Research letter

**Sudden Death can be the First Manifestation of Hypertrophic Cardiomyopathy. Data from a United Kingdom Pathology registry.**

**Authors:** Gherardo Finocchiaroa MD, Michael Papadakisa MRCP, MD, Gaia Tanzarellaa, MD, Harshil Dhutiaa BSc, MRCP, Chris Milesa, MRCP, Maite Tomea MD, PhD, Elijah R. Behra MA, MBBS, MD, FRCP, Sanjay Sharmaa BSc, MBChB, MD, FRCP, Mary N. SheppardbMBBCH, BAO, BSc, MD, FRCPath

**Institutions:**

a Cardiovascular Sciences Research Centre, St George's, University of London, London, United Kingdom

b Cardiovascular Pathology Department, St George's, University of London, London, United Kingdom

c Istituto di Cardiologia, Università di Bologna

Keywords: sudden death, hypertrophic cardiomyopathy

Words count: 800

**Author for correspondence:**

Sanjay Sharma, MD, Professor of Clinical Cardiology,

Cardiology clinical and academic group.

St. George’s, University of London

Cranmer Terrace, London, SW17 0RE, UK.

E-mail: sasharma@sgul.ac.uk

**Abstract**

Hypertrophic cardiomyopathy (HCM) is an inherited cardiomyopathy which is characterized by left ventricular hypertrophy (LVH) and propensity for fatal arrhythmias. We analysed a cohort of individuals who died suddenly and were diagnosed with HCM at autopsy. Sudden cardiac death (SCD) was the first manifestation of the condition in the majority (78%) of cases and only 50 (26%) decedents reported cardiac symptoms prior to death. Death during exercise or during emotional stress occurred in 46 individuals (23%) who were predominantly males (89%) and young (30±11 years). The diagnosis of HCM was often made only after death (78% of the cases). Sudden death from HCM mostly occurred during rest or usual life activities (77% of the cases) other than strenuous exercise, suggesting that exercise may be a risk factor for fatal arrhythmias only in young males.

**Clinical implications:** The early identification of HCM in asymptomatic individuals is the first step for risk stratification for SCD.. The role of exercise in precipitating SCD in HCM is unclear and although previous studies have suggested a high prevalence of HCM in young athletes who died suddenly, it is possible that this increased risk is limited to young males.

**Translational outlook:** Better strategies are required for detecting asymptomatic individuals with HCM. . Future prospective randomized studies should assess the benefits and harms/risks of exercise in patients with HCM.

Hypertrophic cardiomyopathy (HCM) is an inherited cardiomyopathy which is characterized by left ventricular hypertrophy (LVH), myocyte disarray at histology and a propensity for fatal cardiac arrhythmias(1). Sudden cardiac death (SCD) is the most feared complication particularly among individuals in the second and third decade of life and several clinical predictors are used to identify high risk patients who may benefit from an implantable cardioverter defibrillator (ICD)(2). Unfortunately, SCD may be the first manifestation of the disease in apparently healthy and asymptomatic individuals including athletes.

The aim of the study was to report the characteristics and circumstances of death in a large cohort of decedents of SCD with a diagnosis of HCM at autopsy.

We reviewed a database of 5100 consecutive cases of SCD referred to our specialist cardiac pathology centre between January 1994 and March 2017 and identified 196 (4%) cases with HCM. Sudden cardiac death was defined as death from a cardiovascular cause within 12 hours of apparent wellbeing. Clinical information was obtained from referring coroners who were asked to complete a questionnaire inquiring about the demographics of the deceased, past medical history, family history and circumstances of death. All cases underwent detailed autopsy evaluation of the heart, including histological analysis, by expert cardiac pathologists. The heart weight was recorded in grams and ventricular wall thickness and internal cavity dimensions were measured at mid-ventricular level. A minimum of 10 blocks of tissue were taken for histological analysis as reported previously (3). Results are expressed as mean ± standard deviation (SD) for continuous variables or as number of cases and percentage for categorical variables.

Sudden cardiac death was the first manifestation of HCM in the majority (78%) of cases. The majority of decedents were male (n=143, 73%). The mean age at death was 43±18 years and 20 (10%) individuals died suddenly aged above 60 years old (Figure 1).

Cardiac symptoms were reported in 50 cases (26%): chest pain (n=14, 7%), palpitations (n=14, 7%), dyspnea (n=10, 5%) and syncope (n=9, 5%). A pre-mortem diagnosis of HCM was known in 43 (22%) patients, of which 15 had previous cardiac symptoms. One patient had a concomitant diagnosis of Wolff-Parkinson-White syndrome and one had an implantable cardioverter defibrillator (ICD) . Death during exercise or during emotional stress occurred in 46 individuals (23%) who were predominantly male (89%) and aged 30±11 years (age range 11-54 years). Conversely, 150 (77%) individuals died at rest or during daily activities, including 26 (13%) who died during sleep. Twenty (10%) individuals were recreational or competitive athletes.

The mean heart weight was 558 ± 186 g. The average left ventricular wall thickness was 21.4 ± 6.3 mm at the level of the interventricular septum, 19 ± 5.7 mm at the anterolateral wall and 17.4 ± 4.7 mm at the posterior wall; 19 (10%) patients had a maximal wall thickness ≥ 30 mm. Left ventricular (LV) fibrosis was detected in 115 (59%) patients mainly at the level of the interventricular septum and the anterolateral walls. Associated coronary artery stenosis (> 70% of the lumen) was found in 5 patients (2/5 aged above 60 years of age).

Our study reports on one of the largest autopsy cohorts of individuals with HCM where the post-mortem was performed by an expert cardiac pathologist following a standardized protocol. Most deaths occurred at rest and only a 26% reported cardiac symptoms prior to death, underscoring how HCM often remains undiagnosed in the community. SCD affected individuals with HCM at all ages (even above 60 years), with a peak between 30 and 50 years.

Most individuals diagnosed with HCM during life were probably not considered at sufficiently high risk to warrant an ICD, which confirms the need for an improvement in risk stratification protocols and mechanisms implicated in the development of fatal arrhythmias in HCM(2). In contrast with arrhythmogenic cardiomyopathy, where there is a clear association between intense exercise and increased risk of SCD, in our case series, the majority of SCD in HCM occurred at rest or during usual activities. Current recommendations advise against competitive sport in all individuals with HCM, based on data that is derived largely from adolescents or young adults who have died during exercise.(4). We observed that such deaths were confined to young males and call for a more liberal approach in other exercising populations. Indeed, a recent study suggests that moderate exercise may be beneficial and safe in patients with HCM(5).

It is possible that we may have overestimated the proportion of individuals with HCM who presented with SCD as the first manifestation because pathologists may not have referred decedents with an established pre-mortem diagnosis of HCM to our expert center. However, our center usually receives a high volume of referrals from SCD (> 400 per year), in mostly young decedents including athletes and given the rarity of SCD in the young it is likely that our cohort provides a genuine representation of SCD in HCM.

**Acknowledgements:** Cardiac Risk in the Young (CRY)

**Funding:** Cardiac Risk in the Young (CRY) and Charles Wolfson Charitable Trust.

**REFERENCES:**

1. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet (London, England) 2013;381:242–55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22874472.

2. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur. Heart J. 2014;35:2733–79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25173338.

3. Basso C, Aguilera B, Banner J, et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch. 2017;471:691–705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28889247.

4. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA 1996;276:199–204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8667563.

5. Saberi S, Wheeler M, Bragg-Gresham J, et al. Effect of Moderate-Intensity Exercise Training on Peak Oxygen Consumption in Patients With Hypertrophic Cardiomyopathy: A Randomized Clinical Trial. JAMA 2017;317:1349–1357.

**Figure 1.** Sudden cardiac death in patients with HCM. **Legends:** CAD: coronary artery disease; MWT: maximal wall thickness