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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a diverse inherited disease affecting 1 in 500 individuals irrespective of gender and ethnicity. A fraction of HCM patients will eventually develop drug refractory dynamic obstruction of the left ventricular outflow tract. For such patients, septal myectomy is the procedure of choice to alleviate their symptoms and improve their quality of life. The current histopathological study, the first from the Greek region, aims to examine the hallmark histopathological characteristics of Hypertrophic Obstructive Cardiomyopathy in a population of patients undergoing septal myectomy at a single center over a ten year period. Medical records and histopathology specimens of thirty nine (n=39) patients were evaluated. The sample comprised 22 males (56.4%) and 17 females (43.6%). Mean patient age at myectomy was 53.9±16.7 years, ranging from 12 to 79 years. Maximal IVS thickness on echocardiography was available for 35 patients with a median value of 2.08cm. Peak resting LVOT Pressure Gradient was available for 33 patients with a mean value of 104.88 ± 44.20mmHg. Central tendency of each histopathological attribute expressed as the median value was: moderate for myocyte hypertrophy, mild for cytoplasmic vacuolization, moderate for subendocardial fibrosis, moderate for interstitial fibrosis, mild for replacement fibrosis, moderate for myofibrillar disarray and mild for capillary stenosis. Myocyte hypertrophy, present in all specimens, was positively correlated with maximal IVS thickness (tau-b=0.43, p=0.002). Replacement fibrosis was positively correlated with the grade of microvascular stenosis (tau-b=0.45, p=0.004). LVEF was negatively correlated with the grade of interstitial fibrosis (tau-b=-0.43, p=0.035) and with the extent of myocardial fiber disarray (tau-b=-0.42, p=0.034). Histopathological attributes were not correlated with patient gender or age thus proving that HCM has a histological phenotype unique to each patient, mainly depending on each specific sarcomeric mutation.
List of abbreviations

HCM: Hypertrophic Cardiomyopathy
HOCM: Hypertrophic Obstructive Cardiomyopathy
IQR: Interquartile Range
IVS: Interventricular Septum
LVEF: Left Ventricular Ejection Fraction
LVOT: Left Ventricular Outflow Tract
LVOTO: Left Ventricular Outflow Tract Obstruction
NYHA: New York Heart Association
PG: Pressure Gradient
RBC: Red Blood Cell
SD: Standard Deviation

Introduction
The first description of Hypertrophic Cardiomyopathy (HCM) from a pathology standpoint was published in 1869 by the two French pathologists Hallopeau and Liouville, who at that time did not classify the observed asymmetrical interventricular septum (IVS) hypertrophy as a primary myocardial disorder (McKenna and Sen-Chowdhry, 2008). In 1958 Teare described a series of eight distinct cases, 14 to 44 years old, with prominent hypertrophy of the interventricular septum which caused narrowing of the left ventricular outflow tract (Teare, 1958). Upon microscopic examination Teare recognized the classic histological hallmarks of HCM, more specifically cardiac fiber disarray, interstitial fibrosis and fiber hypertrophy. HCM was initially considered a rare disease but in the modern era of medicine it is defined as the most common inherited cardiomyopathy. It is a genetic disease of the cardiac myocytes macroscopically characterized by: cardiac muscle hypertrophy (usually asymmetrical and mainly localized at the basal interventricular septum) which cannot be attributed to altered hemodynamic load, a normal or increased left ventricular ejection fraction and a non-dilated left ventricle (Marian and Braunwald, 2017). Its prevalence in the general population is estimated at about 1 in 500 individuals (Elliott and McKenna, 2004). Both genders are equally affected
as well as diverse races and ethnic groups. The most devastating feature of HCM is undoubtedly sudden cardiac death. The root genetic cause of HCM, for the majority of cases, are sarcomere gene mutations, although an exact genetic etiology is discovered in only 34% of patients (Geske et al., 2018). The disease is inherited in an autosomal dominant pattern and is characterized by incomplete penetrance. Mutations in 11 sarcomeric genes have been described, with MYH7 (encoding β-myosin heavy chain) and MYBPC3 (encoding myosin-binding protein C) mutations accounting for almost 50% of familial cases (Millat et al., 2010). Detected mutations are often unique to each affected family (Efthimiadis et al., 2014). Almost one third of patients will develop severe left ventricular outflow tract obstruction (LVOTO) at rest and another one third during exercise. Patients with severe LVOTO and clinical as well as echocardiographic signs of heart failure are candidates for septal myectomy which significantly reduces disabling symptoms and improves quality of life (Maron et al., 2017). The histologic features of HCM are referred to as tertiary phenotypes, which stem from initial transcriptional and translational alterations and myofilament functional changes followed by secondary molecular events, like altered calcium signaling (Marian and Braunwald, 2017). Histology is the cornerstone of diagnosis and the classic pathologic hallmarks of HCM are: myocyte hypertrophy, myocyte disarray and a notable increase of collagen content (Hughes, 2004). Myocyte hypertrophy is usually accentuated in the subendocardial region. Disarray is defined as a disorganized myocyte architecture and spatial layout in which myocytes are organized in circular arrays around central foci of connective tissue (Sheppard, 2000). A specific cut-off value regarding the extent of myocyte disarray has not been unanimously established but a value of at least 10% has been proposed (Hughes, 2004). In most HCM cases disarray is observed in over 20% of the examined myocardium and thus qualifies as a valuable histologic marker of the disease (Maron et al., 1981). However, some argue that it should not be used as a histologic hallmark since it is completely absent in a noteworthy 21% of patients who underwent septal myectomy (Lamke et al., 2003). The increase of collagen content is defined as the observation of extensive interstitial fibrosis and replacement fibrosis appearing as large patches of collagen. In HCM microvascular remodeling is also observed with characteristic perivascular fibrosis of the small intramural coronary arteries which
exhibit hypertrophy of the tunica intima as well as the tunica media and luminal stenosis (Foà et al., 2019). The diagnosis of HCM relies heavily on clinical examination, family pedigree analysis, cardiac imaging modalities and genetic testing (Elliot et al., 2014). Endomyocardial biopsy is exclusively indicated in scenarios of uncertainty when a cardiac storage or infiltrative disease is suspected and is characterized as a weak recommendation (Class IIb) in the 2014 ESC guidelines on the diagnosis and management of HCM (Elliot et al., 2014). Therefore, cardiac tissue obtained from septal myectomes proves to be a valuable material to further elucidate the pathology of HCM and the intriguing phenotypic complexity of the disease. The current study aims to provide basic insights regarding the histopathology of HOCM in a Greek population sample, which underwent septal myectomy at a single center and is the first of its kind from the Greek region. Moreover, it seeks to investigate possible correlations between histopathological features and clinical, demographic and echocardiographic characteristics.

**Materials and Methods**

**Study Population**

We retrospectively reviewed the HCM patient registry of the 1st Cardiology Department at AHEPA University Hospital in Thessaloniki and the database of the Cardiothoracic Surgery Department at St. Luke’s Hospital in Thessaloniki. Thirty nine (39) patients who underwent septal myectomy for the relief of drug refractory symptoms from 2007 to 2017 were identified, more specifically, twenty two (22) patients from the 1st Cardiology Department at AHEPA University Hospital and seventeen (17) patients from the Cardiothoracic Surgery Department at St. Luke’s Hospital. All myectomes were performed at the Cardiothoracic Surgery Department at St. Luke’s Hospital in Thessaloniki. Included patients were considered to have a diagnosis of primary HCM according to clinical criteria. Patients with left ventricular hypertrophy due to aortic valve stenosis or hypertension were excluded. All patients provided consent regarding the participation in the study and the processing of their anonymized data and samples. Our study was approved by the Bioethics Committee of the Aristotle University of Thessaloniki.
**Demographic and clinical characteristics**

Medical records of the study population were reviewed and each patient's age, gender, diagnosis and NYHA functional class (I to IV) were obtained. Preoperative echocardiographic findings, where available, were reviewed, from which Left Ventricular Ejection Fraction (LVEF), maximal IVS thickness and peak resting LVOT pressure gradient were obtained.

**Surgical Technique**

The surgical technique used for septal myectomy was the one introduced by Andrew Morrow and traditionally applied at the Cardiothoracic Surgery Department at St. Luke's Hospital in Thessaloniki (Morrow, 1978; Efthimiadis et al., 2014). After sternotomy the technique begins with a vertical aortotomy. Through the aortotomy the basal IVS is visualized below the right coronary cusp of the aortic valve. Two parallel longitudinal incisions are made in the basal IVS, connected by a third vertical incision below the right coronary cusp of the aortic valve. A trough of approximately 4-5cm in length is formed by the beforementioned incisions, which extends to just beyond the mitral-septal contact. In specific cases, when required, the incision was extended more distally, reaching the base of the papillary muscles. The procedure aimed to resect 5-10 grams of tissue. Throughout the procedure, transesophageal echocardiography was used in order to monitor and confirm the extent of myectomy.

**Pathology**

Excised interventricular septal tissue was placed into 10% neutral buffered formalin (NBF) immediately after each myectomy procedure. Following NBF fixation the tissue was dehydrated over ascending alcohols (ethanol), cleared with xylene and subsequently embedded in paraffin. Each paraffin-embedded block contained tissue particles representing the full thickness of the surgical specimen from the endocardial to the myocardial layer and was stored under controlled conditions. Thin sections, 4μm-thick, were cut with a microtome and stained with hematoxylin-eosin (H+E) for light microscopy. In order to identify and qualitatively quantify the degree of fibrosis an additional Masson's Trichrome stain was prepared. Apart from
examination by light microscopy, all slides stained with Masson's Trichrome were
digitized for additional detailed examination, archiving and future research by using
a whole slide scanner at a scan magnification of 20X (VENTANA DP 200 slide scanner,
Roche Diagnostics, Basel, Switzerland). Digital slides were examined and images
presented in the current study were extracted with the dedicated software Ventana
Image Viewer (Roche Diagnostics, Basel, Switzerland). All slides were evaluated by
two pathologists, experienced in cardiovascular pathology (the authors S.M. and
N.S.I.) for the following histological parameters, which were recorded in a pathology
report form: myocyte hypertrophy, cytoplasmic vacuolization, subendocardial
fibrosis, interstitial fibrosis, replacement fibrosis, myocardial fiber disarray and
stenosis of intramural coronary arteries. Myocyte hypertrophy was defined as the
presence of an enlarged hyperchromatic nucleus as well as a myocyte diameter
greater than 20μm (greater than the diameter of three red blood cells). In order to
semi-quantitatively report the degree of myocyte hypertrophy we adopted the
grading of McLeod et al. (2009) and considered it mild if myocyte diameters overall
were 21 to 29μm (3-4 RBCs), moderate if 30 to 38μm (4-5 RBCs) and severe if >38μm
(>5 RBCs). Cytoplasmic vacuolization and subendocardial fibrosis were graded as
absent, mild, moderate or severe based on the pathologists' experience. Interstitial
fibrosis and replacement fibrosis were graded separately (from Masson's Trichrome
slides) as absent, mild if its extent was ≤30% of the myocardial area on the slide,
moderate if >30 and <60% and severe if ≥60%, following the semi-quantitative
grading scheme of Galati et al. (2016). Myofibrillar disarray was defined as the
presence of disorganized myocardial fibers following an interlacing, whirling or
herringbone pattern. Disarray was graded as absent, mild if its extent was 1 to 25% of
the myocardial area, moderate if 26 to 50% and severe if >50%, a grading scheme
in concordance with the one proposed by McLeod et al. (2009). Stenosis of coronary
microcirculation was graded as follows: absent, mild if luminal stenosis was <30%,
moderate if ≥30 but <60% and severe if ≥60%.
Statistical Analysis

Statistical analysis was performed using the SPSS Software (version 25, IBM SPSS Statistics, Chicago, Illinois, USA). Normally distributed data were expressed as means (SD) and non-normally distributed as medians (IQR), unless indicated otherwise. Statistical tests were two-tailed and were considered significant for a p-value < 0.05. Normality of continuous data was tested by using the Kolmogorov-Smirnov test. Correlations between categorical ordinal data were tested by using Kendall’s tau-b coefficient. We opted for Kendall’s tau-b over Spearman’s Rho since the former is more robust in small to moderate sample sizes and results in a more meaningful interpretation (Lapata, 2006). Correlations between continuous and categorical ordinal data were tested by using Kendall’s tau-b coefficient, whereas correlations between continuous and categorical dichotomous data (i.e. gender) were tested by using Point Biserial correlation. Correlations between continuous variables were tested by using Pearson’s r coefficient. Missing values were excluded pairwise where required.

Results

Patient characteristics

A total of 39 patients were included in the study (n=39) comprising 22 males (56.4%) and 17 females (43.6%). Mean patient age at the time of myectomy was 53.9 (16.7) years. Patient age at operation ranged from 12 to 79 years. NYHA functional class was available for 35 patients with a median value of 3 (Class III). LVEF measurement was available for 18 patients with a mean of 72.37% (10.65). Maximal IVS thickness by echocardiography was available for 35 patients with a median value of 2.08 (0.34) cm. Peak resting LVOT PG measured by Doppler echocardiography was available for 33 patients with a mean value of 104.88 (44.20) mmHg. A summary of the demographic and echocardiographic features is provided in Table 1. A significant negative relationship of moderate strength (r = −0.49, p = 0.004) was observed between patient age and LVOT PG. Maximal IVS thickness and LVOT PG were not significantly correlated with patient gender. NYHA functional class was positively correlated with patient age at myectomy (tau-b = 0.33, p = 0.016).
Table 1. Demographic and echocardiographic features

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
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</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>53 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>12 - 79</td>
<td></td>
</tr>
<tr>
<td>Gender (n=39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (56.4%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (43.6%)</td>
<td></td>
</tr>
<tr>
<td>NYHA Functional Class (n=35)</td>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>LVEF (n=18)</td>
<td>Mean (SD)</td>
<td>72.37% (10.65)</td>
</tr>
<tr>
<td>Max. IVS thickness in cm (n=35)</td>
<td>Median (IQR)</td>
<td>2.08 (0.34)</td>
</tr>
<tr>
<td>Peak Resting LVOT PG in mmHg (n=33)</td>
<td>Mean (SD)</td>
<td>104.88 (44.20)</td>
</tr>
</tbody>
</table>

**Histopathology**

Myocyte hypertrophy was present in all specimens with the majority (64.1%) exhibiting moderate hypertrophy. Central tendency of each histopathological attribute expressed as the median value was moderate for myocyte hypertrophy (Figure 1), mild for cytoplasmic vacuolization (Figure 2), moderate for subendocardial fibrosis (Figure 3), moderate for interstitial fibrosis (Figure 4), mild for replacement fibrosis (Figure 5), moderate for myocardial fiber disarray (Figure 6) and mild for intramural microvascular stenosis (Figure 7). The aforementioned results are summarized in Table 2. Myocyte hypertrophy was positively correlated with maximal IVS thickness (\(\tau-b=0.43, p=0.002\)). Replacement fibrosis was positively correlated with the grade of microvascular stenosis (\(\tau-b=0.45, p=0.004\)). LVEF was negatively correlated with the grade of interstitial fibrosis (\(\tau-b=-0.43, p=0.035\)) and with the extent of myocardial fiber disarray (\(\tau-b=-0.42, p=0.034\)). No significant relationship was revealed between gender or age at myectomy and histopathological features. No significant relationship was observed between other histopathological features except from those stated above.
**Figure 1.** Myocyte hypertrophy. Hypertrophied cardiomyocytes with increased diameter and enlarged hyperchromatic nuclei
(Masson's Trichrome Stain - 40x magnification)

**Figure 2.** Severe cytoplasmic vacuolization
(Masson's Trichrome Stain - 20x magnification)

**Figure 3.** Subendocardial fibrosis. (a) 28 year-old male with mild subendocardial fibrosis (Masson's Trichrome Stain - 10X magnification) (b) 16 year-old female with moderate subendocardial fibrosis (Masson's Trichrome Stain - 10X magnification) (c) 37 year-old male with severe extensive subendocardial fibrosis (Masson's Trichrome Stain - 2X magnification)

**Figure 4.** Interstitial fibrosis. (Masson's Trichrome Stain - 20X magnification)

**Figure 5.** Replacement fibrosis. 71 year-old male: extensive scar-like replacement fibrosis accompanied by microvascular stenosis (Masson’s Trichrome Stain - 4X magnification)

**Figure 6.** Myofibrillar disarray. (a) 63 year-old female exhibiting whirling myocardial fibers around a small area of collagen deposition (Masson's Trichrome Stain - 10X magnification) (b) 42 year-old female exhibiting a whirling pattern of disoriented myofibrils around small fibrotic foci (Masson's Trichrome Stain - 20X magnification)

**Figure 7.** Stenosed interstitial vessels. (a) 28 year-old male: wall thickening, luminal stenosis, medial hypertrophy, increased collagen within the media and perivascular fibrosis (Masson's Trichrome Stain - 10X magnification) (b) 58 year-old male: severe luminal stenosis, increased collagen within the media (Masson’s Trichrome Stain - 20X magnification)
Table 2. Frequencies of each histopathological attribute. A total of 39 specimens, equal to 39 patients (n=39), were examined. Central tendency (median value) is highlighted in bold.

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Grade</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocyte Hypertrophy</td>
<td>Mild</td>
<td>8 (20.5)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>25 (64.1)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Cytoplasmic Vacuolization</td>
<td>Absent</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>23 (59)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>10 (25.6)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Subendocardial Fibrosis</td>
<td>Mild</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>21 (53.8)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Interstitial Fibrosis</td>
<td>Mild</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>22 (56.4)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>15 (38.5)</td>
</tr>
<tr>
<td>Replacement Fibrosis</td>
<td>Mild</td>
<td>29 (74.4)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Myocardial Fiber Disarray</td>
<td>Mild</td>
<td>16 (41)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>18 (46.2)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Microvascular Stenosis</td>
<td>Mild</td>
<td>25 (64.1)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1 (2.6)</td>
</tr>
</tbody>
</table>
Discussion

The aim of the current retrospective study was to examine the hallmark histopathological characteristics of HOCM in a population of Greek patients undergoing septal myectomy. No previous histopathological study of septal myectomy specimens has been carried out in the Greek region to date. Basic insights regarding age and gender distribution and the spectrum of histopathological findings are worthy of further discussion. In our study, patient ages at myectomy ranged from 12 to 79 years, in relative concordance with ages reported by similar studies on surgical specimens, more specifically by Tazelaar and Billingham (1987) (range 11 to 75 years) and by Lamke et al. (2003) (range 1 to 86 years). Mean age at operation was not significantly different between the two genders. Hypertrophy was observed in all patients. In comparison to our study, similar percentages and central tendencies regarding myocardial fiber disarray and microvascular stenosis were reported by Moravsky et al. (2013), who included 29 myectomy patients in their study. In the current study the extent of myocardial fiber disarray was inversely related to LVEF. Muscle cell disorganization in HOCM is known to affect left ventricular systolic function by impairing contraction (Morimoto et al., 2000). Myocardial fiber disarray was not related to interstitial fibrosis, replacement fibrosis and microvascular stenosis, in accordance with the findings of Varnava et al. (2000), thus suggesting it is a primary phenomenon most probably related to each unique sarcomeric mutation. Microvascular stenosis and dysplasia is a well described feature of HOCM which is present even from the early stages of the disease and is an independent predictor of clinical deterioration (Cecchi et al., 2003). In our series microvascular stenosis, which was present in all specimens, and cytoplasmic vacuolization, which is a feature of chronic ischemia (Lamke et al., 2003), were not related to patient age. Moreover, the degree of microvascular stenosis was positively correlated with the degree of replacement fibrosis. Kwon et al. (2009), in a study which combined Cardiac Magnetic Resonance (CMR) and histopathology after septal myectomy, conclude that the degree of small intramural coronary artery stenosis is independent from demographic characteristics and myocyte disarray and correlates with the degree of myocardial scarring on CMR. It should be noted that
microvascular stenosis did not always co-localize with scar-like patches of collagen in our study. The aforementioned observations support a combinatorial hypothesis regarding the cause of replacement fibrosis, more specifically an intricate interplay between the following mechanisms: a) each unique sarcomeric mutation affects the process of collagen formation even from the early asymptomatic stages of the disease, as observed by Ho et al. (2010), b) paracrine signaling from hypertrophied myocytes to myocardial fibroblasts enables the latter to produce extracellular matrix proteins and c) progressive microvascular stenosis, thus reduced coronary reserve, results in myocyte death which promotes the deposition of collagen to form a scar.

Limitations

It should be noted that the current study exhibits certain limitations. The genetic profile of each patient was not available. Therefore, no conclusions regarding the impact of each unique sarcomeric mutation to the histopathological phenotype of the patients can be drawn. Moreover, detailed echocardiographic data of the patients were partially available, more specifically parameters of diastolic function, degree of mitral regurgitation and regional strain patterns and were subsequently not included in the study. Considering the retrospective design of the study as well as the fact that each patient was evaluated by different physicians, detailed clinical evaluation parameters (presenting symptoms, time from symptoms to diagnosis, time from diagnosis to myectomy, BMI, medications, comorbidities and adverse events) were partially unavailable for a number of patients and were not included in the study.

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Conflicts of interest

None declared

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