The dilemma of left ventricular outflow tract obstruction and sudden death in hypertrophic cardiomyopathy: do patients with gradients really deserve prophylactic defibrillators?

Barry J. Maron1*, Iacopo Olivotto2, and Martin S. Maron3

1Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, 920 E. 28th Street, Suite 60, Minneapolis, MN 55407, USA; 2Department of Cardiology, Referral Center for Myocardial Diseases, Azienda Ospedaliera Universitaria Careggi, Florence, Italy; and 3Department of Cardiology, Hypertrophic Cardiomyopathy Center, Tufts-New England Medical Center, Boston, MA, USA

Online publish-ahead-of-print 3 July 2006

This editorial refers to ‘Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy1 by P. Elliott et al., on page 1933

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, as well as the most frequent cause of sudden cardiac death in young people including competitive athletes.1 The devastating consequence of sudden death has, in fact, been central to our perception of the natural history of HCM for almost 50 years, as its initial contemporary description by Teare in 1958.1 Now that HCM has assumed an important place in the implantable cardioverter-defibrillator (ICD) era,2 the issue of risk stratification and sudden death prevention has become a major clinical consideration and central to the management of these patients, adding enormously to the complexity of the disease.

Indeed, the ICD was initially promoted specifically for HCM in 20002, and subsequently thousands of young patients have been afforded this potentially life-saving therapy. The efficacy of the ICD in HCM, for both secondary and primary prevention, is now well established.2,3 Despite this encouraging development, a mismatch persists between the power of ICD technology to recognize and successfully ablate potentially lethal ventricular tachyarrhythmias, and our ability to prospectively identify, with precision, each individual patient who may benefit from a prophylactically implanted device. Indeed, in a heterogeneous disease with a low cardiac event rate such as HCM, decisions regarding sudden death prevention are frequently encumbered by risk profiles of individual patients which fall into uncertain grey areas of ambiguity between high and low risk.

At this point, six major risk factors for sudden death have been proposed in HCM, including prior cardiac arrest for which there is general agreement regarding the role of secondary prevention ICDs.1,2,4,5 The five traditional risk markers for primary prevention include: (1) sudden death due to HCM in one or more relatives; (2) massive left ventricular (LV) hypertrophy (wall thickness ≥30 mm); (3) non-sustained ventricular tachycardia on ambulatory Holter ECG, if repetitive on sequential recordings; (4) hypotensive or attenuated blood pressure during exercise; and (5) unexplained syncope, particularly if related to exertion. Because of the low annual event rate characteristic of HCM, all these primary prevention risk factors have low positive predictive value (about 20%), but very high negative predictive value (about 90–95%). Other small high-risk subgroups have emerged within this heterogeneous disease, including LV apical aneurysm associated with regional myocardial scarring and the end-stage phase with systolic dysfunction.

Current US clinical practice for HCM involves full disclosure concerning the potential level of risk for sudden death to any patient with at least one of the aforementioned major risk markers (as judged with respect to the individual clinical profile),1,4,6 rather than rigid adherence to two or more risk factors.5 This strategy is supported by data from the largest HCM–ICD trial to date, an internationally assembled cohort of >500 high-risk patients, of whom 40% experienced an appropriate shock with only one primary prevention risk factor as justification for their prophylactic ICD.7

In the study by Elliott et al.,8 which appears in this issue of the journal, LV outflow tract obstruction at rest (gradient ≥30 mmHg) is promoted as a novel risk factor in HCM. The data presented by Elliott et al. develop a linkage between LV outflow tract obstruction and sudden cardiac death in HCM. This important issue has been previously addressed in reports by Maki et al. from Japan9 and in a 2003 New England Journal of Medicine multicentre study co-authored

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author. Tel: +1 612 863 3996; fax: +1 612 863 3875. E-mail address: hcm.maron@mhif.org

† doi:10.1093/eurheartj/ehl041

© The European Society of Cardiology 2006. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
by the authors of this editorial. It is noteworthy that each of these three studies produced virtually identical data showing a statistically significant increase in sudden death risk among obstructive HCM patients. Specifically, data from the study of Elliott et al. and our report are based, respectively, on cohorts of similar size (n = 900–1100), patient age (43–45 years), and have a similar proportion of obstructive patients (25–31%). Both studies show a relative risk of sudden death because of LV outflow obstruction equal to about 2.0 (i.e. two-fold that of non-obstructive patients), a positive predictive value of <10% (9 and 7%, respectively), and 95% negative predictive value.

Yet, while the findings are essentially the same, there are major differences regarding the authors’ interpretation of the data and implications for management. Of note, our 2003 study reported a strong and independent association between outflow obstruction and progressive heart failure and death, but judged the evidence for subaortic gradient as a marker for sudden death risk to be weak and per se insufficient to justify intervention with a primary prevention ICD. Indeed, the positive predictive values reported for outflow gradient and sudden death in both these studies are sufficiently low (i.e. lower than for any other risk factor reported in HCM) to regard obstruction as a very poor predictor in these patients.

It is also important to recognize that obstruction to LV outflow in HCM has certain unique limitations as a potential risk marker for future sudden death events. The HCM gradient is dynamic and often changes spontaneously, and can be influenced by a myriad of environmental factors, i.e. level of hydration, meals, modest alcohol consumption, and change in posture or blood pressure. In addition, a significant number of HCM patients without obstruction at rest will generate a significant provokable gradient with exertion, even with routine activities performed on a daily basis. The unique ability of HCM patients to convert transiently (or permanently, following a septal reduction procedure) from an obstructive to a non-obstructive state, thereby alters the entire significance of this risk factor in some patients. In this respect, the dynamic outflow gradient differs from other much more ‘static’ risk factors in HCM, such as a family history of sudden death or massive LV hypertrophy.

By promoting the LV outflow gradient as a major sudden death risk factor, Elliott et al. may have unintentionally introduced a further measure of misunderstanding into the HCM risk stratification and prophylactic ICD debate. The vast majority of practicing cardiologists treat relatively few patients with HCM, and are not immersed in the nuances of the voluminous, rapidly changing, and often contradictory literature. They look to (and depend upon) the few major centres focused on HCM for specific guidance and advice on critical management issues.

Will these data eventually be interpreted by the practicing cardiovascular community as a directive to use small resting outflow gradients of only 30–40 mmHg as a major and primary determinant of life-long ICD implants in young patients? As 70% of all hospital-based HCM patients will generate a ≥30 mmHg gradient at rest and/or with physiologic exercise, such an approach could in effect justify ICD implants in the vast majority of all patients identified with this disease, most of whom would not be at risk for sudden death.

Alternatively, should a finding as common as a gradient ≥30 mmHg be considered a secondary clinical risk marker to reach the two-risk factor model commonly employed in Europe for recommending ICDs to HCM patients? This would also have the theoretic effect of implanting virtually all HCM patients with ICDs, since reportedly almost 50% already have one or more of the generally accepted primary prevention risk factors. Needless to say, as the authors prudently suggest, their data should not be used to promote septal reduction therapy (i.e. surgical septal myectomy or alcohol septal ablation) in asymptomatic or mildly symptomatic HCM patients in an effort to minimize sudden death risk by reducing outflow gradient.

Although the contribution of Elliott et al. offers further evidence for a relationship between LV outflow obstruction and sudden cardiac death in HCM, it fails to provide either a clear clinical message or specific benchmarks for practice, i.e. how to translate statistically derived data to the management of individual patients. These authors have emphasized the statistically significant relative risk of obstruction to sudden death. However, the absolute risk remains very small with the positive predictive value for identifying high-risk patients very low. Small absolute risk implies an unacceptably high number of patients treated in the hypothetical event of systematic prophylactic ICD implantation, including a substantial proportion who will not require device therapy.

Therefore, we wish to sound a cautionary note, which is appropriate until further clarity is achieved in this area by future investigation. At present, the evidence for obstruction to LV outflow as a sudden death risk marker is not sufficiently strong to represent an indication for a primary prevention ICD. Unless this limitation is clearly recognized, the data of Elliott et al. could well lead to substantial misunderstanding in the practicing community and the placement of many unnecessary ICDs. These are irreversible and life-long clinical decisions with the potential for device complications over many years.

Management guidelines for the HCM patient population have frequently been fraught with a large measure of confusion. Now that the ICD provides a reasonable aspiration for prevention of sudden death in young people, more than ever patients with HCM deserve clear and prudent treatment strategies to achieve this important goal.

Conflict of interest: B.J.M. is a grantee of Medtronic.

References


Clinical vignette
doi:10.1093/eurheartj/ehi791
Online publish-ahead-of-print 9 February 2006

Simultaneous triple kissing stenting in an unprotected left main coronary artery

Christophe L. Dubois*, Peter R. Sinnaeve, and Walter J. Desmet
Department of Cardiology, U.H. Gasthuisberg, Herestraat 49, Leuven, Belgium

* Corresponding author. E-mail address: christophe.dubois@uz.kuleuven.ac.be

A 76-year-old hypertensive male smoker with diabetes mellitus and a family history of coronary artery disease was urgently referred to the cardiac catheterization laboratory after a prolonged episode of chest discomfort, soon progressing to cardiogenic shock. Electrocardiogram showed a new left bundle branch block.

Coronary angiogram was performed using an 8 French guiding catheter and revealed an ostial thrombotic occlusion of the left anterior descending artery (LAD) in the left anterior oblique caudal projection (Panel A). A small circumflex artery (Cx) showed only moderate disease at the ostium.

A thrombus aspiration was performed in the LAD using an EXPORT catheter (Medtronic), restoring flow in the LAD and a very early originating diagonal branch (Dx). In an attempt to maintain patency in this trifurcation, three PRO-Kinetic stents (Biotronik) were positioned (Panel B) in the unprotected left main coronary artery (LMCA) to LAD (2.5/22 mm), Dx (2.5/22 mm), and Cx (2.5/15 mm) and simultaneously deployed at 10 atm (Panel C). Although TIMI 3 flow was restored through a widely patent LMCA trifurcation (Panel D), progressive deterioration to profound cardiogenic shock could not be prevented. The patient expired 24 h after recanalization.

Although long-term outcome of simultaneous kissing stenting technique for the treatment of bifurcation lesions is unknown, this case shows that even triple kissing stenting technique using newer generation stents is feasible through 8 French guiding catheters with good immediate angiographic success. Nevertheless, this approach should be reserved for bailout situations, as in the case presented.