The relation of ventricular arrhythmia electrophysiological characteristics to cardiac phenotype and circadian patterns in hypertrophic cardiomyopathy

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Background
The triggers of ventricular arrhythmias (VAs) leading to sudden cardiac death in hypertrophic cardiomyopathy (HCM) are ill defined. We sought to examine the electrophysiological characteristics of VAs in HCM and study their relation to cardiac phenotype and circadian patterns using stored intracardiac electrocardiograms from implantable cardioverter defibrillators (ICDs).

Methods and results
A single centre, observational cohort study of 230 consecutively evaluated ICD recipients with HCM (median age 42 years, 97% primary prevention, 51% with anti-tachycardia pacing (ATP)). Fifty-six non-clustered VAs (39 initially treated with ATP and 17 with shocks) from 29 patients were analysed. Monomorphic ventricular tachycardia was the culprit arrhythmia in 86% of cases, ventricular fibrillation/flutter in 9%, and polymorphic ventricular tachycardia in 5%. Prior to the onset of VA the rhythm was sinus in 67%, atrial fibrillation/flutter in 19%, and 15% were paced ventricularly; tachycardia (cycle length < 600 ms) was present in 25%. Ventricular arrhythmias were triggered by premature ventricular complexes (PVCs) in 72%, which were late-coupled (84%). Short-long-short initiation was seen in 2% and 26% of VAs were sudden-onset without preceding PVCs. Ventricular arrhythmia peaked at midday (with 20% occurring between 2300 and 0700), on Sundays and in May. The cardiac phenotype and time of the day did not predict the mode of initiation. Age at ICD implantation was the only independent predictor of VA cycle length (linear regression coefficient 0.67, 95% CI 0.02–1.32, \( P = 0.04 \)). Anti-tachycardia pacing terminated 67% of VAs, but patients with ATP therapy had a similar incidence of appropriate shocks (log-rank test \( P = 0.25 \)) and syncope (log rank \( P = 0.23 \)) to patients with shock as initial therapy.

Conclusions
Most VAs are monomorphic ventricular tachycardias triggered by late-coupled PVCs. They are frequently terminated by ATP, but ATP does not reduce the frequency of ICD shocks. Younger HCM patients have more rapid VAs, which may explain the peak of sudden cardiac death in early adulthood. The circadian periodicity is different from that observed in ischaemic heart disease, and is likely to relate to the distinct character of the arrhythmogenic substrate in HCM and its modulators.

Keywords
Implantable cardioverter defibrillator • Ventricular arrhythmia • Hypertrophic cardiomyopathy • Circadian rhythm • Electrocardiography • Sudden cardiac death
**Introduction**

Hypertrophic cardiomyopathy (HCM) is a frequent cause of arrhythmic sudden cardiac death (SCD), but the pathophysiological triggers of these events are ill understood. In the era before implantable cardioverter-defibrillators (ICDs), data from fortuitous electrophysiologic recordings suggested that ventricular fibrillation (VF) can be precipitated by runs of ventricular tachycardia (VT) or rapid atrial fibrillation. Premature ventricular complexes (PVCs) have been noted just prior to the onset of ventricular arrhythmia (VA) in HCM patients and act as triggers in other cardiac diseases. However, the contribution of these electrical triggers and their relation to the cardiac phenotype has not been systematically examined in HCM. Now that ICD therapy is routine in HCM and their relation to the cardiac phenotype has not been systematically considered at high risk in the presence of risk factors other than abnormal loading conditions or in accordance with criteria for the diagnosis of familial disease in patients with at least one first-degree relative with an unequivocal diagnosis. Patients with Friedreich's ataxia, Noonan's syndrome, and metabolic disorders were excluded. All patients aged ≥ 16 years of age at the time of device implantation were included.

**Methods**

**Study design**

A single centre, observational, retrospective cohort design was used. The study conforms to the principles of the Helsinki declaration. All authors have read and agreed to the manuscript as written.

**Study population and design**

The study cohort consisted of all consecutively evaluated patients with HCM in a dedicated cardiomyopathy clinic at The Heart Hospital (London, UK) between 1 April 2003 and 1 June 2009 who underwent ICD implantation. This cohort is included in a recently published study. Hypertrophic cardiomyopathy was defined as left ventricular hypertrophy (left ventricular wall thickness ≥ 15 mm) in the absence of abnormal loading conditions or in accordance with criteria for the diagnosis of familial disease in patients with at least one first-degree relative with an unequivocal diagnosis. Patients with Friedreich's ataxia, Noonan's syndrome, and metabolic disorders were excluded. All patients aged ≥ 16 years of age at the time of device implantation were included.

**Patient assessment, risk stratification, and implantable cardioverter defibrillator implantation**

Patients were evaluated using electrocardiography (resting and ambulatory), echocardiography, and exercise testing as previously described. Survivors of SCD and patients with sustained ventricular tachyarrhythmia received an ICD for secondary prevention. Implantable cardioverter defibrillators were implanted for primary prevention of SCD in accordance with international guidelines. A minority were considered at high risk in the presence of risk factors other than abnormal loading conditions or in accordance with criteria for the diagnosis of familial disease in patients with at least one first-degree relative with an unequivocal diagnosis.

**Table 1 Clinical characteristics at time of implantable cardioverter defibrillator implantation**

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>All (n = 230)</th>
<th>Shock as initial therapy (n = 112)</th>
<th>ATP as initial therapy (n = 118)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex; n (%)</td>
<td>149 (65%)</td>
<td>71 (63%)</td>
<td>78 (66%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Age at implant; median years (IQR)</td>
<td>42 (33–55)</td>
<td>41 (29–53)</td>
<td>46 (35–58)</td>
<td>0.01</td>
</tr>
<tr>
<td>Primary prevention; n (%)</td>
<td>224 (97%)</td>
<td>111 (99%)</td>
<td>113 (96%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Family history of HCM; n (%)</td>
<td>119 (52%)</td>
<td>62 (55%)</td>
<td>57 (48%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Family history of SCD; n (%)</td>
<td>107 (48%)</td>
<td>57 (51%)</td>
<td>52 (44%)</td>
<td>0.30</td>
</tr>
<tr>
<td>NYHA III/IV; n (%)</td>
<td>20 (9%)</td>
<td>11 (10%)</td>
<td>9 (8%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Syncope; n (%)</td>
<td>83 (37%)</td>
<td>38 (34%)</td>
<td>45 (38%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Myectomy; n (%)</td>
<td>30 (13%)</td>
<td>18 (16%)</td>
<td>12 (10%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Alcohol septal ablation; n (%)</td>
<td>9 (4%)</td>
<td>7 (6%)</td>
<td>2 (2%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Amiodarone; n (%)</td>
<td>54 (24%)</td>
<td>27 (24%)</td>
<td>27 (23%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Sotalol; n (%)</td>
<td>5 (2.2%)</td>
<td>2 (1.8%)</td>
<td>3 (2.5%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Abnormal BPRE; n (%)</td>
<td>60 (27%)</td>
<td>38 (34%)</td>
<td>23 (20%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter; n (%)</td>
<td>49 (21%)</td>
<td>27 (24%)</td>
<td>22 (19%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia; n (%)</td>
<td>111 (48%)</td>
<td>45 (40%)</td>
<td>66 (56%)</td>
<td>0.02</td>
</tr>
<tr>
<td>PVC/24 h; median (IQR)</td>
<td>68 (13–317)</td>
<td>49 (7–314)</td>
<td>89 (15–331)</td>
<td>0.19</td>
</tr>
<tr>
<td>Left atrial diameter; mean mm ± SD</td>
<td>47 ± 9</td>
<td>47 ± 9</td>
<td>47 ± 9</td>
<td>0.62</td>
</tr>
<tr>
<td>LVOTG ≥ 50 mmHg; n (%)</td>
<td>59 (26%)</td>
<td>22 (20%)</td>
<td>37 (31%)</td>
<td>0.06</td>
</tr>
<tr>
<td>MLWVT; mean mm ± SD</td>
<td>22 ± 6</td>
<td>22 ± 6</td>
<td>22 ± 6</td>
<td>0.84</td>
</tr>
<tr>
<td>MLWT ≥ 30 mm; n (%)</td>
<td>26 (12%)</td>
<td>14 (13%)</td>
<td>12 (10%)</td>
<td>0.73</td>
</tr>
<tr>
<td>FS; mean % ± SD</td>
<td>37 ± 9</td>
<td>38 ± 10</td>
<td>37 ± 9</td>
<td>0.35</td>
</tr>
</tbody>
</table>

PVC: premature ventricular ectopic; MLWVT: maximal left ventricular wall thickness; LVOTG, left ventricular outflow tract gradient; BPRE: blood pressure response to exercise; FS: fractional Shortening.

*aNine additional patients had a myectomy post ICD implantation.

*bOne additional patient had alcohol septal ablation post ICD implantation. One patient had a myectomy post alcohol septal ablation.

*cPermanent/persistent/paroxysmal.

*dIn those patients with >1 ambulatory monitor, the maximum recorded ectopic burden was used.
than those specified by the current guidelines, e.g. exercise-induced non-sustained VT. Implantable cardioverter defibrillator implantation was performed using conventional methods. Treatment zones, anti-tachycardia pacing (ATP), and anti-bradycardia pacing were programmed on an individual patient basis.

**Classification of implantable cardioverter defibrillator therapies**

Implantable cardioverter defibrillator interrogation was routinely performed every 6 months or earlier if there was a clinical event. All devices had the capacity to store intracardiac electrograms and therapies were independently reviewed by two of the authors (C.O. and P.L.) using previously published criteria. Therapy was considered appropriate if the treated tachyarrhythmia was ventricular in origin. Ventricular fibrillation or flutter was defined as a VA with a regular or irregular polarity, amplitude and morphology with a mean cycle length of \( \leq 240 \text{ ms} \). VT was defined as a VA with a regular (monomorphic) or irregular (polymorphic) polarity, amplitude, and morphology with a mean cycle length of \( >240 \text{ ms} \). All other therapies were considered inappropriate.

The mode of VA initiation was determined using the methodology described by Saeed et al. Briefly, ventricular complexes with a different morphology from the baseline rhythm and a coupling interval \(<90\%\) of the preceding sinus or paced cycle length were classified as PVCs. The first complex of monomorphic VT was classified as a PVC if its morphology was different from the subsequent VA complexes. In cases where the first complex of monomorphic VT was morphologically similar to the subsequent arrhythmia complexes and in cases of polymorphic VT, the first complex was still considered a PVC if its coupling interval was \( >110\% \) of the ensuing VT mean cycle length. In cases of VT after paced ventricular beats, pacing was considered inappropriate if there was undersensing of the native R-wave. Pause-dependent initiation of VT was defined as the presence of a short-long-short sequence immediately before a VA (intervals with a duration of \( <80\% \) of mean baseline cycle length were considered short; intervals \( >120\% \) of mean baseline cycle length were considered long). The application of these rules is illustrated with examples in the Results section.

For each treated spontaneous VA, the following parameters were determined:

(i) date and time
(ii) treatment with class III anti-arrhythmic medication at the time of device therapy
(iii) mean cycle length of the baseline rhythm preceding the arrhythmia
(iv) baseline rhythm
(v) mode of initiation: sudden-onset without preceding PVCs, PVC-dependent, pause-dependent, or relating to inappropriate ventricular pacing
(vi) first ventricular complex coupling interval (the interval between the first beat of VT and the previous beat for sudden-onset arrhythmias; the first PVC and the previous beat for arrhythmias initiated by ventricular pacing)
(vii) prematurity index: ratio of first ventricular complex coupling interval and the immediately preceding cycle length. Premature ventricular complexes with a prematurity index of \( \geq 0.5 \) were classified as late-coupled
(viii) mean VA cycle length (10 beats before therapy)
(ix) effect of treatment.

![Figure 1](https://academic.oup.com/europace/article-abstract/14/5/724/473567/14574475867) by guest on 11 April 2019

**Figure 1** Kaplan–Meier survival curves. (A) Shows freedom from appropriate anti-tachycardia pacing in 118 hypertrophic cardiomyopathy patients whose devices had programmed anti-tachycardia pacing therapy. Freedom from appropriate shocks in 230 patients treated with implantable cardioverter defibrillator is shown in (B). (C) Shows freedom from appropriate shocks, stratified according to initial therapy (anti-tachycardia pacing versus shock).
Ventricular arrhythmias with an identical mode of initiation and cycle length with ≤40 ms variation within the same 24-h period in a particular patient were interpreted as single events as previously described.\(^\text{15}\)

**Statistical analysis**

SPSS (v17.0) and STATA (v10) were used for all statistical analyses. A two-sided \(P\) value <0.05 was considered significant. Normally distributed continuous data are expressed as mean ± standard deviation (SD) and as median and interquartile range (IQR) for non-normally distributed data. The percentage of categorical data is shown in parentheses. Means were compared using the Student’s \(t\)-test, one-way analysis of variance, and the Mann–Whitney U-test depending on the data characteristics. The \(\chi^2\) test and Fisher’s exact test was used for comparison of categorical data. The \(\chi^2\) goodness of fit test was used to compare observed to hypothesized proportions.

Time-to-event analyses were carried out using first-appropriate ATP, first-appropriate ICD shock, and syncope as separate independent endpoints. The follow-up period was calculated from the date of device implantation to the endpoint of interest. In patients without an event, the follow-up period extended to the most recent ICD evaluation or censoring event up to January 2010.

The association between pre-specified baseline clinical characteristics and the mode of VA initiation and cycle length was examined using the generalized estimating equations technique, which takes...
into account the correlation among the multiple VAs contributed by each patient. A univariable analysis was first carried out and predictors with a significance level of <20% were included in a multivariable model.

A harmonic regression technique was used to model the periodicity of VAs occurring at different hours of a day, days of the week, and months of a year. The general harmonic regression equation is given by

$$X(t) = \mu + \sum_{i=1}^{p} \alpha_i \sin(\omega_i t) + \sum_{i=1}^{p} \beta_i \cos(\omega_i t) + \varepsilon_t, \quad 0 \leq t \leq T$$

where $X(t)$ is the observed value at time $t$, $p$ is the number of harmonics, $\mu$ is the intercept, $\alpha$ and $\beta$ are the coefficients of sine and cosine terms, $\omega = 2\pi/T$ is the angular frequency, and $\varepsilon_t$ is the error term. The stepwise (forward inclusion) method was applied to select the number of pairs of sine and cosine terms (i.e. number of harmonics that improve the fit of the model) to develop a third-order harmonic regression model. The model was fitted with the ordinary least-squares method. The F-test was used to test the overall significance of the model and the t-test to examine the significance of the individual coefficients of sine and cosine terms.

### Results

#### Baseline clinical characteristics

The study cohort consisted of 230 patients: 224 (97%) received an ICD for primary prevention and 6 (3%) for secondary prevention (19 patients were excluded because access to their complete medical records was not possible). In 118 patients (51%), the device was programmed to deliver ATP in the VT therapy zone as an initial therapy and the remainder had a VF therapy zone only with a shock as initial therapy. The clinical characteristics of the cohort at the time of ICD implantation are shown in Table 1. Two hundred and nine patients (91%) had an atrial tachyarrhythmia. Eighteen patients (8%) at risk of SCD had concurrent heart failure symptoms and received cardiac resynchronization therapy (CRT) at the time of first implant: 8 of 18 (44%) patients had impaired systolic function and 10 of 18 (56%) had preserved systolic function. The latter group received CRT as part of a randomized trial (ClinicalTrials.gov identifier: NCT00504647).

#### Incidence of appropriate anti-tachycardia pacing

The 118 patients with ICDs programmed to deliver ATP were followed up for 287 patient-years (median: 2.3 years, IQR 1.0–3.9 years) during which 26 patients (22%) received appropriate ATP (9.1%/year; 5-year cumulative incidence 41%, 95% CI 25–57); Figure 1A. The median time from implant to first-appropriate ATP was 0.8 years (IQR 4.8 months to 2.3 years, range 31 days to 4.8 years). Ventricular arrhythmias treated by ATP had a mean cycle length of 310 ± 29 ms. Of the 39 VAs treated with ATP, 26 (67%) were terminated by ATP, 6 (15%) required a shock for termination following ATP, and 7 (18%) terminated spontaneously after unsuccessful ATP. A single burst of ATP was delivered to 82% of arrhythmias, two bursts to 11%, and three bursts to 7% with 4–10 pacing stimulations at a rate of 81–88% of the arrhythmia cycle length.

#### Incidence of appropriate shocks

During a follow-up period of 676 patient-years (median: 3 years, IQR 1.4–4.3 years), 17 patients (7%) received appropriate ICD shocks (2.5%/year; 5-year cumulative incidence 15%, 95% CI 7–23; Figure 1B). The median time from implant to first-appropriate ICD shock was 2.0 years (IQR 4.7 months to 3.7 years, range 35 days to 4.8 years). Ventricular arrhythmias treated with shocks had a mean cycle length of 251 ± 39 ms. The mean shock energy was 33.8 J (minimum: 21 J, maximum: 41 J). The majority of arrhythmic events (75%) were terminated by a single shock. In 11 patients, four VAs required multiple shocks for termination: two patients [maximal wall thickness (MWT) 36 and 16 mm].

![Figure 2](https://academic.oup.com/europace/article-abstract/14/5/724/473567/10.1093/europace/epq053/1157867?download=true)
Ventricular arrhythmias in HCM

The incidence of appropriate ICD shocks was similar in patients with programmed ATP compared with those with VF-only therapy (log-rank test \( P = 0.25 \)). The Kaplan–Meier curve is shown in Figure 1C. Twelve patients (5%) experienced syncope during follow-up. There was no difference in the incidence of syncope in patients with ATP therapy compared with those with a VF zone only [eight (7%) patients and four (4%) patients, respectively, log rank \( P = 0.23 \)].

**Characteristics of treated ventricular arrhythmias**

In total, 56 VAs (39 treated with ATP and 17 with shocks) in 29 patients were included in the analysis. Four patients had clustering of VAs with an identical mode of initiation and ≤40 ms cycle length variation within the same 24 h period (two patients had two VAs in 24 h, one patient had five VAs in 24 h, and another patient had two VAs in 24 h on three separate occasions, and three VAs on a single occasion; these were considered as single events in the analysis).

The baseline rhythm prior to the development of VA was sinus in 67%, atrial fibrillation/flutter in 19% with ventricular pacing in 15%. The mean cycle length of the baseline rhythm was 798 ± 229 ms (range 374–1271 ms). Baseline rhythm tachycardia (cycle length <600 ms) was present in 25%. The median first ventricular complex coupling interval was 488 ms (IQR 407–645 ms, range 248–1388). The median VA cycle length was 292 ms (IQR 270–319 ms; range 181–387 ms). Monomorphic ventricular tachycardia was the culprit arrhythmia in 86% of cases, followed by ventricular fibrillation/flutter in 9%, and polymorphic ventricular tachycardia in 5% (\( P < 0.0001 \)). The mean cycle length of monomorphic ventricular tachycardias was 300 ± 27 ms, 338 ± 52 ms for polymorphic ventricular tachycardias, and 198 ± 17 ms for ventricular fibrillation/flutter (\( P < 0.0001 \)). None of the episodes of ventricular fibrillation/flutter were secondary to degenerated rapid atrial fibrillation or ventricular tachycardia.

**Mode of initiation of treated ventricular arrhythmias**

Initiation of VA was PVC dependent in 72%, sudden-onset without preceding PVCs in 26%, and pause dependent in 2% (\( P = < 0.0001 \)). We did not identify any cases of VAs caused by inappropriate ventricular pacing. Examples of these modes of initiation are shown in Figure 2. In cases of PVC-dependent initiation, the median coupling interval was 521 ms (IQR 408–885 ms, range 248–1063 ms) and the initiating PVC was late-coupled (prematurity index >0.5) in 84% of the cases. The initiating PVC had a different morphology from the ensuing VA in 59% of cases.

**Intra-patient ventricular arrhythmia characteristics**

Fourteen of the 29 (48%) patients with treated VAs had multiple events (range 2–8 episodes, mode 2 episodes; the initiation was not available for one patient). Four of the 13 (31%) patients with

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**Figure 3** The diurnal, weekly, and monthly variation in the incidence of treated ventricular arrhythmias. Red circles represent the observed frequency, and the blue lines represent predicted events derived from the third-order harmonic regression equations. The diurnal variation is shown in (A) and the estimated third-order harmonic regression model was \( X(t) = 2.43 - 1.07 \sin(\omega t) - 1.05 \cos(\omega t) - 0.31 \sin(2\omega t) + 0.09 \cos(2\omega t) + 0.58 \sin(3\omega t) - 1.35 \cos(3\omega t), 0 < t \leq 24 \), where \( \omega = 2\pi/24 \). The weekly variation is shown in (B), and the estimated equation of the model was \( X(t) = 7.98 + 0.87 \sin(\omega t) + 1.06 \cos(\omega t) + 0.99 \sin(2\omega t) + 0.72 \cos(2\omega t) - 2.66 \sin(3\omega t) + 2.22 \cos(3\omega t), 0 < t \leq 7 \), where \( \omega = 2\pi/7 \). A third-order harmonic regression model was fitted to predict the periodic structure of ventricular arrhythmia occurring at different months of the year (C). The estimated equation of the model was: \( X(t) = 4.93 + 0.65 \sin(\omega t) - 2.05 \cos(\omega t) - 0.33 \sin(2\omega t) + 0.07 \cos(2\omega t) + 1.12 \sin(3\omega t) + 1.18 \cos(3\omega t), 0 < t \leq 12 \), where \( \omega = 2\pi/12 \).
multiple VAs exhibited a single mode of initiation, while the majority (69%) had VAs initiated by more than one mechanism.

Circadian variation of the incidence of ventricular arrhythmias

There was a peak incidence of VAs at midday with a secondary peak in late afternoon (third-order harmonic regression model F-test $P < 0.001$ and $R^2 = 0.71$). Eleven VAs (20%) occurred during potential sleeping hours (2300 to 0700)\(^\text{17}\). The weekly variation showed a highest incidence of VAs on Sundays (third-order harmonic regression model F-test $P < 0.001$, $R^2 = 0.71$). With regard to monthly variability, the peak incidence was observed in May (third-order harmonic regression model F-test $P < 0.001$ and $R^2 = 0.85$). These findings are illustrated in Figure 3.

Determinants of premature ventricular complex initiation and ventricular arrhythmia cycle length

The univariable and multivariable analyses are shown in Tables 2 and 3. We did not identify any independent predictors of PVC initiation. Ventricular arrhythmia cycle length was directly proportional to age at ICD implantation, which was the only independent predictor of VA cycle length.

Discussion

The analysis revealed that late-coupled PVC initiated the majority of VA, which were primarily monomorphic and occurred during daytime with a peak incidence on Sundays and in May. Age at time of device implantation was an independent determinant of VA cycle length.

In common with other cardiac diseases,\(^6–8\) the majority of VA in HCM were triggered by PVCs. Premature ventricular complexes are seen in 80–90% of HCM patients, with 12–24% having $>30$/h.\(^18\) However, despite the daily occurrence of PVCs and the constant presence of an arrhythmic myocardial substrate that predisposes to conduction block and re-entry,\(^2\) the overall incidence of VA in most reported HCM populations is paradoxically low.\(^3,9–22\) This suggests that the probability that a PVC will initiate a VA is dependent on transient pathophysiological factors such as maladaptive automatic responses, myocardial ischemia, and left ventricular outflow tract obstruction which modulate the arrhythmogenic potential of the myocardial substrate.\(^2\) The intra-patient variability in the mode of VA initiation suggests that the transient pathophysiological factors vary, allowing PVC-dependent initiation on some occasions and favouring other electrical triggers at other times.

Once established, the majority of VA were monomorphic and effectively terminated by ATP, in keeping with a previous study.\(^15\) The success of ATP in terminating VA provides an insight into the underlying mechanism of arrhythmia generation as termination by overdrive pacing, in addition to PVC-dependent initiation is characteristic of re-entry.\(^23\) Myocardial fibrosis and myofibril disarray, both characteristic histological features of HCM,\(^3\) are likely to provide the anatomical substrate that allows unidirectional conduction block and delay which promote re-entry.\(^24,25\)

Sudden-onset VAs without preceding PVCs are likely to involve abnormal automaticity, triggered activity, or a combination of arrhythmogenic mechanisms.\(^8\) Sarcomeric protein gene mutations cause abnormal intracellular calcium homeostasis which may lead to delayed early depolarization and thus triggered activity.\(^26\)

However, re-entry can also potentially give the appearance of sudden-onset VAs without preceding PVCs since a PVC from a site very close to the re-entry circuit may have the same morphology as the complexes of the ensuing VT.\(^8\)

In our study, the VA cycle length was primarily determined by age, with older patients sustaining slower rates. This may explain the predilection of younger patients to SCD as faster arrhythmias are more likely to lead to haemodynamic compromise.\(^12\) Sudden cardiac death in HCM has been associated with physical

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**Table 2** Determinants of premature ventricular complex initiated ventricular arrhythmia (logistic regression)\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age at ICD implantation (years)</td>
<td>1.01</td>
<td>0.96 to 1.06</td>
</tr>
<tr>
<td>Male sex</td>
<td>5.17</td>
<td>1.08 to 24.9</td>
</tr>
<tr>
<td>MLVWT (mm)</td>
<td>1.09</td>
<td>0.97 to 1.23</td>
</tr>
<tr>
<td>LVOTG $\geq$ 50 mmHg</td>
<td>0.60</td>
<td>0.15 to 2.46</td>
</tr>
<tr>
<td>Fractional Shortening (%)</td>
<td>1.02</td>
<td>0.95 to 1.08</td>
</tr>
<tr>
<td>Left atrium diameter (mm)</td>
<td>0.98</td>
<td>0.93 to 1.03</td>
</tr>
<tr>
<td>Sinus baseline rhythm</td>
<td>1.48</td>
<td>0.47 to 4.66</td>
</tr>
<tr>
<td>Baseline rhythm cycle length (ms)</td>
<td>1.002</td>
<td>0.99 to 1.005</td>
</tr>
<tr>
<td>Class III anti-arrhythmic</td>
<td>0.96</td>
<td>0.27 to 3.42</td>
</tr>
<tr>
<td>Potential sleeping hours(^b)</td>
<td>0.96</td>
<td>0.87 to 3.08</td>
</tr>
<tr>
<td>PVC/day on Holter monitoring</td>
<td>1.0003</td>
<td>0.999 to 1.006</td>
</tr>
</tbody>
</table>

\(a\)The 56 VA were divided into two groups according to mode of initiation: PVC depended and non-PVC depended. The baseline category for comparison consists of the non-PVC depended VA (i.e. sudden onset without PVC combined with VA initiated by short-long-short sequences).

\(b\)Between 2300 and 0700.\(^17\)
exertion.2,27 Unfortunately, the retrospective nature of our study meant that level of activity at the time of device treatment was not available. A previous study reviewed intracardiac electrograms from nine HCM patients with treated VAs and reported that a portion of VA occurred while tachycardic,15 in keeping with our findings. The baseline rhythm heart rate in our study indicates that most VAs did not occur at a state of heightened sympathetic stimulation associated with severe physical exertion. However, we cannot exclude that some of the arrhythmias occurred post intense exercise or during warm-up.

Similar to previous studies in HCM patients,17,28,29 VAs occurred less frequently at night, presumably during sleep when metabolic demands are reduced and autonomic activity is stable. The daily transition from sleep to wakefulness is a period of heightened cardiac function.2,27 The daily peak in the occurrence of VA was not observed in this and previous studies of HCM ICD recipients.17,28,29 Similarly, the weekly and seasonal variation of VAs in HCM patients appears to be different from the reported pattern of sudden deaths and appropriate ICD shocks in ischaemic heart disease patients.10,31 However, this early morning peak in the occurrence of VA was not observed in this and previous studies of HCM ICD recipients.17,28,29 Similarly, the weekly and seasonal variation of VAs in HCM patients appears to be different from the reported pattern of sudden deaths and appropriate ICD shocks in non-HCM populations who exhibit peaks in winter and on Mondays.32,33 These discrepancies are likely to reflect differences in arrhythmogenic substrate and demographic characteristics of the populations studied. Hypertrophic cardiomyopathy patients are younger and likely to have different lifestyles and environmental exposures than older patients with ischaemic heart disease. In addition, sarcomere protein gene mutations responsible for HCM may disrupt cardiomyocyte circadian regulation, which under normal circumstances offers the heart the advantage of anticipation, i.e. the ability to prepare for a stimulus before it occurs to provide an optimal response.34 Abnormal circadian function can lead to abnormal expression of proteins involved in metabolism, cell signalling, and contractile function, leading to uncoupling of the stimulus from the gene expression with pathological consequences.34

Anti-tachycardia pacing has been shown in randomized trials to reduce the incidence of appropriate shocks by safely terminating both fast and slow ventricular tachycardias.35 However, HCM patients were specifically excluded.35 Based on the high success rate of ATP in terminating VAs in a small observational study of HCM patients, some investigators have recommended programming ATP in an attempt to reduce painful ICD shocks15 but the usefulness of this approach has been disputed.36 In the present analysis, ATP did not reduce the incidence of appropriate ICD shocks, despite the effectiveness of ATP in terminating VAs. This paradox may be explained by the occurrence of additional, independently occurring VAs which enter the VF treatment zone directly, where ATP has no role. Furthermore, the incidence of syncope during follow-up was similar in the two treatment groups and if one assumes that both groups had the same burden of VAs (they have similar baseline characteristics; Table 1), these two observations suggest that most ATP-treated VAs would have self-terminated without haemodynamic compromise if untreated. However, since the patients in this analysis were not randomized into the two therapy groups, differences in clinical characteristics e.g. incidence of non-sustained VT and therapy zones prevent concrete conclusions to be drawn.

This study was primarily designed to gain an insight into the arrhythmogenic substrate in HCM and to correlate this with clinical characteristics. Nevertheless, the findings have several potential clinical implications. Age appears to be an important determinant of VA cycle length, and our findings support the hypothesis that younger patients should be treated more aggressively for the prevention of SCD. The demonstration that most VAs are probably triggered by re-entrant mechanisms also influences device programming. Short-long-short sequences were not common, suggesting that anti-bradycardia pacing with rate smoothing algorithms is unlikely to reduce the development of VAs.37

**Limitations**

This study is limited by the relatively small number of events, which limits the number of predictor variables that can be used in the statistical analysis. In addition, the assessment of ventricular electrograms is subjective as complexes with an apparently identical morphology may not necessarily arise from the same ventricular site and conversely complexes with a different...
morphology may be fusion beats arising from the same place in the myocardium. 8

Conclusion
Most treated VAs in HCM are triggered by late-coupled PVCs and are likely to be mediated by re-entry. Younger HCM patients have faster VAs, which may explain the peak of SCD in early adulthood. Whether a particular PVC initiates a VA is likely to depend on transient pathophysiological events that modulate the arrhythmogenic vulnerability of the myocardial substrate. These modulators, in addition to the distinct myocardial sub-strate of HCM, are probably responsible for the differences in the circadian variation when compared with other patient popula-
tions. Identification of such modulators will allow novel thera-
peutic targets to be developed.

Author contribution
C.O'M. designed the study, collected and interpreted the data, carried out the statistical analysis, and wrote the manuscript. P.D.L. was involved in study design, data collection and interpretation, and wrote the manuscript. G.Q., M.Car., M.Cal., S.Al-S., and K.T. collected and interpreted the data, as well as contributed to the writing of the manuscript. S.M.R. carried out statistical analysis and contributed to the manuscript. P.E. was involved in the design of the study, interpretation of data, and writing of the manuscript. W.M. was involved in the drafting of the manuscript and revising it critically for important intellectual content.

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