Are We Nearly There Yet? Progress in the Prevention of Sudden Cardiac Death in the Young

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The classic paper discussed in this essay:
Sen-Chowdhry S, McKenna WJ: Sudden cardiac death in the young: a strategy for prevention by targeted evaluation. *Cardiology* 2006;105:196–206.

The Context

Our article on the prevention of sudden cardiac death (SCD) in the young was written in 2005, just after I (S.S.-C.) had completed a clinical academic fellowship supervised by William J. McKenna [1]. Although the focus of my research was the role of cardiovascular magnetic resonance (CMR) in the evaluation of arrhythmogenic right-ventricular cardiomyopathy (ARVC), the placement also afforded experience in all aspects of inherited cardiovascular disease (ICVD): the key cause of SCD in the young.

As we clarified in our 2006 review, ischaemic heart disease (IHD) accounts for the overwhelming majority of sudden deaths in the general population. Since the prevalence of IHD increases with age, however, SCD in the young can be considered a paradigm for non-ischaemic SCD. The age cut-off is typically 35 years, ranging from 25 to 40 in different studies, but essentially arbitrary. As the proportion of older subjects increases, so does the frequency of IHD among the causes of SCD. That is not to say that the young do not die from IHD, or that older people are insusceptible to the non-ischaemic cardiovas-

cular diseases subsequently discussed. On the contrary, many ICVD show age-related clinical expression and/or have late-onset forms. The main difference is that IHD overshadows ICVD as a cause of SCD in the older population [1].

Prior to commencing the fellowship, my clinical training had left me with a perception of ICVD that was dominated by the heritable risk factors for IHD. Disorders with archetypal physical signs had also received attention, particularly Marfan's syndrome and obstructive hypertrophic cardiomyopathy (HCM). Patients with HCM came to attention in the presence of debilitating symptoms from resting left-ventricular outflow-tract obstruction or atrial fibrillation. That HCM was a familial disease associated with SCD was tacitly acknowledged, but had limited impact on clinical practice. There was little awareness of available guidelines or impetus to risk stratify HCM cases and offer assessment to relatives. The genetic contribution to dilated cardiomyopathy (DCM) was not even recognised; instead, DCM was presumed viral, although the requisite viral serology seldom shed light on its aetiology. ARVC was still termed 'dysplasia', overlooking its genetic basis; it was the main differential diagnosis

in patients with right-ventricular tachycardia, but diagnosed only in the presence of gross abnormalities on imaging.

As a result, nothing in my background of internal medicine and general cardiology prepared me for the unique approach to patients at the ICVD clinic, with its emphasis on families. Clinicians discussed individual cases in the broader context of the familial phenotype. With mutual consent, family members were often seen together in the clinic. The large departmental cohorts for HCM, DCM and ARVC included both symptomatic index cases and relatives identified by prospective evaluation. Also encountered, albeit less frequently, were the lesser known familial forms of the Wolff-Parkinson-White syndrome, bicuspid aortic valve and mitral valve prolapse (MVP) [2, 3].

Not only was the screening programme tailored to specific disorders, but it also took the complexities of familial disease into account. The autosomal dominant inheritance pattern common to ICVD is often associated with reduced penetrance, age-related expression and variable expressivity. Consequently, it was necessary to explain to some families that the disease might appear to 'skip a generation'; periodic rescreening was offered where indicated; and interpretation of investigations in relatives required modified diagnostic criteria for each disease, reflecting incomplete phenotypic expression [4, 5]. Confirmation of the diagnosis prompted prognostic assessment, which – in view of dynamic risk profiles – was repeated at intervals, and, for patients with HCM in particular, was based on evidence-based consensus guidelines [6]. Even the follow-up patterns differed from general cardiology, with the many slowly progressive disorders requiring infrequent but lifelong monitoring.

Hand in hand with my growing appreciation of what was known about ICVD, and what could be done for those affected, came an awareness of the limits of existing knowledge. Not uncommonly observed among ARVC families, for example, were arrhythmia of left-ventricular origin, (infero)lateral T-wave inversion and late gadolinium enhancement of the left-ventricular myocardium on CMR, in the setting of preserved right-ventricular function. While left-ventricular involvement in ARVC was already well recognised, it was purported to occur as a late complication of advanced disease, following the onset of isolated right-heart failure [7]. The 1994 Task Force criteria for ARVC even stipulated a normal or only mildly impaired left ventricle and had the added limitation, in our familial population, of lacking sensitivity for early disease. Modified criteria to facilitate diagnosis in first-

degree relatives were developed and implemented in the clinic, but another challenge remained largely unsolved: that of risk stratification in early disease [5]. In ARVC, mild or absent structural abnormalities may belie significant arrhythmic risk.

More enigmatic still was the entity of left-ventricular non-compaction (LVNC), initially under- and subsequently overdiagnosed, owing to lack of stringent imaging criteria. The dilemma here was reminiscent of the historical controversy surrounding MVP in more ways than one, with little consensus as to the clinical significance of the finding [8].

Nowhere was the knowledge gap so profound, however, as the initiative to evaluate the surviving relatives of sudden unexplained death victims [9]. By definition, the initial post-mortem examination and toxicology screen in the index cases were non-contributory, but reassessment of blocks and slides by an expert cardiac pathologist yielded many a previously missed diagnosis, not uncommonly ARVC. Cases with unequivocally normal histopathology were assigned a diagnosis of SADS: sudden adult death syndrome, later sudden arrhythmic death syndrome to incorporate instances among infants ('cot deaths') and children [9]. SADS had long been suspected to be caused, at least in some cases, by inherited arrhythmia syndromes such as the long QT, short QT and Brugada syndromes, and familial catecholaminergic polymorphic ventricular tachycardia, which all confer a propensity towards ventricular tachyarrhythmia in the structurally normal heart. Seeking clinical manifestations of inherited arrhythmia syndromes among the relatives of SADS victims was, at inception, a largely unprecedented endeavour that led to a spate of high impact reports. It was the continuation of this work that formed the basis for the tentative recommendations for evaluating SADS families in our 2006 article [1].

The challenges of working in ICVD were not, however, confined to being at a clinical cutting edge. Many of the referrals to the ICVD service were instigated by the sudden death of a young and ostensibly healthy individual. Relatives attending the clinic in the immediate aftermath of a loss were understandably tormented by disbelief and anger, the latter often directed – at least in part – at the medical establishment, particularly when the loved one had experienced premonitory symptoms, and justifiably so when they had been disregarded. Even when years had elapsed since the loss, a clinic appointment might serve as a grief trigger. Nevertheless, given time, most families found outlets for their grief, commonly the altruistic goal of preventing the same thing from happen-

ing to anyone else. Patient advocacy groups and charities such as SADS UK and Cardiac Risk in the Young not only provided emotional support and resources for bereaved families, but also campaigned for screening programmes to identify at-risk individuals. Among the aspirations voiced by many affected families was prospective cardiac evaluation of the general population, particularly the <35 age group.

For the reasons we detailed in our 2006 article, we did not consider universal cardiac screening a tenable option [1]. Foremost among the obstacles was not so much the potential drain on resources as the limited net gain from a population-based strategy. Constraints include the modest negative predictive value of a normal 12-lead ECG, the need for periodic reassessment to identify age-related disease expression, and above all the bayesian effect, which markedly reduces the positive predictive value of an abnormal test. Commonly overlooked in the wake of clinician enthusiasm for screening programmes is the risk of healthy individuals undergoing unnecessary medical investigations – or interventions – with their attendant adverse psychological impact.

The alternative advocated by Prof. McKenna involved selective screening of three potentially at-risk subgroups: individuals with cardiac symptoms; blood relatives of SCD victims, and competitive athletes. The evidence base was strongest for evaluating competitive athletes thanks to the long-standing Italian pre-participation screening programme, but more modest for blood relatives and symptomatic individuals, being derived primarily from disease-specific studies; >30% of athletes suffering SCD from anomalous coronary arteries, for example, had experienced premonitory symptoms [10]. The ICVD clinic offered a platform for assessing the validity of these putative selection criteria, albeit in a sample limited by referral bias (Appendix 1 – Pilot Study).

The Impact

The main findings of our pilot study were presented at the Europace Meeting in 2006 and bolstered the case for targeted evaluation to prevent SCD in the young, as presented in our 2006 article [1]. By this time, the media had already gone some way towards accomplishing the goal of health promotion through education. Not only had the preceding years seen a number of high profile deaths – notably Marc-Vivien Foé, the Cameroonian football player who collapsed during an international game in 2003 – but coverage of off-the-field deaths in the commu-

nity was also increasing, partly because of the ease with which information is disseminated online. It was gradually taking root in the public consciousness that young people, not just elite athletes, may die suddenly and unexpectedly of occult cardiac disease. In the UK, the concerted efforts of opinion leaders in cardiology and pressure from advocacy groups were also effecting the requisite healthcare reforms, culminating in the issuance of National Service Framework Chapter 8: Arrhythmia and Sudden Cardiac Death in 2005 and the advent of rapid access arrhythmia clinics. The ACC/AHA/ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD followed in 2006, also recommending evaluation of symptomatic individuals and the relatives of SCD victims [11].

The Hiatus

Developments in the field of ICVD since the publication of our 2006 article have both fulfilled expectations and altered them. The genetic basis of disorders such as familial MVP is gradually emerging, one clue being the identification of a filamin A mutation in X-linked myxomatous valvular dystrophy [2]. Additional disease-causing genes have also been identified in the cardiomyopathies and inherited arrhythmia syndromes, some functionally related to their predecessors, others affecting different cellular and molecular processes, necessitating rethinking and extension of final common disease pathways. While most of the mutations isolated in arrhythmogenic cardiomyopathy, for example, affect components of the desmosome, the past few years have seen implication of a number of extra-desmosomal genes, including founder mutations in *TMEM43* and phospholamban in the Newfoundland and Dutch populations, respectively [7, 12].

Advances in genetic technology have been paradigm shifting but not the diagnostic panacea originally envisioned. The commentary on genetics in our 2006 review was limited to a few words on cascade screening and molecular autopsy [1]. Our circumspection understated the erstwhile excitement surrounding the likely clinical impact of anticipated developments in genetic technology. Specialists in mendelian disorders had long toiled with linkage analysis, cumbersome and time-consuming mutation screening of candidate genes, and prohibitive costs. Next-generation sequencing platforms promised rapid, high-throughput, cost-effective genetic testing and, above all, the capacity to simultaneously analyse panels of genes

with unparalleled accuracy and pick-up rates. Seven years on, all of these expectations have been met, bar one: translation of the technological revolution into the game-changing clinical tool that has been so long awaited.

No conceivable technical advance could obviate the need to prove that a putative pathogenic gene variant is causal before opening the door for predictive testing. This is one of the key challenges in the genetics of ICVD, owing to the prevalence of private, often novel mutations within families. Proof as such is typically established by a combination of *in vitro* expression studies, *in silico* molecular modelling and demonstration of co-segregation with phenotype within a kindred, although the latter may be complicated by reduced penetrance and variable expressivity. In this regard, the wealth of genetic information yielded by next-generation sequencing has become a double-edged sword, compounding the existing difficulties in distinguishing contributory gene variants from background genetic noise [13].

High-throughput genomics has changed the playing field to the point where the traditional dichotomy between 'simple' mendelian and 'complex' multifactorial models has been rendered largely defunct. Supplanting it is a conceptual continuum, extending from a primary gene interacting with modifiers to increasingly shared influence by multiple genetic and environmental factors [14]. Allele dose effects and allele-allele interactions have long been recognised in ICVD, but the new paradigm demands that sequence variants previously discarded as 'benign polymorphisms' be considered potential contributors to disease expression. Determining the relationship between the myriad of gene variants, epigenetic modifiers, environmental factors and complex phenotypes is a gargantuan task, but one that promises to transform our understanding of biology and pave the way for individualised medicine.

In the clinical arena, the past few years have seen progress in both advancement of knowledge and health care reform. Studies of LVNC have confirmed what has long been observed on an anecdotal basis: healthy African-Caribbean individuals and elite athletes may satisfy conventional criteria for LVNC [8, 15]. There is a pressing need for refinement of either the diagnostic criteria or the paradigm itself. Rather than being the root cause of myocardial dysfunction, LVNC may represent an epiphenomenon, a remodelling response that is well tolerated in the normal heart but maladaptive in the presence of underlying cellular and molecular pathology. To date, the significance of isolated LVNC – a relatively rare entity – remains unresolved [8].

In contrast, more insights are emerging into the role of MVP as an aetiological factor for SCD. Not only has MVP been reported in association with arrhythmogenic cardiomyopathy, but a subset of patients with apparently isolated malignant MVP syndrome have been described [16, 17]. The clinical profile was of young women with bileaflet MVP, ventricular arrhythmia of the outflow tract/papillary muscle/fascicular origin and increased risk of SCD, although numbers are small and further characterisation is awaited [17].

As anticipated, the Task Force criteria for the diagnosis of ARVC were revised in 2010, increasing their sensitivity for early and familial disease [18]. Accumulating evidence of early left-ventricular involvement in ARVC, from our cohort and others, supported adoption of the broader term arrhythmogenic cardiomyopathy and led to the description of the left-dominant and biventricular subtypes [16, 19]. One of the most significant advances in the therapeutic arena has been the development of subcutaneous implantable cardioverter-defibrillators, which free device recipients from the hazards of transvenous lead complications and failures [20, 21].

While genetic discoveries have not yet translated into widespread clinical application, the resulting insights into disease mechanisms have paved the way for disease-modifying therapies. In HCM, for example, cellular energy depletion has been invoked as the final common pathway. The carnitine palmitoyltransferase inhibitor perhexiline shifts mitochondrial metabolism from fatty acid to carbohydrate utilisation, thereby enhancing myocardial efficiency. In a small study of 46 symptomatic HCM patients, perhexiline appeared to improve diastolic function and increase exercise capacity [22]. Another promising development is the use of cardiomyocytes derived from induced pluripotent stem cells to recapitulate the ICVD phenotypes, including DCM, long QT syndrome and arrhythmogenic cardiomyopathy, and to evaluate therapeutic interventions [23, 24]. In arrhythmogenic cardiomyopathy, modelling as such has identified antagonists of PPAR- α and PPAR- γ , and scavengers of reactive oxygen species – such as ascorbic acid – as promising disease modifiers, although clinical studies are awaited [25].

At the level of implementation, targeted evaluation of both symptomatic individuals and blood relatives of ICVD index cases and SADS victims is now widely recognised as standard of care. Family screening programmes are being piloted for disorders such as bicuspid aortic valve, with echocardiographic assessment of both valvular anomalies and aortic root dilation, to facilitate timely

identification of individuals at increased risk of dissection [26]. One testimony to the growing awareness of arrhythmogenic disease in the UK is the advent of rapid access arrhythmia clinics and a steady rise, since 2007, of the referrals received from primary care [27].

Controversy remains, however, over what measures – if any – need to be taken to prevent SCD among athletes. Opponents of pre-participation screening assert that these events are too infrequent to pose a significant public health challenge. It has even been argued that limiting a national mandatory screening programme to competitive athletes would be discriminatory, since SCD from ICVD is not exclusively – or even predominantly – a sport-related phenomenon [28]. The main counters to this line of reasoning are the accumulating evidence that prolonged participation in strenuous activities accelerates disease progression in certain disorders, notably arrhythmogenic cardiomyopathy, and that the surge of adrenergic stimulation associated with intense physical exertion may trigger ventricular tachyarrhythmia [10, 19, 29]. This latter point is the primary rationale for the recommended restrictions on sport activities for individuals with ICVD [30].

Variations in practice also loom large, due at least in part to the lack of consensus on the clinical management of patients after diagnosis. In the setting of a confirmed diagnosis of ICVD, the next step is prognostication. This is facilitated in HCM by evidence-based guidelines, but more challenging in diseases such as arrhythmogenic cardiomyopathy and Brugada syndrome, particularly for relatives with incomplete or non-classic phenotypic expression [31].

Perhaps the foremost unresolved issue, however, is the optimal management of patients with ventricular premature beats (VPB), whether symptomatic or picked up during health screening. There remains a widely held perception that VPB are prevalent in the general population, but frequent and complex VBP are not particularly common. The Copenhagen City Heart study and others have shown that $\leq 5\%$ of subjects have >300 VPB/24 h, >2 different VPB configurations, >2 couplets or more repetitive forms [32, 33].

At the discretion of the clinician, patients with VPB may or may not receive any further work-up; if they do, conventional echocardiography is the usual first-line investigation. Stress testing or coronary angiography may be performed in the presence of risk factors and/or clinical suspicion of IHD. VBP of right-ventricular origin may additionally instigate CMR to identify features of arrhythmogenic cardiomyopathy, although left-ventricu-

lar-type ectopy is no less compatible with the diagnosis. If this preliminary work-up is unremarkable, then the bases are often felt to have been covered and the patient is reassured.

The traditional tenet that unexplained VPB are benign is, however, based on a limited number of small-scale studies. One of the most widely cited followed 70 subjects for an average of 6.5 years. Healthy status was affirmed by non-invasive cardiovascular examination, but cardiac catheterisation of a subsample revealed significant coronary artery disease in 19%, suggesting that subclinical disease was not fully excluded. Nevertheless, the single instance of SCD and 1 death from cancer were less than that predicted by standardised mortality ratios, leading the investigators to infer that long-term prognosis in asymptomatic healthy subjects with VPB was similar to that of the healthy population [34]. Since the annual incidence of SCD in the general population is 1 in 1,000, this study and others have not been adequately powered to detect a difference in outcomes [1].

In contrast, among 2,727 men without coronary artery disease from the Framingham Heart Study, frequent or complex VPB were associated with a twofold increased risk of all-cause mortality [35]. The link between VPB and SCD was further strengthened by a prospective study of 15,637 apparently healthy white men, aged 35–57 years, followed up for an average of 7.5 years. The presence of any VPB on a resting 12-lead ECG was associated with 3-fold greater risk for SCD, which was further increased by characteristics such as frequency and complexity (adjusted relative risk = 4.25) [36]. Although VPB become more prevalent with age, there is some evidence that the prognostic significance is retained. In a 5-year follow-up study of 678 apparently healthy subjects aged 55–75 years, frequent VPB were a significant predictor of cardiovascular event rates (hazard ratio 2.85) after adjustment for conventional risk factors [37].

Other investigators have followed individuals with monomorphic VPB of right-ventricular origin, compatible with a diagnosis of idiopathic right-ventricular arrhythmia, to assess progression to ARVC. In a study of 61 such patients recontacted after 15 ± 2 years, there were no instances of SCD during follow-up; in 24 patients (51%), VPB were no longer present on Holter monitoring, and none attained a clinical diagnosis of ARVC. Although the study suggests a benign prognosis in a proportion of subjects with a specific type of VPB, interpretation of these data warrants several caveats. A forme fruste of ARVC cannot be excluded in this cohort. The sample number was small and the diagnostic work-up incomplete. A sub-

set of 11 patients underwent CMR, which, despite the use of an abbreviated protocol, showed focal abnormalities in 8 (73%) [38]. Phasic electrical activity is also recognised in ARVC, while the limited disease expression and favourable outcomes enjoyed by this sample are typical of familial disease [7].

The benign nature of right-ventricular outflow-tract tachycardia is also challenged by the development of spontaneous ventricular fibrillation or polymorphic ventricular tachycardia in a minority of patients, despite normal cardiac investigations. In the largest series to date, neither the number nor the coupling interval of the VPB distinguished patients at high arrhythmic risk [39]. It is also increasingly recognised that frequent VPB, including those originating from the right-ventricular outflow tract, may be associated with adverse changes in left-ventricular diastolic dimension, ejection fraction and B-type natriuretic peptide levels. Recovery has been documented following suppression of arrhythmia [40, 41].

Unexplained VPB therefore pose a quandary at both the bench and the bedside, with unanswered questions about aetiology and clinical management. One hypothesis of note is that unexplained VPB, at least in some cases, may represent formes frustes of ICVD. Frequent VPB as an isolated subphenotype is particularly well recognised in affected relatives with arrhythmogenic cardiomyopathy and familial catecholaminergic polymorphic ventricular tachycardia. The prevalence of clinically overt ICVD ranges from 1 in 500 for HCM to 1 in 1,000 for ARVC and 1 in 7,000 for long QT syndrome, but gene carriers with limited disease expression will be more common, comprising ~50% of first-degree relatives according to the common autosomal dominant inheritance pattern [1, 31]. Taken together, these observations suggest that incomplete expression of mutations implicated in ICVD, or common variants in the same genes exerting more modest effects, may contribute to unexplained VPB in the general population.

Of relevance here is the analogous scenario of repolarisation abnormalities on a 12-lead ECG, which – in the past – were widely presumed benign when observed in young athletes. Long-term follow-up demonstrated progression to clinically overt ICVD in a subset, occasionally with adverse outcome [42]. Similar studies have not been conducted for unexplained VPB and a genetic basis as such remains largely speculative. New tools are, however, needed to identify the subset of patients with unexplained VPB who are at risk of arrhythmic events and ventricular dysfunction.

Conclusion

At the time our 2006 review was published, I was firmly convinced that targeted evaluation – as advocated by my colleagues – was the optimal approach to the prevention of non-ischaemic SCD in the general population. Seven years later, my support has not wavered, but I am more conscious of the conundrum posed by diagnosis without reliable prognostication. One of the cornerstones of modern public health promotion is population screening, the purpose of which is to advance the time of diagnosis so that prognosis can be improved by earlier intervention. The advantages of screening programmes are much touted by clinicians, often without appropriate perspective.

Breast cancer screening by mammography is a topical example that illustrates some of the controversial aspects of such programmes – not from the standpoint of cost-effectiveness, which is a separate issue, but in terms of the risk/benefit ratio for individual participants. Often underplayed to the lay public is the potential for harm from repeated mammography per se, although it is well established that exposure to ionising radiation from diagnostic X-rays increases the lifetime risk of breast cancer [43]. At present, the focus of attention is the harm caused by overdiagnosis: the detection of early or subclinical disease that would not otherwise have come to attention in the lifetime of the individual. In breast cancer screening, the problem of overdiagnosis is exemplified (but not confined) to ductal carcinoma in situ, most cases of which will not develop into invasive cancer. The consequences of overdiagnosis of breast cancer may include mastectomy, and hormone, chemo- and radiotherapy, which diminish the quality of life for the individual without enhancing survival. Overdiagnosis would pose less of a problem if there were some means of recognising it, thereby preventing overtreatment. Unfortunately, not every case of screen-detected ductal carcinoma in situ represents overdiagnosis; among women receiving wide local excision only, around 10% will develop invasive breast cancer within 10 years [44, 45]. The key clinical challenge, then, is distinguishing women who will benefit from aggressive therapy from those who have non-progressive disease.

Pending a reliable means of prognostication, women undergoing screening for breast cancer are more likely to be overdiagnosed and overtreated than to have their lives saved. Yet both clinicians and screening participants are apt to view this trade-off as reasonable when preservation of life is at stake. What is less palatable to both parties is

the other limitation of screening: for women with screen-detected cancer, there is no guarantee of survival. In fact, screening appears to afford a mortality benefit to only 6.3% of women, and even this figure may represent an overestimate [44, 45].

Selective evaluation, as advocated to prevent SCD in the young, has the theoretical advantage over population screening of reducing, but not nullifying, the false-positive rate. Furthermore, the subgroups targeted are typically committed to undergoing assessment owing to concerns about their family history and/or symptoms. Since the recommended work-up itself is non-invasive, there is little potential for physical harm from ICVD diagnosis. Nevertheless, targeted evaluation to prevent SCD is subject to many of the same limitations as population screening programmes.

Scenarios that parallel overdiagnosis in breast cancer include the identification of phenotypically mild disease among relatives, or VPB and ECG abnormalities that remain unexplained despite comprehensive evaluation. A proportion of these individuals will eventually progress to clinically overt disease, and a subset thereof will be at risk of adverse outcomes, but a good many will not develop complications within their lifetimes. The key difference from breast cancer screening is that early diagnosis in ICVD seldom leads to overtreatment; the majority of individuals with early phenotypic expression will not, for example, receive device implants. Instead, the adverse consequences include anxiety, unnecessary medicalisation and lifestyle restrictions, such as disqualification from competitive sports: disadvantages to which physicians, individuals and families alike may be reconciled. The unacceptable here is the loss of screening participants to SCD, typically because their disease was considered too minor to warrant medical intervention. While mercifully rare, such tragedies do occur, particularly in arrhythmogenic cardiomyopathy and the inherited arrhythmia syndromes, in which mild clinical manifestations may belie significant arrhythmic risk. Again, the main hurdle is the need for reliable risk prediction once early diagnosis has been established.

The mammography experience is generalisable to all screening programmes as well as many other aspects of health care. Foremost among them is the need for less browbeating and proselytising zeal towards participants, and more circumspection; until the challenge of risk stratification has been solved, the net advantage of screening for any individual is modest. Yet screening may have less tangible, long-term benefits for the community that are best exemplified by the last 2 decades of experience in

ICVD. Evaluating the relatives of index cases has allowed gene identification studies, which in turn have shed light on underlying cellular and molecular mechanisms: insights that are now facilitating development of disease-modifying therapies. Furthermore, early diagnosis coupled with long-term follow-up offer a unique window on the natural history of these diseases, a key piece of the puzzle that will ultimately enable us to identify and treat at-risk individuals while others are reassured. Patients may be more altruistic than we appreciate and also more accepting of the limitations of current clinical practice, provided that we afford them the courtesy of transparency. As knowledge grows in tandem with an awareness of the extent of our ignorance, the time has surely come to replace paternalism in the doctor-patient relationship with a mutually empowering partnership.

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Appendix 1

Pilot Study

One hundred consecutive families attending the ICVD clinic over a 2-year period were included in the study. Post-mortem reports were obtained from pathologists. At the initial consultation, all relatives present were questioned about the presence of pre-monitory symptoms in the index case and the circumstances of his/her death. A detailed pedigree covering a minimum of three generations was compiled. Clinical evaluation of relatives comprised 12-lead ECG, signal-averaged ECG, two-dimensional echocardiography, exercise testing and ambulatory ECG monitoring. CMR studies and provocative challenge with ajmaline (to unmask the Brugada syndrome) were performed as appropriate.

Profile of Index Cases

The index cases were aged between 12 and 57 at the time of death (mean 31 ± 12 years). Twelve were athletes who participated in organized sports on a regular basis. Autopsy reports were available in 96 probands and untraceable in 2. In the remaining 2 cases, the family had declined a post-mortem at the time of the victim's death.

Post-mortem examination revealed obstructive coronary artery disease in 4, 3 of whom had additional evidence of thrombosis and/or infarction. One 46-year-old man, a heavy smoker, had a 50% mid-vessel stenosis in the left anterior descending artery.

Since there were no signs of acute occlusion or myocardial infarction, however, his death was classified as SADS. HCM was cited as the cause of death in 16%; ARVC in 28%, DCM in 4%, idiopathic fibrosis in 3%, myocarditis in 2%, MVP in 2% and SADS in 38%.

According to family and friends, 62% of the index cases had experienced cardiac symptoms prior to their death: syncope in 25%, palpitation in 24%, pre-syncope in 11%, chest pain in 10% and dyspnoea in 6%. A further 4 index cases had mentioned non-specific symptoms such as excessive fatigue, malaise and dyspepsia. One of the index cases with post-mortem evidence of DCM had been bed-bound with chronic unremitting fatigue for several months prior to his death.

Only 29 of 66 symptomatic index cases (44%) had sought medical attention. Of these, 15 (52%) had been assessed solely in the primary-care setting: by their family practitioner ($n = 14$) or at a local emergency department ($n = 1$). Two index cases with syncope complicated by seizure activity had received a neurological work-up; 1 patient was treated with anti-convulsant therapy and had therapeutic levels in his blood at the time of death. The other was awaiting a CT head scan when he died suddenly, 2 weeks after the initial event.

Twelve index cases were seen by a cardiologist prior to death. Of these, 11 had been referred for symptomatic profiling by their primary-care providers. The 12th was asymptomatic but had been under regular follow-up with a congenital heart disease specialist since childhood for repaired co-aortic of the aorta. He suffered SCD at the age of 15 with a post-mortem diagnosis of ARVC.

Eight index cases received a general cardiology opinion. One young man of 20 had palpitation and a short PR interval on 12-lead ECG, leading to a presumptive diagnosis of Lown-Ganong-Levine syndrome; post-mortem was unremarkable, with a default diagnosis of SADS. An 18-year-old boy under investigation for syncope had abnormal T wave morphology on his ECG but had been reassured; review of his ECG after death elicited a retrospective diagnosis of long QT syndrome. Two men in their 40s with pre-syncope episodes had received exercise tests in the months preceding their death and cleared; post-mortem revealed coronary thrombosis in one and apparent DCM in the other. Four others (age range 26–35) remained under investigation for palpitation and/or symptoms of impaired consciousness at the time of death, when post-mortem examination demonstrated ARVC ($n = 3$) and SADS ($n = 1$).

Three index cases were being worked up by specialists in cardiac rhythm management at the time of death. In 2 cases, investigations had shown non-specific abnormalities, but no firm clinical diagnosis had been established. Findings on autopsy were consistent with ARVC in one and SADS in the other. The remaining patient had presented with syncope and exercise-induced ventricular tachycardia. He was diagnosed with idiopathic right-ventricular outflow-tract tachycardia following an electrophysiological study, but died suddenly a few months later while awaiting ablation. Post-mortem again demonstrated ARVC.

Family History

In 52% of the cases, at least one other member of the extended family had died suddenly and unexpectedly prior to the death of the index case. Multiple instances of sudden premature death were documented in 25% of families.

Evaluation of Relatives

In several instances, familial assessment was strongly suggestive of ARVC despite the apparent absence of the characteristic histopathology on a coroner's post-mortem of the index case. This was true of 2 out of 4 probands with DCM, both MVP cases, both myocarditis cases, 2 out of 3 cases with idiopathic fibrosis, and 10 out of 37 SADS cases. In one of the index cases with presumed DCM, subsequent review of retained blocks and slides by an expert cardiac pathologist confirmed extensive fibrofatty replacement of the myocardium in both ventricles. Tissue was no longer available in most other cases, while sampling of the myocardium (particularly the right ventricle) was incomplete in the remainder.

Overall, familial evaluation of SADS victims was abnormal in 86%, with features of long QT syndrome ($n = 10$), Brugada syndrome ($n = 3$), ARVC ($n = 10$), pre-excitation ($n = 1$), LVNC ($n = 1$) or non-specific arrhythmia and ECG abnormalities ($n = 8$).

Selection Factors

Of 100 index cases, 90 (90%) had premonitory cardiac symptoms and/or a family history of SCD and/or participated in organised sports on a regular basis.

Comment

The disease representation in our pilot sample was skewed in comparison to national surveys of SCD in the young for a number of reasons. The relatively high prevalence of ARVC and SADS cases likely reflected both the special interests of our department and a perception amongst referring clinicians that familial assessment of these diseases was best conducted at tertiary centres. The proportion of HCM cases was lower than expected owing perhaps to growing confidence with familial evaluation among general cardiologists. A distinct explanation might also be invoked for the relative rarity of DCM among individuals who died suddenly from undiagnosed cardiac disease. Although SCD accounts for at least 30% of the overall mortality in DCM, it is seldom the first clinical manifestation. Most individuals with DCM present with symptoms and signs of heart failure, and, in the majority, a clinical diagnosis is readily established with conventional echocardiography. Of the 4 index cases with apparent DCM on post-mortem, the diagnosis was most likely ARVC in 2, while 1 patient had been unwell with fatigue and reduced exercise capacity for years before his death.

Consistent with previous reports, SADS appeared to be a heterogeneous entity that encompassed both inherited arrhythmia syndromes and heart muscle diseases. The recurrent finding of ARVC among relatives of index cases with apparent DCM, myocarditis, and SADS highlighted the critical role of the expert cardiac pathologist. Rigorous sampling and histology of the right ventricle may be necessary to detect the characteristic myocyte loss and fibrofatty replacement of ARVC. From the screening perspective, the high diagnostic yield from evaluation of the families of SADS victims was of paramount importance because it affirmed that these individuals were dying from cardiac disease, which might be amenable to diagnosis and treatment with timely specialist involvement.

Two thirds of the index cases in our series had experienced either cardiac or non-specific symptoms, but less than half of these individuals had sought medical attention. For the remainder, symptomatic status was based on the retrospective accounts of close friends and family members, suggesting that the noteworthy

66% might nonetheless be an underestimate. Of the patients who did report their symptoms to a physician, over half were seen solely in primary care, where assessment is usually limited to physical examination and a resting 12-lead ECG, which may miss both ARVC and inherited arrhythmia syndromes. Syncope complicated by seizure activity may also precipitate a neurological work-up when cardiac disease is, in fact, responsible.

Neither was a general cardiology assessment always adequate for the detection of these diseases. Expert interpretation of the 12-lead ECG is imperative in the diagnosis of inherited arrhythmia syndromes; rather than demonstrating unequivocal prolongation of the QT interval, many long QT syndrome patients have subtle or unusual variations in T wave morphology. Signal-averaged ECG and CMR are key components of the evaluation for suspected ARVC that may not be available outside tertiary centres. Our results further implied that early diagnosis of ARVC and its differentiation from idiopathic right-ventricular outflow-tract tachycardia were challenging even in the hands of cardiac electrophysiologists. Based on the index cases who suffered SCD while still under investigation, there appeared to be a case for urgent inpatient evaluation of individuals with unexplained syncope if a cardiac aetiology was suspected.

In spite of the referral bias, the major causes of SCD in the young (inherited heart muscle diseases and arrhythmia syndromes) were sufficiently represented in our pilot study to attempt extrapolation of the main findings. Our results supported selective evaluation of three high-risk subgroups to prevent, or reduce, SCD in the young: symptomatic individuals, families with a history of SCD and competitive athletes. Absent from our study as a cause of SCD were congenital anomalies of the coronary arteries, a post-mortem diagnosis that obviates the need for familial evaluation. A previous study, however, had shown that premonitory symptoms such as syncope and chest pain are not uncommon among individuals with anomalous coronaries.

Targeted evaluation therefore appears feasible and, when coupled with urgent specialist advice, might have enabled timely intervention in 90% of the index cases in this series. Integral to this global strategy would be the need to promote public awareness of cardiac symptoms and encourage primary-care physicians to refer high-risk individuals to cardiologists with expertise in the management of cardiomyopathies and inherited arrhythmia syndromes.

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