Journal Pre-proof

Mitral valve abnormalities in decedents of sudden cardiac death due to hypertrophic cardiomyopathy and idiopathic left ventricular hypertrophy

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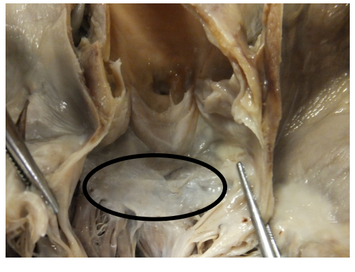
Graphical abstract

‘Mitral valve abnormalities in decedents of SCD due to hypertrophic cardiomyopathy and idiopathic left ventricular hypertrophy’

CRY Centre for Cardiac Pathology
1994 – 2020
6860 consecutive cases of Sudden Cardiac Death (SCD)

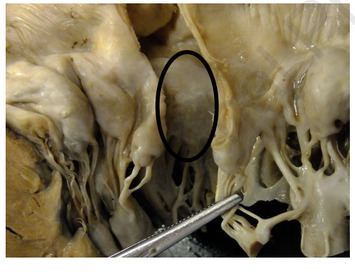
ILVH (n): 253; HCM (n): 264

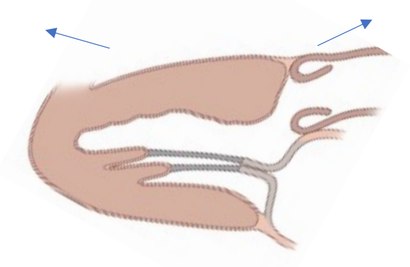
Impact lesion



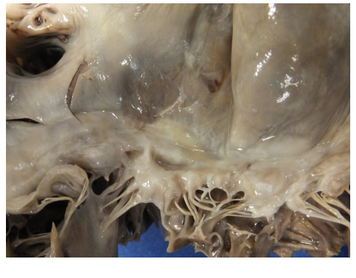
HCM 15 %
ILVH 0.3 %

Thickened leaflet corresponding to impact lesion





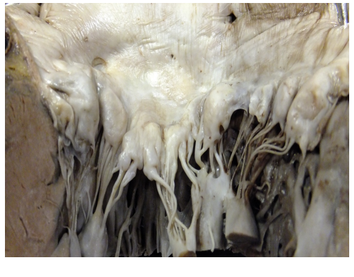
Thickening and nodularity



HCM 8 %
ILVH 2 %

HCM 5 %
ILVH 3 %

Bulging/ ballooning



- **SCD first manifestation of HCM in 82%**

- **MV abnormalities** observed in **22% of HCM** cases Vs **5% of ILVH** cases
- **Impact lesions in LVOT/ aortic outlet** observed in **15% of HCM** cases vs **0.3% of ILVH** cases
- **Decedents with HCM** and MV abnormalities were **younger than ILVH cohort**

- Insights into large autopsy registry in comparison to historic imaging studies
- ☑ Consider MV abnormalities as additional macroscopic features in differentiation between ILVH and HCM
- ☑ Supports standardisation and quantification of MV abnormalities in decedents of SCD including, the sub-MV apparatus

Research letter

Mitral valve abnormalities in decedents of sudden cardiac death due to hypertrophic cardiomyopathy and idiopathic left ventricular hypertrophy

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Conflicts of interest: no author has any relevant conflicts of interest to declare.

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy (LVH), in the absence of abnormal loading conditions and characterised by myocyte disarray at histology.[1] Following sudden cardiac death (SCD) the sole identification of significant LVH at autopsy may lead to an erroneous diagnosis of HCM. Data suggests that idiopathic LVH (ILVH) and HCM may be separate entities.[2] We aimed to report the prevalence and nature of MV abnormalities, in SCD victims with post-mortem findings consistent with HCM and ILVH. We hypothesised that MV abnormalities are more common in individuals with HCM and considered as additional macroscopic features to differentiate between these two entities.

We reviewed 6860 consecutive cases of SCD referred to our specialist cardiac pathology centre between 1994-2020. SCD was defined as death from a cardiovascular cause within 12-hours of apparent well-being. All cases underwent detailed autopsy and a minimum of 10-tissue blocks underwent histological analysis.[5] ILVH was defined as unexplained LVH (heart weight >500g in males and >400g in females) and left ventricular (LV) wall thickness >15mm, in the absence of myocardial disarray or secondary causes of LVH.[2] The MV was examined for patency, circumference, thickening, nodularity, ballooning, bulging between cords, perforation, endocarditis, and the presence of impact lesions in the LV outflow tract (LVOT) and aortic outlet.

Ethical approval was granted for this study (10/H0724/38).

Of the total cases of SCD, 264 (4%) were due to HCM (mean age 41±18 years, 78% males, LV maximal wall thickness 19±6mm) (Figure 1). Ante-mortem symptoms were reported in 44 (17%) cases, and for the majority (n=217, 82%) the diagnosis of HCM was established at post-mortem. Death was attributed to ILVH in 253 (3%) cases (mean age 43±16 years, 80% males, LV maximal wall thickness 18±4mm). MV abnormalities were found in 58 (22%)

decedents with HCM (mean age 38±17 years; 72% males) and 13 (5%) decedents with ILVH (mean age 55±5 years; 77% male), p<0.001. Myocardial fibrosis was observed in 162 (61%) cases of HCM and 99 (39%) cases of ILVH, p<0.001.

Amongst 58 (22%) cases with HCM and MV abnormalities, 15 (6%) cases had multiple MV abnormalities. These included impact lesions associated with thickening of the anterior MV leaflet (n=39) and degenerative changes (n=34) such as bulging and ballooning; and thickening and nodularity. Decedents with HCM exhibiting MV abnormalities were younger than decedents with a normal MV (38±17 versus 45±19 years; p=0.08).

Among the 253 decedents with ILVH, 13 (5%) cases exhibited MV abnormalities, which largely included degenerative changes (n=12). Among decedents with HCM and ILVH exhibiting MV abnormalities, the former was significantly younger (38±17 versus 55±15; p=0.001).

MV abnormalities were identified in 22% and 5% of decedents of SCD attributed to HCM and ILVH, respectively. Imaging studies, predominantly on cohorts with dynamic LVOT obstruction have reported mitral malformations in up to 70% of HCM patients.[3,4] The lower prevalence of significant MV abnormalities in our cohort may be due to a lower proportion of obstructive cases, since most decedents did not have any pre-existing cardiovascular symptoms and SCD was the first manifestation. Although LV outflow tract obstruction is regarded as a risk factor for fatal arrhythmias, an impact lesion was observed in 39 out of 264 cases of HCM (15%), suggesting that systolic anterior motion of the MV (SAM) and possible dynamic obstruction were relatively rare in this population. MV abnormalities were rare in ILVH and were found in older individuals, suggesting an underlying mechanism that is unrelated to a sarcomeric disease. A limitation of our study is the absence of molecular autopsy findings. Furthermore, the inherent descriptive terminologies used when assessing

the MV, support a greater emphasis on the standardisation and quantification of MV abnormalities as part of the autopsy, including, the sub-MV apparatus and geometrical arrangements of papillary muscles, presence of papillary muscle hypertrophy, and abnormal chordae tendineae arrangements.

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References

1. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *European Heart Journal*. 2014;35(39).
2. Finocchiaro G, Dhutia H, Gray B, et al. Diagnostic yield of hypertrophic cardiomyopathy in first-degree relatives of decedents with idiopathic left ventricular hypertrophy. *EP Europace*. 2020;22(4).
3. Kaple RK, Murphy RT, DiPaola LM, et al. Mitral Valve Abnormalities in Hypertrophic Cardiomyopathy: Echocardiographic Features and Surgical Outcomes. *The Annals of Thoracic Surgery*. 2008;85(5).
4. Maron MS, Olivotto I, Harrigan C, et al. Mitral Valve Abnormalities Identified by Cardiovascular Magnetic Resonance Represent a Primary Phenotypic Expression of Hypertrophic Cardiomyopathy. *Circulation*. 2011;124(1).
5. 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 Archiv*. 2017;471(6).

Graphical-abstract

Figure1 Study overview

6860 consecutive cases of SCD

Age (yrs): 38 ± 18

253 cases attributed to ILVH

Female: 52 (20%); male: 200 (80%)
Age (yrs): 43 ± 16
Ethnicity: 200 (80%) Caucasian

Heart weight (g): 543 ± 137
MV circumference (mm): 81 ± 17
Max wall thickness (mm): 18 ± 4
LV cavity (mm): 35 ± 8
Scar (number of cases): LV, 99 (39%)

264 cases attributed to HCM

Female: 74 (28%); male: 190 (78%)
Age (yrs): 41 ± 18
Ethnicity: 191 (72%) Caucasian

Heart weight (g): 549 ± 182
MV circumference (mm): 80 ± 15
Max wall thickness (mm): 19 ± 6
LV cavity (mm): 32 ± 9
Scar (number of cases): LV, 162 (61%)

240 (95%) cases without MV abnormalities

Female: 50 (20%); male: 190 (80%)
Age (yrs): 42 ± 15
Ethnicity: 187 (78%) Caucasian

Heart weight (g): 541 ± 138
MV circumference (mm): 81 ± 17
Max wall thickness (mm): 18 ± 4
LV cavity (mm): 35 ± 9
Scar (number of cases): LV, 93 (38%)

13 (5%) cases with MV abnormalities

Female: 3 (23%); male: 10 (77%)
Age (yrs): 55 ± 15
Ethnicity: 13 (100%) Caucasian
Heart weight (g): 574 ± 113
MV circumference (mm): 86 ± 9
Max wall thickness (mm): 18 ± 4
LV cavity (mm): 35 ± 6
Scar (number of cases): LV, 6 (46%)

- Impact lesion in LVOT/ aortic outlet associated with thickening of anterior MV leaflet (n): 1
- Degenerative changes (n): 12; e.g., bulging and ballooning: 8; thickening and nodularity: 6
- Cases with >1 MV abnormality (n): 2

58 (22%) cases with MV abnormalities

Female: 16 (28%); male: 42 (72%)
Age (yrs): 38 ± 17
Ethnicity: 46 (80%) Caucasian
Heart weight (g): 578 ± 157
MV circumference (mm): 83 ± 15
Max wall thickness (mm): 20 ± 4
LV cavity (mm): 31 ± 8
Scar (number of cases): LV, 38 (65%)
Distribution of hypertrophy: asymmetrical septal n=16; asymmetrical non-septal n=21; symmetrical n=21

- Impact lesion in LVOT/ aortic outlet associated with thickening of anterior MV leaflet (n): 39
- Degenerative changes (n):34 e.g., bulging and ballooning: 14; thickening and nodularity: 20
- Cases with >1 MV abnormality (n): 15

206 (78%) cases without MV abnormalities

Female: 58 (28%); male: 147 (71%)
Age (yrs): 45 ± 19
Ethnicity: 145 (70%) Caucasian
Heart weight (g): 560 ± 161
MV circumference (mm): 78 ± 15
Max wall thickness (mm): 19 ± 6
LV cavity (mm): 32 ± 9
Scar (number of cases): LV, 124 (60%)
Distribution of hypertrophy: Asymmetrical septal n=63; asymmetrical non-septal n=50; symmetrical n=76; microscopic myocyte disarray with no overt increase in heart weight or LVH n=17

ILVH without MV abnormalities vs ILVH with MV abnormalities P values

Age: 0.008 *
Heart weight: 0.44
MV circumference: 0.62
Max wall thickness: 0.30
LV cavity: 0.80

HCM with MV abnormalities vs ILVH with MV abnormalities P values

Age: 0.001 *
Heart weight: 0.94
MV circumference: 0.97
Max wall thickness: 0.004 *
LV cavity: 0.29

HCM without MV abnormalities vs HCM with MV abnormalities P values

Age: 0.08
Heart weight: 0.18
MV circumference: 0.12
Max wall thickness: 0.85
LV cavity: 0.57

HCM, hypertrophic cardiomyopathy; ILVH, idiopathic left-ventricular hypertrophy; LV, left ventricle; LVOT, left ventricle outflow tract; MV, mitral valve; RV, right ventricle; SCD, sudden cardiac death. *Statistically significant (P<0.05).
MV terminology; Ballooning of leaflets: prominent saccular bulging of the scallop's inwards and upwards into the atria. **Bulging of leaflets**: saccular extension of the scallop's inwards and upwards into the atria.