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Programmed ventricular stimulation predicts arrhythmic events and survival in hypertrophic cardiomyopathy

Konstantinos A. Gatzoulis [a,*,1], Stavros Georgopoulos [a,b,1], Christos-Konstantinos Antoniou [a,1], Aris Anastasakis [a,b,1], Polychronis Dilaveris [a,1], Petros Arsenos [a,1], Skevos Sideris [c,1], Dimitris Tsiachris [a,1], Stefanos Archontakis [a,1], Elias Sotiropoulos [c,1], Artemisia Theopistou [a,1], Ioannis Skiadas [c,1], Ioannis Kallikazaros [c,1], Christodoulos Stefanadis [a,1], Dimitrios Tousoulis [a,1]

[a] First Department of Cardiology and Electrophysiology Laboratory, Hippokration General Hospital, National and Kapodistrian University of Athens School of Medicine, Athens, Greece
[b] Unit of Inherited Cardiovascular Diseases (EKKAN), First Department of Cardiology, Greece
[c] State Department of Cardiology, Hippokration General Hospital, Athens, Greece

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ABSTRACT

Background: Sudden cardiac death (SCD) risk stratification in hypertrophic cardiomyopathy (HCM) in the context of primary prevention remains suboptimal. The purpose of this study was to examine the additional contribution of programmed ventricular stimulation (PVS) on established risk assessment.
Methods: Two-hundred-and-three consecutive patients with diagnosed HCM and ≥1 noninvasive risk factors were prospectively enrolled over 19 years. Patients were risk stratified, submitted to PVS and received an implantable cardioverter-defibrillator (ICD) according to then-current American Heart Association (AHA) guidelines and inducibility. Participants were prospectively followed-up for primary endpoint occurrence (appropriate ICD therapy or SCD). Contemporary (2015) AHA and European Society of Cardiology (ESC) guidelines were retrospectively assessed.
Results: During a median follow-up period of 60 months the primary endpoint occurred in 20 patients, 19 of whom were inducible and received an ICD. Overall, 79 patients (38.9%) were inducible and 92 patients (45.3%) received an ICD (PVS sensitivity = 95%, specificity = 67.2%, positive predictive value = 24%, negative predictive value = 99.2%). AHA and ESC guidelines application misclassified 3 and 9 primary endpoint-meeting patients, respectively. Inducibility was the most important determinant of event-free survival in multivariate Cox regression (hazard ratio = 33.3). A combined approach of ESC score ≥ 6% or AHA indication for ICD with PVS inducibility yielded absolute sensitivity and negative predictive value, the former at a more cost-effective and specific way.
Conclusions: Inducibility at PVS predicts SCD or appropriate device therapy in HCM. Non-inducibility is associated with prolonged event-free survival, while the procedure was proven safe. Reintegration of PVS into established risk stratification models in HCM may improve patient assessment.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a common nonischemic cardiomyopathy with a prevalence of 1:500 up to 1:200 adults [1,2]. Sudden cardiac death (SCD) remains the most serious complication of the disease, with annual occurrence rates ranging from 6% down to 0.5% following introduction of implantable cardioverter-defibrillators (ICDs) [3].

Although several risk stratification methods for primary prevention have been developed and are currently included in the American and European guidelines [4,5], published data suggest that there still exists a population suffering SCD while deemed to be at low risk [6,7]. Furthermore, a number of significant complications have been observed when implanting an ICD in young patients with a need for multiple replacements in a lifelong commitment therapeutic approach [8,9]. Consequently, several alternative methods are explored for the improvement of risk stratification algorithms [10–14].

Programmed ventricular stimulation (PVS) has largely been abandoned in contemporary HCM SCD risk stratification [4,5], considered

* Corresponding author at: 181 Dorieon str., P.O. Box 175, Postcode 19009 Drafi, Attica, Greece.
E-mail address: kgatzoul@med.uoa.gr (K.A. Gatzoulis).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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clinically irrelevant, not specific enough and lacking additional prognostic significance over noninvasive prognosticators [15,16]. In contrast to these positions, older studies supported the use of PVS in HCM [17,18].

It has also been claimed that programmed ventricular stimulation (PVS) may add prognostic information and guide therapy when some single "weak" risk factors (such as short and isolated runs of nonsustained ventricular tachycardia or an abnormal blood pressure response to exercise)[2] are encountered [14]. Furthermore, a comprehensive electrophysiology study may assist in clarifying the underlying mechanism of "unexplained" syncope in this population.

It was thus attempted to study the prognostic value of a standardized PVS protocol in better defining the high risk HCM patient most likely to benefit from ICD therapy.

2. Methods

2.1. Patients

Between December 1995 and May 2015, 203 consecutive HCM patients were referred to our Electrophysiology Laboratory by the Unit of Inherited Cardiovascular Diseases (EKKAN), where they had been prospectively evaluated and followed-up. HCM diagnosis was confirmed by the Unit and clinical risk stratification was performed, based on the 2003 ESC/AHA and AHA 2011 guidelines. In the 1995–2003 period, the model later established by the 2003ESC/AHA guidelines was already being implemented. HCM was diagnosed according to standard contemporary AHA criteria at the time and diagnosis was retrospectively confirmed to comply with the 2014 ESC guidelines [5]. Left ventricular outflow tract obstruction was diagnosed if the intracavitary pressure gradient was ≥30 mm Hg on spectral Doppler analysis during the Valsalva maneuver. All patients presented at least one conventional noninvasive risk factor for SCD, thus being intermediate to high risk by the aforementioned risk stratification algorithms. All referred patients were then prospectively enrolled in the study and further SCD risk stratification was attempted by means of invasive PVS.

Coronary heart disease was diagnosed following either past history of acute myocardial infarction or coronary angiography revealing significant (>70% of lumen) stenosis. Familial HCM was defined as the presence of a first or second degree relative with diagnosed disease.

SCD risk factors were documented according to the presence of the following criteria:

1. Family history of ≥1 HCM-related sudden death in first degree relatives at any age or SCD of undiagnosed cause at age <40 years
2. ≥1 recent episodes of unexplained syncope and/or presyncope
3. One or more nonsustained ventricular tachycardia (nsVT) episodes (lasting at least 3 QRS complexes at a rate of ≥100 beats per minute) on 24-hour ambulatory (Holter) ECG
4. Hypotensive/attenuated (<20 mm Hg increase) blood pressure response to exercise (only assessed in those younger than 50 years of age)
5. Massive left ventricular hypertrophy (wall thickness ≥ 30 mm) by echocardiography

All patients were echocardiographically assessed at enrollment.

2.2. Electrophysiology study and programmed ventricular stimulation protocol

All patients underwent PVS while antiarrhythmic medications, except for beta-blockers, were discontinued for ≥5 half-lives before the study. In patients on amiodarone the drug was discontinued at least 30 days before PVS. A standardized protocol which remained constant during the whole study period was used. It consisted of up to three extrastimuli (S2S3S4) delivered at two paced cycle lengths (550 ms and 400 ms) at the right ventricular apex and right ventricular outflow tract. Extrastimuli were applied after six-beat drive trains with a 3-second interdrive pause. Ventricular extrastimuli were introduced beginning late in diastole and moved progressively earlier in 10 ms steps until either ventricular refractoriness or a coupling interval of 200 ms was reached. In case patients complained of not tolerating the tachycardia induced by PVS, interdrive pause was increased up to 6 s.

The arrhythmia induced was defined as sustained monomorphic VT when sharing a uniform morphology of QRS complexes with a rate between 120 and 220 bpm, while persisting ≥30 s (or shorter, if termination was necessary due to hemodynamic instability). Faster rates of regular unimorphic VT (≥220 bpm), not permitting to readily distinguish QRS complexes from T waves were defined as ventricular flutter, but were included in the monomorphic VT category. Polymorphic VT (PVT) was diagnosed when constantly changing QRS morphology and axis were observed, eventually degenerating to ventricular fibrillation (VF).

In order to define the presence of sinus node or/and atrioventricular conduction system disease, we assessed the corrected sinus node recovery and sinoatrial conduction times, the chronotropic response to atropine, the atrioventricular nodal conduction, His-Purkinje function and the point of Wenckebach and 2:1 atrioventricular block during right atrial pacing, according to previously described protocols [19]. Briefly, corrected sinus node recovery time ≥525 msec, sinoatrial conduction time ≥ 140 msec, highest sinus rate after 1.5 mg of intravenous atropine ≤90 bpm, His-V interval ≥60 msec, Wenckebach point at cycle lengths ≥500 msec, 2:1 atrioventricular conduction at cycle lengths ≥400 msec, as well as an effective refractory period of the atrioventricular node ≥450 msec were considered diagnostic for the presence of either production (the first three) or/and conduction abnormalities.

All patients gave informed consent for inclusion in the present study and study protocol was approved by our institution's ethics committee (Hippokration G.H. Committee of Bioethics) as conforming to the ethical guidelines of the 1975 Declaration of Helsinki.

2.3. Device implantation and programming

Recommendations for ICD implantation were made using contemporary AHA guidelines at any given time as guidance. ICDs were usually offered if patients had ≥2 clinical risk factors between the years 1995–2011 and according to the 2011 AHA guidelines afterwards [4]. ICD implantation decisions were made on a case by case approach, taking also into account clinical features, EP study results as well as the fully informed patients' wishes. Regarding ICD programming, the shock-only VF zone was >200 beats per minute in all cases, with an antitachycardia pacing zone with 3–4 burst and ramp pacing attempts for VTs in the 180–200 bpm range, followed by low-energy cardioversion attempts. Detection intervals were the longest possible for the device model at the time of implantation. In patients with syncope as the only risk factor, a pacemaker was offered in clear-cut electrophysiologic evidence of bradyarrhythmic mechanism. Following implantation, patients were placed on an optimized heart rate-lowering regimen.

2.4. Follow-up

Patients were followed-up by the Unit of Inherited Cardiovascular Diseases until the primary or secondary endpoints occurred. The primary endpoint consisted of the occurrence of either SCD (unexpected death occurring either within one hour after symptom onset or during sleep) or the SCD surrogate of appropriate, as verified by stored electrograms, device therapy (shock or antitachycardia pacing). Events with initial unsuccessful antitachycardia pacing followed by cardioversion were classified as appropriate shock therapies.

Adjudication process included tracing review by two non-treating electrophysiologists (i.e. not having implanted the device). In case of ambiguity a third senior electrophysiologist (K.A.G.) reviewed the tracing and his interpretation was considered final.

Although this approach may overestimate true risk (self-terminating arrhythmias), we attempted to reduce this effect by programming long detection intervals and high detection rates. Secondary endpoint included non-cardiac death, cardiac non-sudden death and cardiac transplantation. Careful adjudication of the cause of death was performed to ensure that the secondary endpoint only included deaths irrelevant to the process comprising the primary endpoint (ICD activation/SCD).

2.5. Statistics

Independent samples Student's t-test was used for parametric and Fisher's exact test for categorical variables. Normality of distributions for parametric variables was tested by means of the Shapiro–Wilk test and, in case of non-normality, a two-step transformation procedure was pursued, as previously described [20]. If this did not achieve normalization, non-parametric tests were performed (Mann–Whitney *U* test).

Multivariate Cox regression was used in order to assess and compare impact of parameters on survival free from primary endpoint occurrence. In order to ascertain the validity of hazard proportionality hypothesis, both the log(−log(survival)) vs log(time) graph method (categorical covariates) and time-dependent Cox covariate analysis (all variables) were used (parallelity of lines and $p > 0.05$, respectively). Given the number of events ($n = 20$) and to avoid model overfitting, a four-variable model was used in the multivariate event-free survival analysis.

Net reclassification improvement was used to assess the effect of adding PVS results to the established models proposed by AHA and ESC guidelines. Net reclassification improvement was used as a statistical criterion for the assessment of the effects of combining several tests on patient evaluation. Its most significant advantages over the receiver–operator characteristic curve approach are [21,22] the ability to be used in the case of binary test results, the ability to take into account the effects of even minor contributors, and the assessment of clinical relevance of the additions (whether it alters patient risk level).

Of note, both components of net reclassification improvement, event and nonevent, were reported separately given that they express how the addition of a test improves/worsens classification regarding false negatives (event) and false positives (nonevent).

A p-level of <0.05 was considered statistically significant in all cases. In the case of parametric variables, all p-values presented have been calculated following normalization or use of non-parametric tests.

SPSS 23 statistics software (IBM — Armonk, NY, U.S.A.) was used for all analyses, except for net reclassification improvement calculation, where STATA 13 software (StataCorp — College Station, TX, U.S.A.) was used instead.

Data were analyzed by K.A.G., S.G., C.K.A. and P.A.

[2] Abbreviation list: 1. AHA: American Heart Association, 2. ESC: European Society of Cardiology, 3. HCM: Hypertrophic cardiomyopathy, 4. ICD: Implantable cardioverter-defibrillator, 5. nsVT: non-sustained ventricular tachycardia, 6. PVS: Programmed ventricular stimulation, 7. PVT: Polymorphic ventricular tachycardia, 8. SCD: Sudden cardiac death, 9. VF: Ventricular fibrillation, 10. VT: sustained monomorphic ventricular tachycardia