Hypertrophic Cardiomyopathy: Job Done or Work in Progress?

Perry M. Elliott

MBBS, MD, FRCP, FESC, FACC

Professor of Cardiovascular Medicine

University College London and St. Bartholomew's Hospital, London, UK

Address for Correspondence:

Institute of Cardiovascular Science

Paul O'Gorman Building (room G26)

University College London

72 Huntley Street

London, WC1E 6DD

United Kingdom

Email: perry.elliott@ucl.ac.uk

Word count: 1136

Everything should be made as simple as possible but not simpler.
Albert Einstein

Hypertrophic cardiomyopathy is a common inherited disease that affects around 1 in 500 people. In 50-60% of adolescents and adults with the condition, it is inherited as an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes. A further 5% of patients have metabolic or storage disorders, neuromuscular disease, chromosome abnormalities and genetic syndromes such as cardio-facial-cutaneous disorders. While the disease is compatible with normal life expectancy, it is associated with premature death from ventricular arrhythmia, heart failure and stroke in a substantial minority of patients [1,2].

Approximately 25% of patients with HCM have a resting pressure gradient between the body and outflow tract of the left ventricle. This is nearly always caused by contact between the anterior mitral valve leaflet and the interventricular septum in systole. Some patients with no evidence of outflow obstruction at rest can develop it during physiologic and pharmacologic interventions which reduce left ventricular end-diastolic volume or increase left ventricular contractility. Current practice guidelines recommend echocardiography during exercise stress testing in non-obstructive patients with exertional symptoms as the demonstration of latent obstruction in this context has a profound effect on their subsequent management [1,2].

In this edition of *the Journal*, Maron and colleagues characterize a subset of patients that have HCM but no evidence of dynamic left ventricular outflow tract obstruction at rest or immediately following exercise [3]. Their major conclusion is that non-obstructive HCM carries a low risk of disease related adverse events including end-stage heart failure and cardiovascular death. Such a message is obviously good news for patients that fall into this category, but there is a danger that it may also be an oversimplification which–if interpreted uncritically in clinical practice–might result in a failure to monitor and treat patients whose disease is progressive and potentially life-threatening.

A considerable body of evidence examining clinical outcomes in patients with HCM already exists. From these data we have learnt that patients with and with obstruction are vulnerable to disease related complications and careful examination of the data in the paper by Maron and colleagues suggests that their cohort is no different in this respect. While the annual mortality in their study was less than 1%, the rate of disease related events–many of which were life-threatening or potentially disabling–was in fact quite high. Specifically, 34 out of 249 non-obstructive patients (13.7%) died suddenly, had an appropriate ICD discharge or developed progressive heart failure, meaning that ≈2% of the cohort experienced a serious event each year. Add to this, the 19% that developed atrial fibrillation or stroke and the cumulative disease related morbidity and mortality is considerable. This finding is made all the more remarkable when one considers that the study cohort was biased towards individuals that most probably had a better outcome by excluding patients with severe heart failure symptoms at their initial evaluation.

The low mortality in this study can be seen as a testament to the beneficial effect of targeted therapy–specifically, implantable cardioverter defibrillators, cardiac transplantation and stroke prophylaxis. However, the low annual death rate should not mask the fact that sudden cardiac death and progressive heart failure remain a significant problem in non-obstructive patients [4,5,6]. Prevention of sudden cardiac death is facilitated by the use of validated prediction tools and ever more sophisticated defibrillator technology [1,2]. In contrast, the treatment of progressive left ventricular dysfunction is largely empiric and is extrapolated (with no supporting evidence) from trials in patients with systolic heart failure caused by ischemic heart disease and dilated cardiomyopathy [1,2]. Nevertheless, as the study by *Maron and colleagues* corroborates, it is possible to identify a subset of patients at risk of end-stage heart failure by using a relatively simple clinical approach [1,2,4,5,6]. Patients at risk of heart failure require more frequent monitoring–usually in a specialist setting–not only to treat symptoms, but also to detect the consequences of adverse cardiac remodeling including atrial arrhythmia and pulmonary hypertension, the latter a key factor determining the timing and suitability for cardiac transplantation.

It is often implied that the attempt to understand hypertrophic cardiomyopathy is a fool's errand because of its uniquely heterogeneous nature, but most published evidence suggests that adverse events are in fact predictable and often preventable. Modification of the underlying disease processes that result in ventricular failure is–at least for the moment–an aspiration, but research into this fascinating family of diseases is moving rapidly towards a focus on preventative and personalised interventions, built on an evermore sophisticated appreciation of their complex phenotypes.

References

1. Authors/Task Force members, Elliott PM (chairman), Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H; Authors/Task Force members. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014 Oct 14;35(39):2733-79

2. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60.

3. Maron M et al. Contemporary natural history and management of hypertrophic cardiomyopathy. *Reference to be supplied by Journal*.

4. Harris KM, Spirito P, Maron MS, Zenovich AG, Formaisano F, Lesser JR, Mackay-Bojack S, Manning WJ, Udelson JE and Maron BJ. Prevalence, Clinical Profile, and Significance of Left Ventricular Remodeling in the End-Stage Phase of Hypertrophic Cardiomyopathy. Circulation 2006; 114:216.

5. Biagini E, Coccolo F, Ferlito M et al. Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. J Am Coll Cardiol 2005; 46(8):1543-1550.

6. Coats CJ, Rantell K, Bartnik A, Patel A, Mist B, McKenna WJ, Elliott PM. Cardiopulmonary Exercise Testing and Prognosis in Hypertrophic Cardiomyopathy. Circ Heart Fail. 2015 Nov;8(6):1022-31