Extreme interatrial conduction delay and regularization of atrial arrhythmias in a subgroup of patients with hypertrophic cardiomyopathy

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Background: Hypertrophic cardiomyopathy (HCM) patients may develop interatrial activation delay, indicated by a complete separation of the right and left atrial activation on the ECG. This study aimed to determine the prevalence of interatrial activation delay and the relation to atrial tachycardia (AT) cycle length (CL) in HCM patients.

Methods: 159 HCM patients were included (mean age 52 ± 14 y). In group I (n = 15, 9%) patients had atrial arrhythmias and progressive ATCL. In group II (n = 22, 14%) patients had a stable ATCL. In group III (n = 122, 77%) HCM patients without AT were included. P wave morphology and change in P wave duration (ΔP and P max) and changes in ATCL (ΔATCL) were analyzed. Mean follow-up was 8.7 ± 4.7 years.

Results: In group I 33% (n = 5) had separated P waves. In group II no P wave separation was identified. In HCM patients with ATCL, ΔP was significantly lower (105.1 ± 22.0 ms and 8.9 ± 13.2 ms, both p < 0.001). Group I patients had an increased LA size compared to group II (61.1 ± 11.6 vs. 53.7 ± 7.5 mm, p = 0.028) and higher E/A and E/E prime ratios (p = 0.007; p = 0.037, respectively). In group I 93.3% of the identi ed mutations were typical Dutch founder mutations of the MYBPC3 gene.

Conclusion: In HCM patients a unique combination of separated P waves and regularization of ATs is associated with larger atria, higher LA pressures and myosin binding protein mutations.

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1. Introduction

Hypertrophic cardiomyopathy (HCM) is recognized to be an important cause of morbidity and mortality in people of all ages [1]. Patients with HCM have a higher risk of developing ventricular as well as atrial arrhythmias [2–4]. Intra- and interatrial conduction and refractory properties are significantly influenced by the degeneration of the atrial septum and the Bachmann’s bundle [5–7]. Prolongation of interatrial conduction times (reflecting in longer P waves) and LA diameter are significant predictors for atrial fibrillation and other atrial tachyarrhythmias [8–11]. Our group recently observed a unique association with P wave separation on the ECG and development of progressively slowing regular atrial tachycardia in a patient diagnosed with hypertrophic cardiomyopathy [12]. The primary aim of this study was to assess the clinical magnitude of this phenomenon and to evaluate its possible clinical impact in a larger cohort of patients with HCM. The secondary aim of this study was to identify prognostic factors and possible clinical predictors for this novel clinical entity.

2. Methods

In this case–control study data was used from our HCM registry from 1995 until the present, which includes patients with a confirmed genetic mutation. Data were collected and analyzed in accordance with the hospital institutional review board policies. A total of 175 patients (67.4% male) were analyzed with a mean age of 53 ± 14 years. Diagnosis of HCM was based on echocardiographic presence of a hypertrophi ed, non-dilated left ventricle (LV) with a maximal LV wall thickness ≥ 15 mm and an absence of other cardiac or systemic disease that might lead to LV hypertrophy.

2.1. P wave measurements

P wave measurements were performed in all recorded 12-lead ECG recordings at a sweep speed of 25 mm/s and 10 mV/cm standardization. Both P wave morphology and changes in P wave duration (PWD) were

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* All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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analyzed. PWD was defined as the time between the first visible positive signal from baseline and returning to baseline for positive waveforms, and the first negative deflection until returning to baseline for negative waveforms. Measurements were performed manually and ECGs were carefully analyzed using up to 12 times magnifications using Adobe Reader 8.0 (Adobe Systems Incorporated, CA, USA). PWD was measured in the limb leads and maximum PWD was considered the actual atrial conduction time. If the P wave had respectively two upward or downward departures from baseline it was defined as a separated P wave, indicating separated activation of the atria. In all patients both Pmax and ΔP were analyzed, indicating maximum P wave and change of PWD during follow-up. The ΔP was defined as the difference between the maximum and minimum PWD and was only calculated for patients suffering only from atrial arrhythmias. In total, 20.6% (n = 36) of the patients who underwent at least two years of follow-up. The Pmax was used as a marker of prolonged atrial conduction time, whereas the ΔP indicated variable conduction properties of the atria.

2.2. Atrial arrhythmias

The incidence of atrial arrhythmias was evaluated for all HCM patients. Data from ECG recordings taken either during routine examination at the out-patient clinic or hospital stay were analyzed. Furthermore, 24 h Holter registrations were examined to determine any incidence of atrial arrhythmias. In total, 20.6% (n = 36) of the patients suffered only from atrial fibrillation (AF), 2.3% (n = 4) had only atrial flutter, 0.6% (n = 1) had only AT, 4.6% (n = 8) had both AF and AFL, 0.6% (n = 1) had AF and AT, and in 1.7% (n = 3) AF, AT and AFL were all documented. From all 12-lead arrhythmia recordings the cycle length of the atrial arrhythmia (ATCL) was measured in precordial leads using the same techniques as for P wave measurements. The ΔATCL was calculated and defined as the difference between the longest and the shortest recorded ATCL during follow-up. It was only calculated if more than two 12-lead ECG captured the atrial arrhythmia with at least one-year time interval (n = 37).

2.3. Study groups

From the baseline population, a total of 16 patients were excluded due to insufficient follow-up (n = 13) or permanent AF (n = 3). From the remaining HCM population two groups of patients were selected and analyzed in this study. All included patients who suffered from atrial arrhythmias (n = 37). In the first study group (group I, n = 15) patients had a progressive ATCL during follow-up. In the second group (group II, n = 22) patients had a stable ATCL (defined as a ΔATCL < 10 ms). From all patients the presence of a visible separated P wave on the surface ECG was evaluated together with other secondary endpoint parameters and compared between the two study groups. Additional comparison of group I patients with the general HCM population (group III, n = 122) without atrial arrhythmias and P wave separation who met the criteria for P wave measurement was also performed.

Patients underwent a median follow-up of 9.0 years (IQR [4.0–13.0 y]) commencing when the first 12-lead ECG was recorded during the initial clinical presentation at our institute up until the most recent ECG recording.

2.4. Echocardiography

In all patients complete transthoracic 2-dimensional echocardiography was performed. Echocardiographic studies were performed with a Sonos 7500 ultra-sound system with a 53 transducer or an IE33 system with a 5–1 transducer (Philips Medical Systems, Best, The Netherlands). From the second harmonic M-mode recordings the following echocardiographic parameters were taken: LA size, intraventricular septal thickness, LV end-diastolic volume, degree of mitral regurgitation, E/A ratio, E/E' prime ratio and fractional shortening (FS). The FS was calculated using the following formula: [LV end-diastolic diameter – LV end-systolic diameter] / LV end-diastolic diameter × 100%. Echocardiography showed that 29.7% of patients (n = 11) had an obstructive HCM and 70.3% a non-obstructive HCM (n = 26). Obstructive HCM was defined as a resting peak LVOT gradient >30 mm Hg. All measurements were calculated according to ACC/AHA guidelines [13].

2.5. Genetics

All included patients underwent genetic mutation testing prior to this study. These tests revealed mutations in the myosin binding protein C (89.2%), myosin heavy chain beta (5.4%), troponin T type 2 (2.7%) and troponymycin 1 (1.1%). In the reference HCM population the following genetic mutations were found: myosin binding protein C (82.8%), myosin heavy chain beta (13.1%), troponin T type 2 (0.8%), troponin I type 3 (0.8%), tropomyosin 1 (0.8%) and myosin regulatory light chain 2 (1.6%). In this study correlations were made between any of these known genetic mutations.

2.6. Statistics

The Kolmogorov–Smirnov test was used to assess the normality of distribution. Descriptive statistics was presented as mean ± SD for continuous variables if normally distributed. In the case of non-normal distribution of data, median and interquartile range (IQR) were reported. Continuous data was compared with the Student’s t test or Mann–Whitney U test, where appropriate. Categorical data was presented as percentages and compared with the Chi-square test or Fisher’s exact test when appropriate. Univariate analyses were performed for all variables and odds ratios (OR) and 95% confidence intervals (95% CI) were determined. Statistical analysis was performed with PASW version 18 (IBM Corp., Somers, NY). Statistical significance is defined as p < 0.05 (two-tailed).

3. Results

3.1. Study population

The demographics and clinical presentation of all patients are shown in Table 1. Group I and group II patients were homogenous with respect to gender and clinical symptoms. Furthermore, both groups had equal distribution of atrial tachyarrhythmias (AF, AT and AFL). There were no differences in the amount of implanted devices and the need for electrical cardioversion therapy. Furthermore, in one group I patient 83 episodes of anti-tachycardia pacing (ATP) and one shock was delivered. One patient from group II received 5 ATP episodes and 5 ICD shocks. In group III 21.4% of patients with an ICD received appropriate therapy. The use of diuretics, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, aspirin, warfarin and statin was comparable for both group I and group II. Furthermore, the use of amiodarone was not different for both groups (46.7% vs. 27.3%, p = 0.194). Patients in group I had significantly longer follow-up when compared to group II (13.4 ± 2.2 vs. 10.9 ± 3.9 y, p = 0.033).

The reference HCM population, group III, was also comparable in terms of gender and clinical presentations. The significant differences found in this study were related to the absence of tachyarrhythmias in this group compared to group I (palpitations, AF, AT, AFL, cardioversion, amiodarone), which was the basis of the group selection. However, the study population was significantly older than the reference population and had a longer follow-up (62.6 ± 15.1 vs. 50.2 ± 14.0 y, p = 0.002; 13.4 ± 2.2 vs. 7.8 ± 4.6 y, p < 0.0001).
Pmax was not statistically different for group I or group II patients, although it tended to be higher in group I (142.3 ± 30.9 vs. 126.4 ± 18.1 ms, p = 0.062). The AP wave was also comparable (36.4 ± 25.3 vs. 22.6 ± 16.3 ms, p = 0.066).

In the reference HCM population without atrial arrhythmias, a complete separated P wave was visible in 4 patients. However, the prevalence was significantly higher in group I patients (33.3% vs. 3.3%, p = 0.001). Furthermore, the Pmax and the AP were significantly lower for group III patients (p = 0.0001, Table 2).

### 3.3. Echocardiography

Two-dimensional echocardiography studies showed LA size to be significantly larger in group I patients compared to group II (61.1 ± 11.6 vs. 53.7 ± 7.5 mm, p = 0.028). The same results were found when compared to group III patients (45.4 ± 7.9 mm, p = 0.0001). Both the E/A and E/E prime ratios were higher for patients in group I than in group II (3.0 ± 1.5 vs. 1.8 ± 0.9, p = 0.007; 19.3 ± 9.1 vs. 12.2 ± 6.9, p = 0.0037). FS, degree of mitral regurgitation, IV septum thickness, LV end-diastolic volume, E velocity, A velocity and E deceleration time were all comparable for both group I and group II patients. In patients with a separated P wave, echocardiography showed that the A wave of both atria consisted of separate curves on the M-mode imaging of the mitral flow (Fig. 3). The A1 wave represented the contraction of the RA, whereas A2 indicated the contraction of the LA.

When group I patients were compared to group III patients, echocardiography showed that group I patients had significantly less FS, more mitral regurgitation and higher E/A and E/E prime ratios (Table 2).

### 3.4. Genetic mutations

With respect to genetic mutations no significant differences could be found when patients from all groups were compared (Table 3). The most frequent mutations were typical Dutch founder mutations of the MYBPC3 gene, which was present in 93.3% of group I patients, 86.4% in group II and 82.8% in group III (p = ns).
Fig. 2. Twelve-lead surface electrocardiograms from 2003 until 2013 from a group I patient — The progression of P-wave separation is clearly visible in sinus rhythm. Furthermore, the P-waves from lead I are displayed enlarged for each year. Over time, the surface electrocardiogram shows changed in repolarization as well.
4. Discussion

The major finding of this study is that a subgroup of HCM patients with a unique combination of signs namely separated P wave, regularization and slowing ATs can be identified. Our data strongly suggest that this observation does not represent isolated cases, but is consistent with the presence of a unique clinical entity within the HCM group. Therefore, we propose to call this as "double hump syndrome" naming after the very typical appearance on the surface electrocardiogram. It seems that extreme interatrial conduction delay is the underlying electrophysiological mechanism for the symptoms. This clinical presentation is associated with larger atria and higher LA pressures.

4.1. Genetical background

Most MYBPC3 mutations are truncating mutations and are in contrast with other sarcomeric genes in HCM, which are generally missense mutations [14]. It is thought that these truncated mutations cause a reduction in MYBPC3 protein due to the lack of expression from the mutant allele by the cellular surveillance mechanism of nonsense-mediated decay [15]. The effect of MYBPC3 protein on the atrium is not completely discovered. During experimental setups it has been demonstrated that the deletion of MYBPC3 causes an increase of shortening velocity, force output and force redevelopment on a ventricular level [16–18]. The effect of MYPBC3 deletion on the left atrium in MYBPC3 knockout mice led to a prolonged sarcomere shortening and Ca²⁺ transient [19]. The MYPBC3 deletion on the left atrial level caused a marked increase in sensitivity to external Ca²⁺ and low micromolar Ca²⁺. The consequence was a defect in diastolic relaxation and a smaller dynamic range of cell shortening, as a result of the increased myofilament Ca²⁺ sensitivity [19,20]. Obviously the link between the genetical background and the development of this syndrome should be further investigated. This will lead us to further understand the arrhythmia genesis in patients with HCM.

4.2. The role of amiodarone: unmasking the presence of susceptibility for interatrial conduction delay

Interestingly enough, in this study the use of amiodarone has been associated with the presence of double hump syndrome. This raises the important question of whether the relationship between these entities is simply coincidental or that possibly a causative relationship plays a role. To the best of our knowledge amiodarone has no significant lengthening effect on PWD and actually on the contrary it decreases PWD according to most available literature [21,22]. The effect on the electrophysiological properties of interatrial conduction delay is sparse and further investigation is necessary to understand it clearly. It is fairly remarkable that in our study amiodarone use was associated with increased PWD and P wave separation. As has been demonstrated before in different experimental settings, chronic amiodarone use prolongs the atrial action potential duration, which eventually leads to an increased total atrial activation time and increased PWD [23–25]. This raises the possibility that indeed the effect could be disease specific. Based on the above-mentioned findings, amiodarone may have unmasking effects. In this scenario the electrophysiological effects of amiodarone for the intra-atrial conduction delay would be very useful in patients prone to develop double hump syndrome, by using it to unmask this
syndrome. However, this possibility requires further study. Another possibility is that these patients all developed atrial tachyarrhythmias. Atrial tachyarrhythmias can have a very deleterious effect on the hemodynamics of HCM patients. Therefore, it is not a surprise that eventually most of these patients were treated with the most effective class III antiarrhythmics [26].

4.3. Time as a factor: slow development of double hump syndrome

In this study longer follow-up and older age were clearly associated with the development of double hump syndrome. This means that the development of the syndrome is fairly slow and time-dependent. This is not surprising when looking at the possible underlying mechanisms behind it. Our ECG and echocardiographic Doppler data all support the evidence that the delay in impulse propagation occurs on the level of the interatrial septum, rather than in the atria itself. When the delay is fully developed, almost complete atrial dissociation could be observed. Given the fact that this is associated with the appearance of atrial tachyarrhythmias it is highly suggestive that a certain form of degeneration or scar plays a role. Furthermore, the long course of development indicates that the presence of this syndrome may have no significant effect on mortality. This is slightly overshadowed by the fact that 20% of patients with double hump syndrome had an ICD implanted. The ICDs gave in total 83 appropriate ATP episodes and one delivered shock in one patient. Multicentre studies, even in registry form would be able to answer this question. Another consequence of this slow development is that the HCM patients should be carefully screened for this throughout their life, especially, when they develop atrial tachyarrhythmias.

4.4. Limitations of the study

The major limitation of this study that all findings included is based on non-invasive tests. The accurate electrophysiological mechanisms should be later determined by performing a series of electrophysiology studies. The true prevalence and incidence of this unique subgroup of HCM patients should be studied in a multicentre study. In a later stage the genetical background and possible relations with the clinical and long-term outcome should be investigated in a more meticulous manner.

Furthermore, additional magnetic resonance imaging performed in all patients could provide valuable information regarding interatrial septum thickness. Changes in the interatrial septum could have an influence on the PWD and P wave separation and might explain the differences among the three groups of patients. Therefore, further studies are needed to reveal this issue.

5. Conclusion

A subgroup of HCM patients has a unique combination of symptoms of separated P wave, regularization and slowing of ATs (the “double hump syndrome”). Clinically it is associated with larger atria, higher LA pressures and longer follow-up. The presence of “double hump syndrome” is mostly associated with MYBPC3 myosin binding protein mutations. Extreme interatrial conduction delay might be the underlying electrophysiological mechanisms of this clinical presentation.

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Author contributions

All authors participated in the preparation of this manuscript and approve the final version.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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References


Table 3

Genetic mutations. Percentages, odds ratios and confidence intervals of 95% obtained by univariate analyses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>OR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
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<td>MYBPC3 (%)</td>
<td>93.3% (n = 14)</td>
<td>86.4% (n = 19)</td>
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<td>[0.21–23.56]</td>
<td>0.461</td>
</tr>
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<td>MYH7 (%)</td>
<td>6.7% (n = 1)</td>
<td>4.5% (n = 1)</td>
<td>1.50</td>
<td>[0.09–26.01]</td>
<td>0.653</td>
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<td>TNNT2 (%)</td>
<td>0.0% (n = 1)</td>
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<td>[0.87–1.05]</td>
<td>0.595</td>
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<tr>
<td>TNNI3 (%)</td>
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<td>NA</td>
<td>0.891</td>
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<td>0.96</td>
<td>[0.87–1.05]</td>
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<tr>
<td>MYL2 (%)</td>
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<td>0.0% (n = 0)</td>
<td>NA</td>
<td>NA</td>
<td>0.891</td>
</tr>
</tbody>
</table>


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