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Research Article

Is Congenital Muscular Mitral-Aortic Discontinuity Another Feature of Obstructive Hypertrophic Cardiomyopathy? A Pathology Validation Study

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is an inherited myocardial disease at risk of sudden cardiac death and heart failure, even requiring heart transplantation. A “muscular mitral-aortic discontinuity” has been reported during surgery in the obstructive form. We aimed to validate these findings through pathological analysis of HCM heart specimens from the cardiovascular pathology tissue registry. Hearts with septal asymmetric HCM from sudden cardiac death, other causes of death, or heart transplantation were included. Sex-matched and age-matched patients without HCM served as controls. Gross and histologic analysis of the mitral valve (MV) apparatus and the mitral-aortic continuity were performed. Thirty HCM hearts (median age, 29.5 years; 15 men) and 30 controls (median age, 30.5 years; 15 men) were studied. In HCM hearts, a septal bulging was present in 80%, an endocardial fibrous plaque in 63%, a thickening of the anterior MV leaflet in 56.7%, and an anomalous insertion of papillary muscle in 10%. All cases but 1 (97%) revealed a myocardial layer overlapping the mitral-aortic fibrous continuity on the posterior side, corresponding to the left atrial myocardium. A negative correlation between the length of this myocardial layer and the age and the anterior MV leaflet length was found. The length did not differ between HCM and controls.

Pathologic study of obstructive HCM hearts does not confirm the existence of a "muscular mitral-aortic discontinuity". An extension of left atrial myocardium, overlapping posteriorly the intervalvular fibrosa, is rather visible, and its length decreases with age, possibly as a consequence of left atrial remodeling. Our study highlights the fundamental role of thorough gross examination and the value of organ retention for further analysis in order to validate new surgical and imaging findings.

Introduction

Hypertrophic cardiomyopathy (HCM) is a heart muscle disease characterized by ventricular wall hypertrophy responsible for structural and functional abnormalities occasionally leading to

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sudden cardiac death (SCD). It is regarded as the most common genetically determined cardiomyopathy, usually caused by mutations in genes encoding for proteins of the cardiac sarcomere, with an estimated prevalence of 1:500, although possibly even higher.[1] HCM can be diagnosed during life or by pathological examination at autopsy. The pathologist has the chance to study full heart specimens of HCM obtained either from heart transplantation (HTx) or autopsy. Many features, such as myocyte hypertrophy, architectural disorganization (disarray), interstitial and replacement-type fibrosis, as well as intramural small vessel disease, can help in diagnosing HCM using a microscope.[2] Recurrent myocardial ischemia and replacement-type fibrosis can contribute to SCD or disease progression toward heart failure in patients with HCM, with possible role of intramural small vessel disease and myocardial bridging (intramyocardial course of a major coronary artery segment).[3-5] Among the wide phenotypic heterogeneity of HCM, the asymmetric pattern of left ventricular (LV) hypertrophy, where the interventricular septum (IVS) is more severely thickened compared to the LV free wall, is usually associated with LV outflow tract (LVOT) obstruction. The pathophysiology of the dynamic LVOT obstruction is related to the interaction between the hypertrophied IVS and the mitral valve (MV) apparatus, leading to the systolic anterior motion of the MV and eventually to mitral regurgitation.[6] MV and LVOT abnormalities have been variably reported in HCM in imaging, surgical, and pathology studies.[7-12] Recently, a muscular band dividing the anterior MV leaflet and the aortic valve was identified at surgical inspection in a cohort of patients with HCM undergoing septal myectomy for refractory symptoms secondary to dynamic LVOT obstruction.[13] We aimed to confirm the existence and to assess the prevalence of this peculiar finding, which has been called “muscular mitral-aortic discontinuity,” in explanted or autopsy hearts of patients affected by asymmetric obstructive HCM and to report its correlation with other clinical and pathological data.

Methods

Study Population

Our Cardiovascular Pathology Unit acts as a referral center for SCD cases of young patients (under 40 years) undergoing autopsy in the Veneto Region, North-East of Italy, and for explanted native hearts from HTx. From the SCD collection (1980-2021), we retrospectively retrieved HCM cases affected by asymmetric basal septal hypertrophy (defined as septal-to-posterior wall thickness ratio $\geq$1.3) in which the heart specimen was still available and preserved for analysis. Similarly, we retrieved HCM cases with asymmetric basal septal hypertrophy from the HTx tissue registry (1985-2021). The third subgroup comprised patients affected by HCM with asymmetric basal septal hypertrophy who died due to causes other than SCD and underwent full autopsy at our institution (1980-2021). Whole hearts from autopsies of patients without any relevant cardiac condition served as age-matched and sex-matched controls. The diagnosis of HCM was based on the demonstration of LV hypertrophy in the absence of any other disorder that could be responsible for it.[2]

Measurements

Each heart was examined according to current guidelines.[14] After the conventional short-axis sectioning, the LV was carefully inspected by opening the base of the heart with the inflow-outflow method to expose the valvular apparatuses.

The following features have been evaluated for each cardiac specimen: total heart weight (paying attention to removal of pericardium, postmortem clots, and cutting the great arteries 2 cm above semilunar valves, venae cavae, and pulmonary veins at their junctions with the atria in case of autopsy); transverse and longitudinal diameters; wall thickness of the LV free wall, IVS and right ventricular (RV) free wall, excluding papillary muscles and trabeculae; presence of basal IVS bulging (sigmoid septal morphology) and subaortic endocardial thickening; MV circumference and thickening; and presence and type of anomalous insertion of papillary muscles. Left atrial dilatation was assessed in a qualitative fashion in each specimen. If echocardiographic assessment of the left atrium was available for the last hospital admission of the patient, left atrial dilatation was deemed as present if either imaging or pathological evaluation showed positive findings.

The aortic valve and the MV were systematically inspected in each heart specimen. Specific focus was put on the region between the anterior leaflet of the MV and the posterior and left cusps of the aortic valve, that is, the mitral-aortic fibrous continuity. Any presence of additional muscular tissue in this region was recorded. By inspecting the LVOT with posterior transillumination along the mitral-aortic region, a left atrial myocardium extension (LAMEX) below the nadir of the aortic valve cusps was noted. Similarly to the previously reported "muscular mitral-aortic discontinuity", the length of LAMEX was defined as the distance between the line joining the nadir of the posterior and left aortic cusps and the furthest point of the nontranslucent tissue at the level of the anterior MV leaflet (Fig. 1).

The MV leaflet length was calculated as the maximum distance from the free edge to the hinge line, with the heart opened by an incision through the middle of the posterior MV leaflet.[15] Moreover, because in the imaging setting the anterior MV leaflet length is usually calculated as the distance from its most distal extent to its insertion into the posterior aortic wall,[9] including the portion of the mitral-aortic continuity, we summed the length of both the anterior MV leaflet and the LAMEX to obtain a pathology measure of the anterior MV leaflet length analogous to the clinical one.

Representative histological sections, including the aortic posterior cusp, the anterior MV leaflet, and the left atrial myocardium, were taken. The sections were routinely processed for histology and stained with both hematoxylin-eosin and Heidenhain Azan trichrome.

For interobserver variability, 2 cardiovascular pathologists (M.D.G., C.B.) independently measured anterior and posterior MV leaflet lengths, MV circumference, and length of LAMEX, without prior knowledge of the patients’ data and blinded to the previous morphometric results.

The study was approved by the local institutional review board.

Statistical Analysis

Data are expressed as median $\pm$ IQR for the continuous variables or as raw numbers and percentages for categorical variables. Mann-Whitney test and Kruskal-Wallis test were used to compare variables among 2 or more categories. Pearson correlation coefficient was used to evaluate the correlation between different variables. Where relevant, 2-sided P values $<.05$ were considered as statistically significant. Jamovi project Version 2.3 was used for analysis and for graphic presentations.

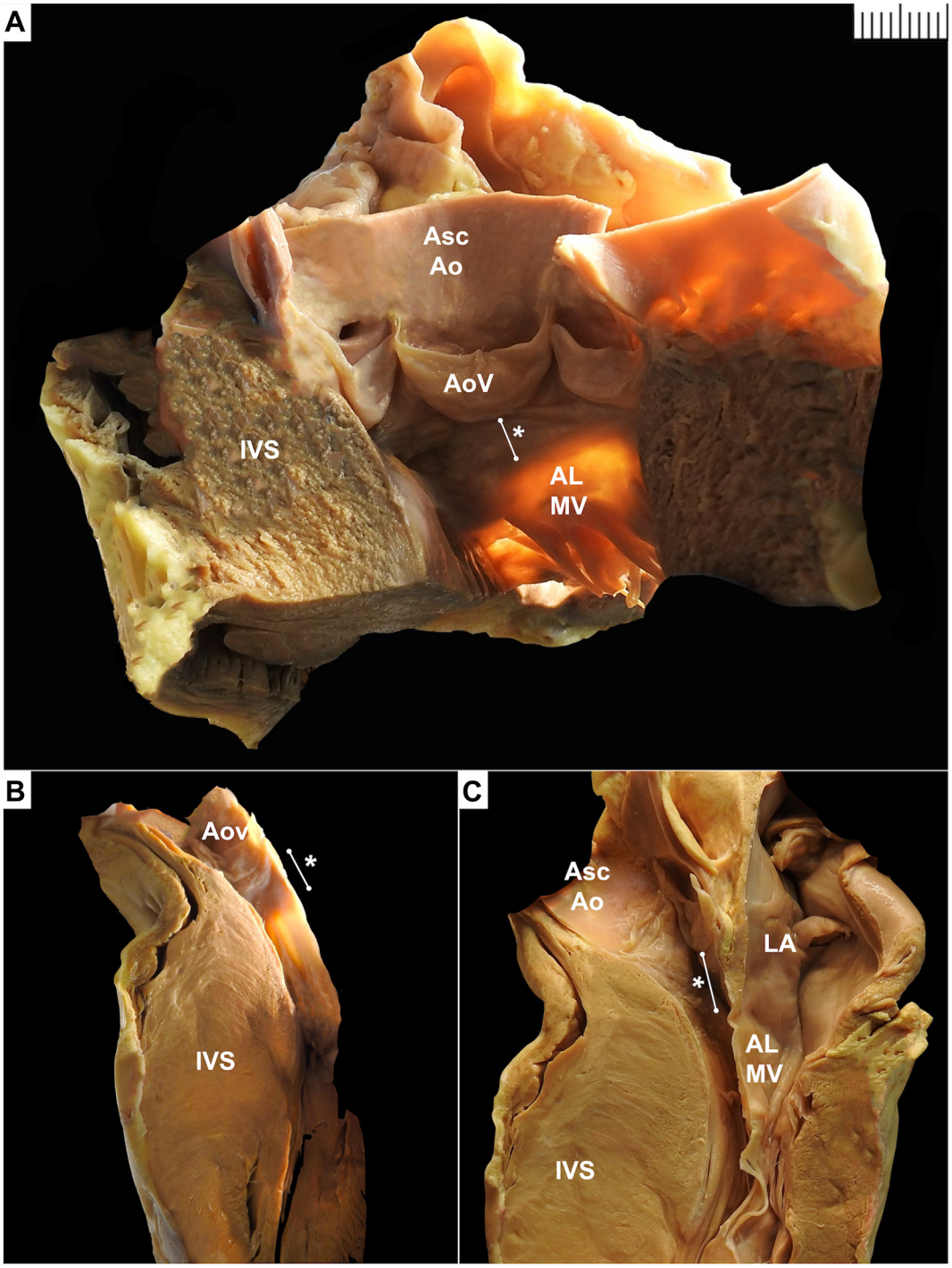

Figure 1.
Gross examination of the left ventricular outflow tract with focus on the mitral-aortic continuity. (A) Transillumination of the opened LVOT allows to identify the presence of a muscular band below the aortic valve (AoV). (B-C) By further inspection, in a long-axis view of the LVOT, the muscular band results to be the inferior part of the left atrial myocardium attaching to the AL MV. *Length of the left atrial myocardium extension (LAMEX) at the level of the mitral-aortic continuity. Asc Ao, ascending aorta; AL MV, anterior leaflet of the mitral valve; IVS, interventricular septum; LA, left atrium.

Results

Study Population

A total of 30 asymmetric basal septal HCM cases with whole heart specimens available for review were evaluated and compared with 30 age-matched and sex-matched cases in the control group. Genetic data were available in 8 of 30 cases (26.7%). Two cases had a negative test, whereas the remaining 6 cases had pathogenic or likely pathogenic mutation: 1 case with double mutation in *MYBPC3* and *TNNI3*, 3 cases with mutation in *MYBPC3*, 1 in *TNNI3*, and 1 in *MYH7* gene. Table 1 shows the characteristics

Table 1
Gross pathology findings in hypertrophic cardiomyopathy and control populations

Characteristic	Hypertrophic cardiomyopathy (n = 30)	Controls (n = 30)	*P*
Age, y	29.5 (22.0-46.7)	30.5 (21.0-50.0)	.90
Male sex	15 (50)	15 (50)	1.00
Heart weight (g)	470.0 (385.6-570.8)	330.0 (269.2-454.2)	.01
LV wall thickness (cm)	13.0 (11.0-14.1)	11.0 (11.0-12.0)	.01
IVS wall thickness (cm)	17.0 (15.0-24.1)	12.0 (10.9-13.0)	.01
RV wall thickness (cm)	4.0 (4.0-5.0)	3.0 (3.0-4.0)	.01
LA dilatation	10 (30)	0 (0)	.01
MV circumference (cm)	9.0 (7.8-10.3)	9.2 (8.5-10.0)	.46
MV anterior leaflet length (cm)	2.2 (1.9-2.3)	2.0 (1.7-2.3)	.19
MV posterior leaflet length (cm)	1.4 (1.3-1.6)	1.2 (0.9-1.3)	.01
LAMEX length (cm)	0.30 (0.20-0.50)	0.20 (0.19-0.30)	.01
MV anterior leaflet length + LAMEX length (cm)	2.5 (2.2-2.7)	2.3 (2.0-2.5)	.02
MV thickening	17 (56.7)	0 (0)	.01
MV papillary muscle anomalous implant	3 (10)	0 (0)	.08
Basal IVS bulging	24[a] (80)	0 (0)	.01
Basal IVS endocardial plaque	19 (63.3)	0 (0)	.01

Data are expressed as median (IQR) for continuous variables and number (%) for categorical variables.
IVS, interventricular septum; LA, left atrium; LAMEX, left atrial myocardium extension; LV, left ventricle; MV, mitral valve; RV, right ventricle.
[a] Six cases without basal IVS bulging presented with either extensive septal replacement-type fibrosis (n = 4) or previous surgical myectomy (n = 2).

of the study groups. As expected, patients with HCM had significantly greater weight and thickness of LV, IVS, and RV walls. The in-depth analysis of the HCM subpopulations is enlisted in Table 2. SCD cases had significantly thicker IVS than HTx and HCM groups with other causes of death. MV measurements were not significantly different among subgroups.

The detailed gross analysis of the mitral-aortic continuity is depicted in Figure 1. Gross and histological evaluation demonstrated the presence of the LAMEX, overlapping the fibrous continuity between the posterior and left cusps of the aortic valve and the anterior leaflet of the MV on the posterior side (Fig. 2), with a length ranging from 0 to 6.5 mm (median, 3.0 mm) in HCM. This muscular layer was also present in the control group. The LAMEX was significantly longer in SCD cases than in HTx cases. Moreover, HCM cases had a longer LAMEX overall than the control group (Fig. 3). The length of the anterior MV leaflet was not calculated to be higher in the HCM group than in the control group; however, by summing the anterior MV leaflet length and the LAMEX, the difference became significant (Table 1).

A negative correlation was demonstrated between the length of LAMEX and the patient age in the HCM population, whereas the correlation was slightly positive in the control population. In patients with HCM, the LAMEX overlapping the mitral-aortic continuity also inversely correlated with the length of the anterior MV leaflet (but there was no correlation between continuity and anterior MV leaflet length plus LAMEX) and the MV circumference

Table 2
Pathology findings in the 3 hypertrophic cardiomyopathy subgroups

Characteristic	Hypertrophic cardiomyopathy (n = 30)			*P*
	SCD (n = 10)	HTx (n = 11)	Other (non-SCD non-HTx) (n = 9)	
Age, y	25.5 (19.6-29.0)	44.0 (23.0-54.8)	41.0 (29.7-60.3)	.02
Male sex	7 (70)	4 (36.4)	4 (44.4)	.28
Asymmetric IVS hypertrophy	10 (100)	10 (100)	10 (100)	1.00
Heart weight (g)	555.0 (420.4-580.0)	400.0[a] (364.5-520.0)	470.0 (376.7-620.0)	.31
LV wall thickness (cm)	13.5 (11.0-16.0)	13.0 (11.2-14.7)	12.0 (10.7-14.0)	.41
IVS wall thickness (cm)	24.5 (17.9-26.3)	15.0 (13.0-19.5)	15.0 (14.3-18.7)	.01
RV wall thickness (cm)	4.0 (3.0-4.0)	5.0 (4.0-6.8)	4.0 (4.0-4.3)	.01
Transverse diameter (cm)	10.0 (9.5-11.0)	11.0 (10.0-11.9)	11.5 (10.2-12.3)	.16
Longitudinal diameter (cm)	10.0 (9.0-10.2)	9.5 (9.0-10.0)	10.0 (9.5-11.3)	.12
LA dilation	0 (0)	7 (63.6)	3 (33.3)	.01
MV circumference (cm)	7.8 (7.4-9.8)	9.6 (8.3-10.3)	9.3 (8.0-10.4)	.38
MV anterior leaflet length (cm)	2.2 (2.0-2.2)	2.3 (1.9-2.6)	2.0 (1.7-2.3)	.22
MV posterior leaflet length (cm)	1.4 (1.3-1.5)	1.4 (1.3-1.4)	1.6 (1.3-1.7)	.16
LAMEX length (cm)	0.45 (0.30-0.51)	0.2 (0.20-0.38)	0.30 (0.20-0.43)	.03
MV thickening	5 (50)	5 (45.5)	7 (77.8)	.30
MV papillary muscle anomalous implant	1 (10)	0 (0)	2 (22.2)	.26
Basal IVS bulging	7 (70)	9 (81.8)	8 (88.9)	.58
Basal IVS endocardial plaque	4 (40)	7 (63.6)	8 (88.9)	.09

Data are expressed as median (IQR) for continuous variables and number (%) for categorical variables.
IVS, interventricular septum; LA, left atrium; LAMEX, left atrial myocardium extension; LV, left ventricle; MV, mitral valve; RV, right ventricle.
[a] HTx cases are missing portion of the atria.

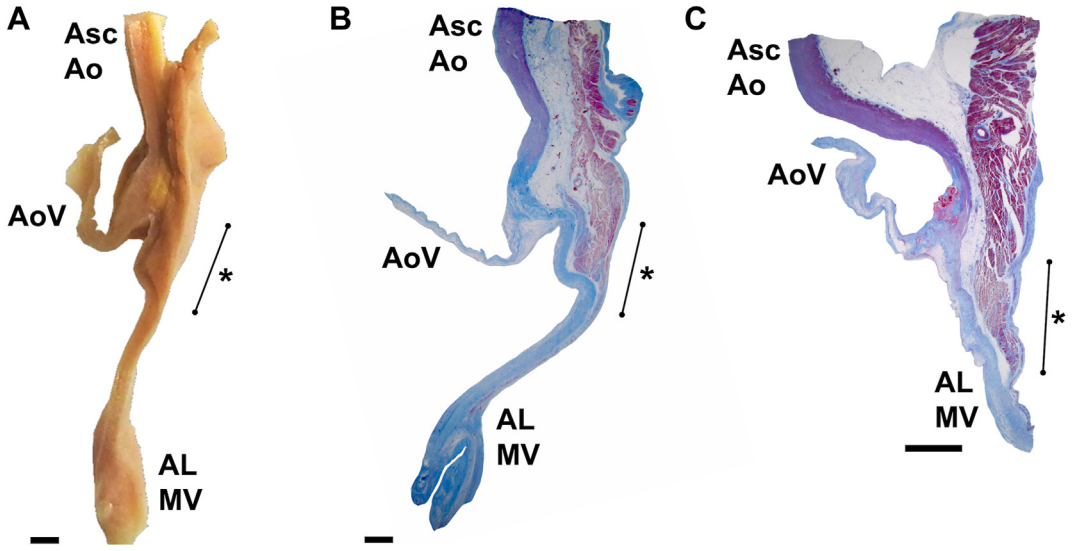

Figure 2.
Gross and histologic investigation of the mitral-aortic continuity. (A-B) Macroscopic view and trichrome stained histology of the mitral-aortic fibrous continuity in a patient with HCM confirm the presence of overlapping left atrial myocardium (LAMEX); (C) In a control patient, a similar finding is present with left atrial myocardium facing the posterior cusp of the aortic valve (AoV) and the upper portion of the anterior leaflet of the mitral valve (AL MV). *Length of the LAMEX at the level of the mitral-aortic continuity. Asc Ao, ascending aorta. (B-C) Heidenhain trichrome stain, panoramic view. All scale bars 2 mm.

(Fig. 4). Additional analyses are available in Supplementary Figures S1 and S2.

Discussion

A muscular mitral-aortic discontinuity has been recently reported as a new congenital abnormality in asymmetric obstructive HCM. According to the authors, a long muscular mitral-aortic discontinuity by displacing the anterior MV leaflet apically could predispose to LVOT obstruction.[13] Our pathology study clearly demonstrates that the surgically observed muscular discontinuity is not a muscular band interposed between the aortic valve and the MV but rather corresponds to an extension of left atrial myocardium, overlapping on the posterior side the fibrous continuity between the posterior and left aortic cusps and the

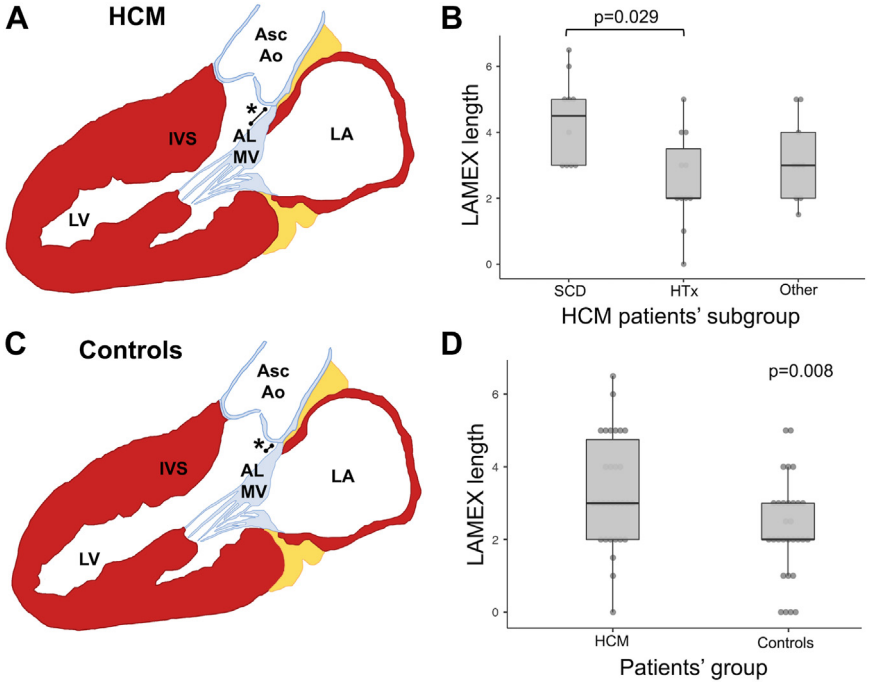

Figure 3.
Left atrial myocardial extension in HCM vs. controls. Left, Schematic view of a long-axis section of the heart in a patient with HCM (A) and in a control patient (C). *Length of the left atrial myocardial extension (LAMEX). Right, Box plot of LAMEX in different HCM subgroups (B) and in HCM vs controls (D). Only significant *P* values are reported.

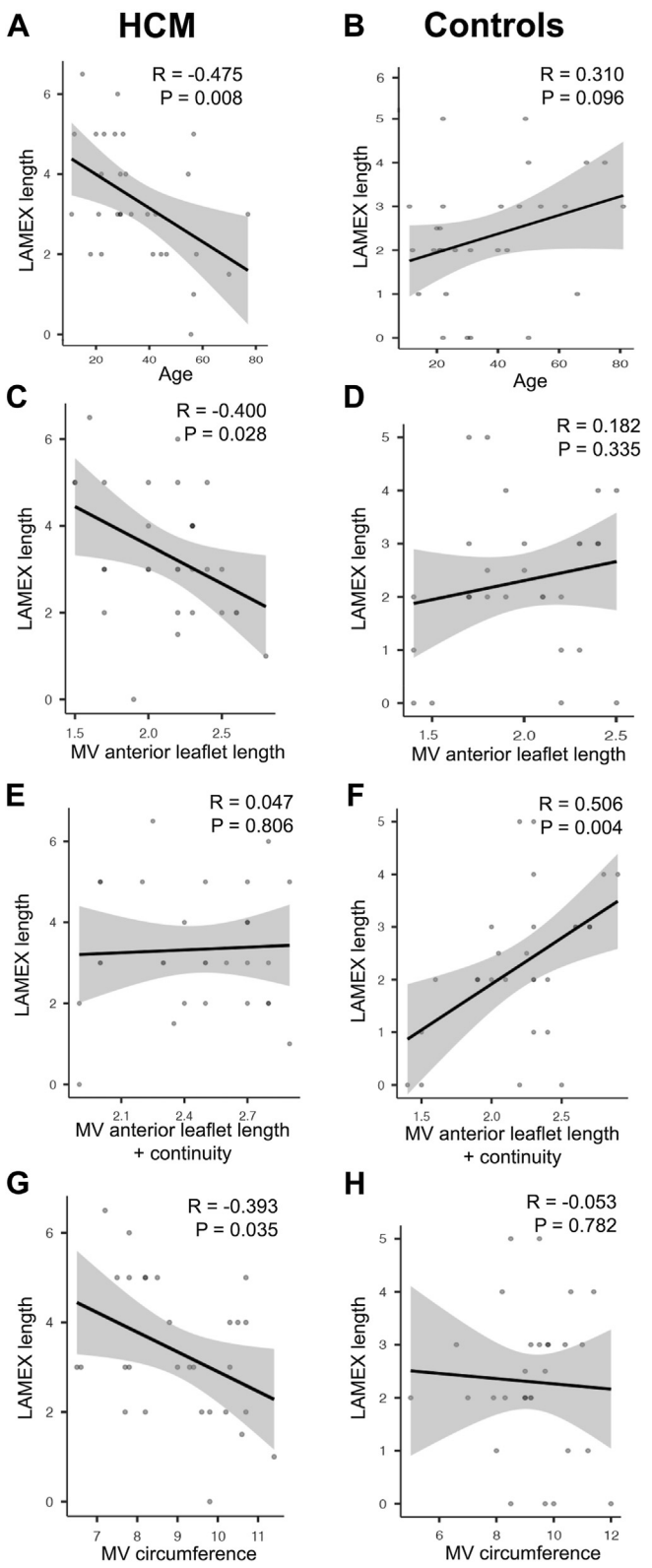

Figure 4.

Correlation between left atrial myocardial extension and different parameters in HCM and in controls. Correlation between the length of the left atrial myocardial extension (LAMEX) and age in HCM (A) and in controls (B); between the length of LAMEX and the length of the anterior leaflet of the mitral valve in HCM (C) and in controls (D); between the length of LAMEX and the length of the anterior leaflet of the mitral valve plus continuity in HCM (E) and in controls (F); between the length of LAMEX and the circumference of the mitral valve in HCM (G) and in controls (H).

anterior leaflet of the MV (Fig. 2). This muscular layer is variably present in our 2 cohorts because only 5 patients (1 HCM and 4 controls) did not present with it, corresponding to 8.3% of the entire population. The atrial muscular band is distinctly recognizable only by transillumination of the opened LVOT, extending in a semilunar shape below the posterior and left cusps.

Indeed, the LAMEX could appear as a red muscular band during surgeries with a transaortic approach, as described intraoperatively at gross inspection by Ferrazzi et al.[13] In contrast to their observations, a gross and histologically proven fibrous continuity between the aortic cusps and MV anterior leaflet is confirmed by the current work, with muscular tissue being only variably superimposed posteriorly along the intervalvular fibrosa.

Further, mitral-aortic discontinuity would be an unprecedented finding in HCM because it has never been reported in previous surgical myectomy or pathology series of obstructive HCM.[12,16] As underlined by Ferrazzi et al, there is no noninvasive technique, including echocardiography, computed tomography, and cardiac magnetic resonance, that could reliably identify the muscular mitral-aortic discontinuity. Therefore, the validation could come only from an investigation of explanted heart specimens of patients with obstructive HCM because only limited intraoperative inspection is possible at surgery and no histology is feasible.

Historically, the term mitral-aortic valve discontinuity has been interchangeably used with mitral-aortic valve separation to define the distance between the base of either the posterior or left cusps and the basal attachment of the anterior MV leaflet.[17,18] Because the anterior MV leaflet is continuous with the aortic valve cusps and aorta, its basal attachment is traditionally defined as the boundary between the free wall of the left atrium and the anterior leaflet of the MV.[19] Thus, the muscular tissue in the area of the anterior leaflet and aortic valve termed muscular mitral-aortic discontinuity corresponds to the LAMEX, which overlaps the fibrous tissue at the base of the aortic cusps.

A true muscular discontinuity has been described only in congenital malformations: in malposition of the great arteries, including double outlet right ventricle, the conal musculature at both subpulmonary and subaortic levels prevents semilunar-atrioventricular fibrous continuity.[20-22] In normal hearts, the measure of the physiological mitral-aortic separation was evaluated as constant through age,[17] whereas an increase was noted in congenital subaortic stenosis caused by fibroelastic tissue originating on the muscular ventricular septum below the right aortic sinus. The authors postulated a role for this increased mitral-aortic separation in the contribution to the etiology of subaortic stenosis by altering of the angle of blood ejection from the LV during a critical period of early heart development.[18]

The hemodynamic functional aortic subvalvar stenosis was indeed the first description of HCM by Brock in 1957.[23] From being considered a mimicker of aortic stenosis, obstructive HCM was then recognized as a myocardial disease directly affecting the MV. The long-standing debate about whether the changes to the MV leaflets are primary rather than acquired is still in place.[24-26] A relationship between anterior MV leaflet elongation, LVOT geometry, and LVOT obstruction exists with implications for treatment choice.

Our data confirm that the length of the anterior MV leaflet is greater in HCM than in controls, if, similarly to the clinical setting, the measure included both the anterior MV leaflet and the LAMEX length. The overall prevalence of basal IVS bulging (80%), basal IVS endocardial fibrous plaque (63.3%), MV thickening (56.7%), and papillary muscle anomalous insertion directly into MV leaflet

(10%) is higher than previously reported, even restricting the analysis to the SCD subgroup, as in the series by Bhatia et al.[11] No significant differences in MV abnormalities were found by comparing the 3 HCM subgroups.

We report a significant difference in the length of the LAMEX between HCM and controls, and we confirm the inverse correlation between its length and age in the HCM group. Being present also in control patients and in young patients with HCM, with progressive disappearance in the older ones, this entity should not be considered a congenital defect, as originally reported by Ferrazzi et al.[13] Its role as a primary morphologic abnormality of HCM appears further weakened by our finding of inverse correlation with the anterior MV leaflet length and MV circumference, even if the correlation between the length of the LAMEX and the sum of the anterior MV leaflet and the LAMEX is clearly nonsignificant. A mechanism for a decrease in the length of LAMEX with increasing MV dimensions and age could be the progressive chamber remodeling with atrial muscular fiber retraction, causing a reduction in thickness and elongation of atrial myocardium.

This is a retrospective study based on postmortem and explanted hearts collected in a referral center for cardiovascular pathology. We acknowledge the relatively small number of patients with asymmetric basal septal HCM who were enrolled for the investigation, but we underline the need to assess full HCM hearts with preserved LVOT and mitral-aortic continuity. Genetic data were available only in a subset of our population; however, the aim of the study was to validate the existence of a congenital abnormality of the mitral-aortic continuity in obstructive HCM.

In conclusion, our morphologic examination of hearts with asymmetric basal septal HCM demonstrates the presence of left atrial myocardium overlapping but not interrupting the mitral-aortic fibrous continuity. This myocardial layer is almost invariably present in all HCM subgroups and in the control population. Its modification with age and MV measurements suggests that it likely represents an epiphenomenon of complex interactions between chamber remodeling and valve morphology, rather than a primary component of the phenotypic spectrum of HCM. This study confirms that persistent myocardium at the level of the mitral-aortic intervalvular fibrosa is extremely unlikely to be an important cause of LVOT obstruction in HCM. Further clinicopathologic correlations are warranted to clarify the real key factors in determining LVOT obstruction in HCM, possibly adopting common methodologies and nomenclature for both clinical and pathological studies.

Author Contributions

M.D.G. drafted the paper, collected the data, and contributed to the data analysis. M.M. collected the data and contributed to the data analysis. M.B.M. contributed to the data analysis. A.A., C.C., M.P.M., K.P., D.C., G.T., and S.R. provided senior supervision. C.B. collected the data and contributed to writing the paper.

Data Availability Statement

All data relevant to the study are included in the article. The original data (from which the aggregated data shown in this report are derived) are available on reasonable request to the corresponding author.

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Declaration of Competing Interest

The authors declare no competing interests.

Ethics Approval and Consent to Participate

This study involves postmortem and explanted tissues and was approved by the local institutional review board.

Supplementary Material

The online version contains supplementary material available at https://doi.org/10.1016/j.labinv.2023.100196.

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