regional segments of the myocardium, and reflect different aspects of regional myocardial deformation. Furthermore, these indices are relatively independent of overall wall motion.⁹ Utilising the colour-coded format, small deformation defects can simply be visualised. In our three sisters we found MDI to be an easy and accurate method in the detection of genetic positive HCM, despite normal tissue Doppler parameters. By utilising the colour-coded curved M-mode, the pathological strain and strain-rate in the mid-septal segments were clearly visualised and easy to detect,

Figure 1. Strain curves of the interventricular septum of sisters A, B, and C. Negative values represent percentage shortening, positive values represent lengthening. Yellow, blue and red curves represent regional deformation from base to apex. Systolic deformation is defined as all deformation occurring between aortic valve opening (AVO) and closure (AVC) as indicated by the green vertical lines. Normal shortening should be >12%. A) Abnormal low values of shortening in the mid-septum of sister A. B) Abnormal low values of shortening and early systolic lengthening in the mid-septum of sister B. C) Normal values of systolic shortening in the complete septum of sister C.

Figure 2. Colour-coded curved M-Mode of the interventricular septum of sisters A, B, and C from base (bottom) to apex (top). Red coding represents shortening, blue coding represents lengthening. The mid-septum of sisters A and B shows diminished shortening (light red). Early systolic lengthening (light blue) is again visualised in sister B.

even though the 2D quality in sister B was poor.

Obviously, a larger controlled study should be conducted to definitely define the reproducibility, robustness, sensitivity and specificity of this technique in the identification of pre-clinical HCM. ■

References

- 1 Teske AJ, De Boeck BW, Melman PG, et al. Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. *Cardiovasc Ultrasound*. 2007;5:27.
- 2 Alders M, Jongbloed R, Deelen W, et al. The 2373insG mutation in the MYBPC3 gene is a founder mutation, which accounts for nearly one-fourth of the HCM cases in the Netherlands. *Eur Heart J*. 2003;24:1848-53.
- 3 Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA*. 2002;287:1308-20.
- 4 Maron BJ, Seidman JG, Seidman CE. Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004;44:2125-32.
- 5 Camm AJ, Lüscher TF, Serruys PW. The ESC textbook of cardiovascular medicine. Second edition. Chapter 9. Genetics of cardiovascular diseases.
- 6 Nagueh SF, McFalls J, Meyer D, et al. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with subclinical disease. *Circulation*. 2003;108:395-8.
- 7 Ho CY, Sweitzer NK, McDonough B, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. *Circulation*. 2002;105:2992-7.
- 8 Germans T, Nijveldt R, Brouwer WP, et al. The role of cardiac magnetic resonance imaging in differentiating the underlying causes of left ventricular hypertrophy. *Neth Heart J*. 2010;18:135-42.
- 9 Sutherland GR, Di SG, Claus P, D'hooge J, Bijnens B. Strain and strain rate imaging: a new clinical approach to quantifying regional myocardial function. *J Am Soc Echocardiogr*. 2004;17:788-802.