Hotline Editorial

Hypertrophic cardiomyopathy and sudden death: new perspectives on risk stratification and prevention with the implantable cardioverter–defibrillator

Hypertrophic cardiomyopathy is a genetic cardiac disease with a particularly heterogeneous presentation and diverse natural history[1–4]. Sudden and unexpected death has been recognized as a prominent and devastating consequence of hypertrophic cardiomyopathy since the initial description of this disease over 40 years ago[5]. Many authors have emphasized that these catastrophic events occur not uncommonly in young asymptomatic patients[6–8] with annual mortality rates reportedly as high as 4–6%[5] in tertiary centre referral populations disproportionately comprised of high-risk patients[9].

Historical context

Teare’s original pathological report of this disease in a small number of patients who died suddenly[5], recognized that a relatively important subgroup of patients with hypertrophic cardiomyopathy are at increased risk for sudden cardiac death. This has, for many years, generated considerable interest in the process of risk stratification[3,10–13], together with a continuing debate regarding the most appropriate measures for effective prevention of these unexpected catastrophes[14]. Historically, the prophylactic management of high-risk patients was initially limited to pharmacological treatment with beta-blockers, verapamil, and antiarrhythmic agents such as procaïnamide and quinidine, and more recently with amiodarone[12,15]. However, in hypertrophic cardiomyopathy, there are limited data supporting the efficacy of prophylactic drug treatment for sudden death[7,15]. For example, since the sole report proposing the protective effects of amiodarone 15 years ago (utilizing a retrospective and non-randomized historical case control design)[15], there has been virtually no new information regarding the efficacy of this drug in hypertrophic cardiomyopathy patients. Also, the frequent adverse consequences associated with chronic use of amiodarone severely limits its application to sudden death prevention in young patients with hypertrophic cardiomyopathy who harbour long periods of risk. Indeed, the prevention of sudden death in hypertrophic cardiomyopathy has been a major management challenge for clinicians.

Sudden death mechanisms

The determinants of sudden cardiac death in hypertrophic cardiomyopathy have never been completely defined, but are thought to be complex and probably multi-factorial, ultimately involving ventricular tachyarrhythmias. However, defining the arrhythmias responsible for sudden and unexpected death in hypertrophic cardiomyopathy has proved difficult, given the paucity of ECG recordings during clinical events[16]. Nevertheless, it is believed that arrhythmias probably emanate from a substrate of electrical instability and distorted electrophysiological transmission created by the disorganized left ventricular architecture[4], or from bursts of myocardial ischaemia leading to myocyte necrosis and areas of replacement fibrosis probably due to abnormal and narrowed intramural arterioles[4]. This myocardial substrate may be vulnerable to a variety of triggers, either intrinsic (i.e. related to the hypertrophic cardiomyopathy disease process, such as an abrupt increase in outflow obstruction) or extrinsic and environmental (such as intense physical exertion).

Implantable cardioverter–defibrillators

Since its introduction by Mirowski et al.[17] 20 years ago, the implantable cardioverter–defibrillator has achieved widespread acceptance as a preventive treatment for sudden death, by virtue of indisputably demonstrating efficacy for terminating life-threatening ventricular arrhythmias and prolonging life, principally in high-risk patients with ischaemic heart disease[17–19]. The superiority of the implantable cardioverter–defibrillator to antiarrhythmic drug
treatment has recently been documented in prospective randomized trials. Of particular importance in this regard has been the evolution of the implantable cardioverter–defibrillator from a thoracotomy-based procedure with epicardial leads to a transvenous endocardial electrode system with pectoral implantation of the pulse generator, which has greatly facilitated clinical employment, particularly for the primary prevention of sudden death. However, despite the widespread use of the implantable cardioverter–defibrillator in subsets of patients with coronary artery disease, to date there had been relatively little application of the device to less common, often genetic, conditions which also constitute a risk for sudden death, such as long QT and Brugada syndromes, arrhythmogenic right ventricular dysplasia, and hypertrophic cardiomyopathy.

**Sudden death prevention trial with the implantable cardioverter–defibrillator in hypertrophic cardiomyopathy**

With these experiences and perceptions as background, the efficacy of the implantable cardioverter–defibrillator was recently investigated in a group of hypertrophic cardiomyopathy patients judged to be at high risk for sudden death, as part of a multicentre, retrospective study of selected U.S. and Italian centres. In the overall group of 128 hypertrophic cardiomyopathy patients who had implantable cardioverter–defibrillators implanted for sudden death prevention and were followed for an average period of just 3 years, appropriate device discharges (either defibrillation shocks or antitachycardia pacing) occurred in almost 25%, with an average discharge rate of 7% per year. Furthermore, about 60% of those patients who received defibrillator therapy experienced multiple appropriate interventions.

**Secondary prevention**

Perhaps not unexpectedly, life-saving defibrillator interventions were more frequent in those patients implanted specifically for secondary prevention, i.e. following fortuitous resuscitation from cardiac arrest (with documented ventricular fibrillation) or with prior spontaneous and sustained ventricular tachycardia; over 40% of these patients received defibrillator therapy during the relatively short follow-up period. Such frequent recurrence of potentially lethal ventricular tachyarrhythmias following cardiac arrest is consistent with a previously reported experience with similar hypertrophic cardiomyopathy patients in the pre-implantable cardioverter–defibrillator era.

**Primary prevention**

Of particular note, those patients receiving implantable cardioverter–defibrillators solely for primary prevention showed a substantial appropriate device intervention rate of about 5% per year. In this context, primary prevention was regarded as purely prophylactic implantation, dictated by a perception of high-risk for sudden death based on a clinical profile characterized by one or more identifiable risk factors: family history of hypertrophic cardiomyopathy-related sudden death, exertional syncope (particularly if repetitive and in the young), multiple-repetitive or prolonged non-sustained ventricular tachycardia on ambulatory (Holter) ECG, or extreme left ventricular hypertrophy (wall thickness ≥ 30 mm). The presence or absence of outflow obstruction is not a risk factor for sudden death.

Furthermore, invasive parameters, such as ventricular arrhythmias induced with programmed electrical stimulation, are not regarded as useful discriminators for risk stratification.

By extrapolating our primary prevention discharge rate, it could be estimated that within 10 years about 50% of the defibrillators prophylactically implanted in young patients would intervene and abort a sudden death event. Indeed, the 5% annual discharge rate cited here is remarkably similar to that reported for sudden death in highly selected patients with hypertrophic cardiomyopathy at tertiary referral centres. Also, it should be emphasized that prophylactic implantable cardioverter–defibrillator employment in hypertrophic cardiomyopathy, as defined here, represents a particularly pure form of primary prevention, with implantation in advance of any major cardiovascular event.

**Triggering mechanisms**

In the multicentre implantable cardioverter–defibrillator in hypertrophic cardiomyopathy study, arrhythmia sequences documented by stored electrocardiographic data in patients experiencing appropriate defibrillator discharges, represented a unique window to achieving an understanding of the mechanisms responsible for sudden death in hypertrophic cardiomyopathy. Ventricular tachycardia or fibrillation proved to be the rhythm initiating appropriate device activations.
in each instance, supporting the hypothesis that the mechanism most commonly responsible for unexpected catastrophes in this disease is primary ventricular tachycardia/fibrillation^{[1]}, emanating from an electrically unstable myocardial substrate^{[2,24]}. It is possible that these mechanisms may ultimately prove to be more complex; examples of premonitory arrhythmias immediately preceding ventricular tachycardia and fibrillation have been reported^{[16,25]}.

### The risk period in hypertrophic cardiomyopathy

Crucial to understanding the role of the implantable cardioverter–defibrillator in patients within the hypertrophic cardiomyopathy disease spectrum is an appreciation of certain demographic distinctions in implantable cardioverter–defibrillator implants in patients with ischaemic heart disease. Such patients are of relatively advanced age (average about 65 years old), and often with advanced disease. In sharp contrast, in hypertrophic cardiomyopathy there is an extended period of risk for sudden death which predominates in young people <30 years old, but also importantly includes mid-life and even beyond^{[8,23]}. Indeed, hypertrophic cardiomyopathy represents a very different clinical circumstance in which at-risk patients are often young and with few or no symptoms. In the multicentre implantable cardioverter–defibrillator in hypertrophic cardiomyopathy trial^{[14]}, patients averaged only 40 years of age at the time of implant (and almost 25% were <30 years old), and the mean age at the first appropriate device intervention was only 40 years. Therefore, preventive treatment for sudden death in hypertrophic cardiomyopathy carries the substantial potential for very significant prolongation of life.

Of particular note, the time interval between implant and first appropriate implantable cardioverter–defibrillator intervention was quite variable, with particularly long time delays of up to 9 years for the first life-saving intervention; initial defibrillation shocks occurred in 20% of patients, ≥4 years after implant. Therefore, in hypertrophic cardiomyopathy, the timing of sudden death is unpredictable and the implantable cardioverter–defibrillator may remain dormant for long periods of time, before ultimately intervening appropriately. Consequently, the decision to implant an implantable cardioverter–defibrillator in a high-risk hypertrophic cardiomyopathy patient is likely to represent a life-long commitment.

### Strategic limitations

#### Risk stratification

While there is now little reason to doubt the efficacy of the implantable cardioverter–defibrillator in preventing sudden death in a relatively uncommon genetic disease such as hypertrophic cardiomyopathy, nevertheless, many important issues regarding prophylactic treatment remain incompletely resolved. For example, the question of precisely which patients within the broad hypertrophic cardiomyopathy disease spectrum should receive implantable devices for primary prevention is presently constrained by certain imperfections in risk stratification profiles, which ultimately emanate from the uncommon occurrence and heterogeneous nature of hypertrophic cardiomyopathy^{[1–4,20]}. In this regard, clinical features in some hypertrophic cardiomyopathy patients, who may be at high risk for sudden death, cannot be explicitly related to the available and acknowledged risk factors.

Therefore, in the absence of a relevant database for all possible at-risk clinical circumstances for individual patients, the ultimate decision regarding implantable cardioverter–defibrillator implantation in some cases may reside with the best clinical judgement of the treating cardiologist. For example, one partially unresolved area is that of a family history of sudden death as an indication for primary prevention, which is pertinent to surviving affected relatives in selected families. In this regard, should ‘only’ one sudden death in a close relative be sufficient to trigger an implant, or should two or more such deaths be the minimum requirement, as previously suggested^{[19]}?

Data governing such focused but critical issues are sparse, definitive answers are not presently available, and therefore individual physician judgement and the motivations and biases of the patient are often important factors in resolving such dilemmas in clinical decision making. Therefore, it is reasonable to conclude that, at present, the potency and sophistication of the implantable cardioverter–defibrillator to effectively abort sudden cardiac death exceeds the power of available risk stratification profiles to reliably distinguish between all appropriate candidates for the implantable cardioverter–defibrillator.

In the recent multicentre implantable cardioverter–defibrillator in hypertrophic cardiomyopathy study^{[14]} there was an insufficient number of patients with appropriate discharges to permit definitive identification of the strongest clinical indicators for primary prevention implants. Further studies with much larger numbers of patients are underway (completion scheduled for 2003) with the expectation of defining...
with greater precision those hypertrophic cardiomyopathy patients among the broad disease spectrum who should be targeted for (and would benefit most from) prophylactic implantable cardioverter–defibrillator therapy. Such investigations will be both retrospective and prospective in design, but necessarily are uncontrolled and non-randomized due to the uncommon and heterogeneous nature of the disease itself[1–4,26], the particularly long potential risk period characteristic of young hypertrophic cardiomyopathy patients[8,14], and certain obvious ethical considerations.

Deserving of emphasis is the fact that while the implantable cardioverter–defibrillator has now been shown to be highly effective in terminating potentially lethal arrhythmias and preserving life, it should not be regarded as a treatment for all (or even most) patients with hypertrophic cardiomyopathy. At present, implantation of this device should be confined to that subset of patients regarded to be at high-risk for sudden death in accord with current risk stratification profiles.

Complications

It is also important to recognize certain complications of implantable cardioverter–defibrillator therapy, the concern for which must always enter into implant decisions, particularly for primary prevention. Complications include inappropriate and spurious device discharges (which occurred in 25% of hypertrophic cardiomyopathy patients)[14], fractured or disrupted leads and infection, as well as considerations for the substantial cost of the implantable cardioverter–defibrillator and its implantation, and its limited access in many countries. Of course, these issues must always be weighed against the ultimate potential benefit of the implantable cardioverter–defibrillator in high-risk patients which is, in fact, the preservation of life.

Conclusions and implications

Prevention of sudden death is now an achievable aspiration for many patients with hypertrophic cardiomyopathy, as the use of implantable defibrillators has now been extended to this relatively uncommon genetic disease. Recently published data from a retrospective, multicentre trial enhances the view that the implantable cardioverter–defibrillator is effective and can be life-saving in hypertrophic cardiomyopathy, and establishes an important role for this therapy, in high-risk patients both for secondary and primary prevention of sudden death. The implantable cardioverter–defibrillator proved highly reliable in sensing and interrupting ventricular tachycardia/ fibrillation despite the substantially increased heart mass characteristic of hypertrophic cardiomyopathy[26]. Of note, more than one half of the study patients were taking amiodarone or other anti-arrhythmic drugs at the time of the appropriate defibrillator discharge, underlining both the superiority of the implantable cardioverter–defibrillator in preventing sudden death and disputing prior claims that amiodarone is absolutely protective against sudden death in hypertrophic cardiomyopathy patients[15]. Annual appropriate intervention rates for hypertrophic cardiomyopathy are lower than those reported in coronary artery disease[18,19], but are nevertheless significant since the implantable cardioverter–defibrillator experience in hypertrophic cardiomyopathy must be considered in the context of a much younger patient population. This population is usually free of significant congestive heart failure and have preserved systolic function. They are exposed to long periods of potential risk but could survive many decades with normal or near-normal life expectancy, given the protection afforded by an implantable cardioverter–defibrillator.

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References


