Original research

Morphology of the mural and commissural atrioventricular junction of the mitral valve

Agata Krawczyk-Ożóg ,[1,2] Jakub Batko,[1] Barbara Zdzierak,[2] Artur Dziewierz,[2,3] Kamil Tyrak,[1] Filip Bolechała,[4] Paweł Kopacz,[4] Marcin Strona,[4] Krzysztof Gil,[5] Jakub Hołda,[1] Mateusz K Hołda[1,6]

[1]Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland
[2]Clinical Department of Cardiology and Cardiovascular Interventions, University Hospital, Krakow, Poland
[3]2nd Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[4]Department of Forensic Medicine, Jagiellonian University Medical College, Krakow, Poland
[5]Department of Pathophysiology, Jagiellonian University Medical College, Krakow, Poland
[6]The University of Manchester, Manchester, UK

Correspondence to
Dr Agata Krawczyk-Ożóg, Department of Anatomy, Jagiellonian University Medical College, Krakow 31-034, Poland;
krawczyk.ozog@gmail.com

Received 13 May 2023
Accepted 23 September 2023

To cite: Krawczyk-Ożóg A, Batko J, Zdzierak B, *et al*. *Heart* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/heartjnl-2023-322965

ABSTRACT

Objective This study investigates mitral annular disjunctions (MAD) in the atrial wall-mitral annulus-ventricular wall junction along the mural mitral leaflet and commissures.

Methods We examined 224 adult human hearts (21.9% females, 47.9±17.6 years) devoid of cardiovascular diseases (especially mitral valve disease). These hearts were obtained during forensic medical autopsies conducted between January 2018 and June 2021. MAD was defined as a spatial displacement (≥2 mm) of the leaflet hinge line towards the left atrium. We provided a detailed morphometric analysis (disjunction height) and histological examination of MADs.

Results MADs were observed in 19.6% of all studied hearts. They appeared in 12.1% of mural leaflets. The P1 scallop was the primary site for disjunctions (8.9%), followed by the P2 scallop (5.4%) and P3 scallop (4.5%). MADs were found in 9.8% of all superolateral and 5.8% of all inferoseptal commissures. The average height for leaflet MADs was 3.0±0.6 mm, whereas that for commissural MADs was 2.1±0.5 mm ($p<0.0001$). The microscopical arrangement of MADs in both the mural leaflet and commissures revealed a disjunction shifted towards left atrial aspect, filled with connective tissue and covered by elongated valve annulus. The size of the MAD remained remarkably uniform and showed no correlation with other anthropometric factors (all $p>0.05$).

Conclusions In the cohort of the patients with healthy hearts, MAD is present in about 20% of all studied hearts. The MADs identified tend to be localised, confined to a single scallop. Moreover, MADs in the commissures are notably smaller than those in the mural leaflet.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mitral annular disjunction (MAD) is a spatial displacement of the leaflet hinge line towards the left atrial wall. It is recognised both as an anatomical variant and as a potential risk factor for adverse events. The observed prevalence of MAD fluctuates based on the patient group, imaging techniques and the specific criteria used to define MAD.

WHAT THIS STUDY ADDS

⇒ In our analysis of the atrial wall-mitral annulus-ventricular wall junction in the cohort of the patients with healthy hearts, we found MAD in 12.1% of mural mitral leaflets, 9.8% of superolateral commissures and 5.8% of inferoseptal commissures. This study offers detailed morphological and histological characteristics of MAD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The noticeable presence of MAD in those with otherwise normal heart structures points to it being an anatomical variation rather than an anomaly. Future investigations should be directed towards defining thresholds for clinically meaningful MAD. This would further refine diagnostic precision and elevate the patient management standard.

INTRODUCTION

The mitral valve annulus is a complex anatomical structure that supports the mitral valve leaflets. The aortic part of the annulus contributes to the aorto-mitral continuity, while the mural part hinges to the junction of the atrial myocardium and ventricular myocardium. While extensive anatomical and clinical studies have analysed components of the mitral valve complex, debates persist regarding the appropriate nomenclature, definitions, boundaries and inter-relationships.[1–4]

The first description and illustration of mitral annular disjunction (MAD) were featured by Henle in 1876.[5] Zimmerman then introduced the notion of lateral and medial disjunctions.[6] Hutchins *et al*'s seminal work in 1986 focused on a histological review of the mitral annulus region in patients with mitral valve prolapse. Their work detailed the relationships among the left atrial wall, mitral leaflet attachment line and the left ventricular wall (atrial wall-mitral annulus-ventricular wall junction). In their analysis, they recognised various patterns of mitral annulus placement, including MAD, defined as an abnormal displacement of the mural mitral leaflet attachment line onto the left atrial wall, distancing it from the left ventricular myocardium. This displacement creates a separation (disjunction) region between the leaflet hinge line and the supported ventricular wall. MAD was proposed

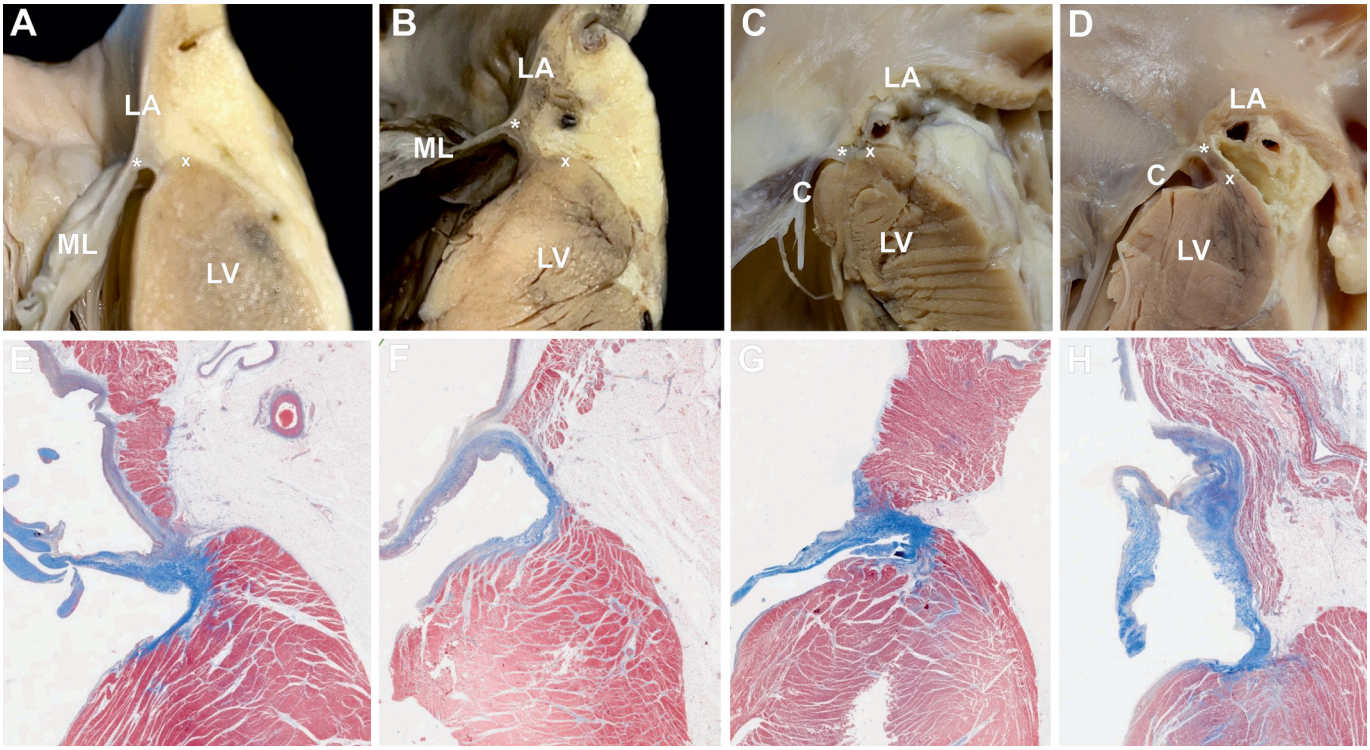

Figure 1 Photographs of various autopsy heart specimens and histological images (Masson's trichrome). These images display longitudinal sections through the different parts of mitral atrioventricular junction (mural leaflet (ML) and commissures), illustrating various types of junction arrangements. (A) ML with no mitral annular disjunction (MAD) (classical type), where mitral ML insertion point (*) is located at the border between the left atrial (LA) myocardium and left ventricular (LV) myocardium. (B) ML with MAD, which presents a spatial displacement of the mitral leaflet hinge line (*) towards the left atrium. (C) Superolateral commissure with classical annular arrangement (MAD not present). (D) Superolateral commissure with MAD. (E–H) Corresponding histological images with and without MAD. x denotes the highest point of the left ventricular myocardium; C denotes commissural leaflet.

as a contributing factor to mitral valve leaflet prolapse.[7] In a subsequent study, Angelini *et al* detected disjunctions in both normal and prolapsed valves across 13 heart specimens.[8] Since this time, no significant autopsy studies have explored the atrial wall-mitral annulus-ventricular wall junction in healthy human hearts.

The morphological nature of MAD, defined as a spatial displacement of the leaflet hinge line towards the left atrial wall, is poorly known. The clinical implications of MAD have been a topic of debate, especially concerning its link to mitral valve prolapse, arrhythmias and sudden cardiac deaths.[9] While imaging has detected MAD in healthy patients,[10] a comprehensive evaluation of its prevalence and extent is lacking. Notably, MAD appears often in those with mitral valve prolapse, correlating with advanced myxomatous degeneration.[11 12] A systematic literature review by Bennett *et al* underscored the evidence linking ventricular arrhythmias with MAD.[10] They found that ventricular arrhythmias' incidence rose with an increased MAD height and circumferential area (width).[13] Nonetheless, the prevalence of MAD varies depending on the patient population, imaging method and MAD's definition.[14] Various imaging modalities including transthoracic echocardiography, transoesophageal echocardiography, cardiac magnetic resonance and coronary CT angiography have been employed to visualise MAD.[12 13 15–22] In

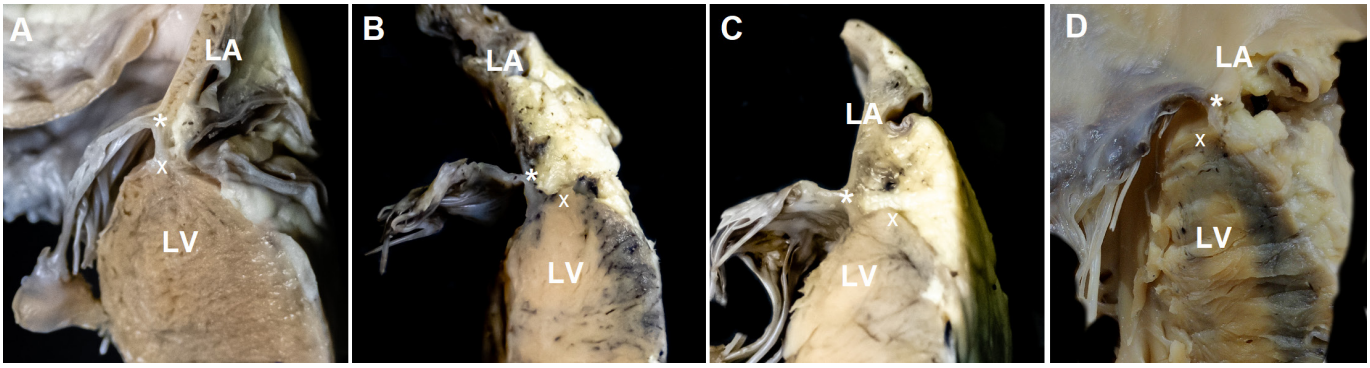

Figure 2 Photograph of autopsy heart specimens. These images display longitudinal sections through the mitral annular disjunctions, presenting different heights of mural leaflet (A–C) and inferoseptal commissure (D) disjunctions towards the left atrium. * denotes mitral leaflet hinge line; x denotes the highest point of the left ventricle myocardium. LA, left atrium; LV, left ventricle.

Table 1 Distribution of mitral annular disjunction (MAD) within the mitral mural leaflet and commissures

Number of hearts with MAD in mural leaflet	27 (100%)
Only in single scallop	15/27 (55.6%)
Only in P1 scallop	9/27 (33.3%)
Only in P2 scallop	5/27 (18.5%)
Only in P3 scallop	1/27 (3.7%)
In multiple scallops	12/27 (44.4%)
Both in P1 and P2 scallops	3/27 (11.1%)
Both in P2 and P3 scallops	1/27 (3.7%)
Both in P1 and P3 scallops	5/27 (18.5%)
In all scallops (P1, P2 and P3)	3/27 (11.1%)
Number of hearts with MAD in commissures	32 (100%)
Only in superolateral commissure	19/32 (59.4%)
Only in inferoseptal commissure	10/32 (31.3%)
In both commissures	3/32 (9.4%)
Number of hearts with MAD coexistence in mural leaflet and commissures	15

this study, we aim to address these gaps in anatomical knowledge by examining atrial wall-mitral annulus-ventricular wall junction across a large cohort of structurally normal hearts.

MATERIALS AND METHODS

This study was conducted at the Department of Anatomy of the Jagiellonian University Medical College in Krakow, Poland. The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki.

We analysed 224 autopsied healthy human hearts (21.9% females, 78.1% males), with a mean age of 47.9±17.6 years. These samples were collected during standard forensic medical autopsies conducted from January 2018 to June 2021 at the Department of Forensic Medicine, Jagiellonian University Medical College, Krakow, Poland. The leading causes of death were suicide, homicide, traffic and home accidents. Data regarding the cadaver's sex, age, body weight and height were obtained. The exclusion criteria comprised a history of heart surgeries or grafts, any noticeable severe macroscopic heart or vascular system pathologies found during the autopsy, heart trauma, macroscopic signs of cadaver decomposition, any valvular diseases, arrhythmias and suspected sudden cardiac death. Hearts exhibiting macroscopic signs of mitral valve disease, such as annular dilatation, thickened leaflets due to excess myxomatous tissue or calcification, were also excluded.

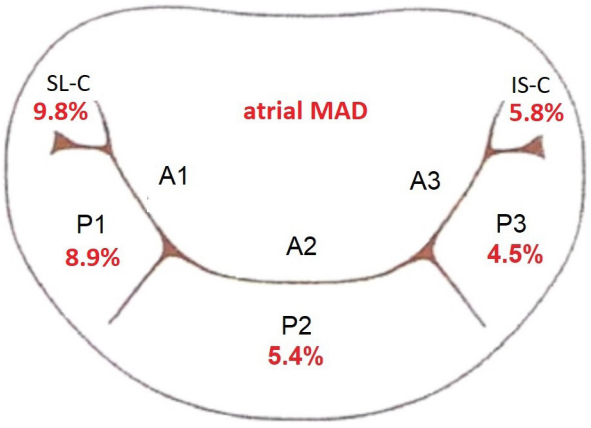

Figure 3 Distribution of mitral annular disjunction (MAD) within the mural mitral valve leaflet scallops (P1, P2 and P3) and mitral commissures (superolateral commissure (SL-C) and inferoseptal commissure (IS-C)) in the whole studied population (n=224).

Macroscopic assessment

Following dissection, hearts were weighed and fixed in a 10% formalin solution for up to 2 months until further observations and measurements were conducted. The left atrium was opened in a routine way (between pulmonary vein ostia) to expose the mitral valve. Mitral leaflet variations (including scallop variations) were investigated according to our previous study's protocol.[1] Measurements of the aortomural diameter and intercommissural diameter of the mitral valve annulus were taken. The atrial wall-mitral annulus-ventricular wall junction was then examined along the mural mitral valve leaflet and adjacent mitral valve commissures (inferoseptal and superolateral commissures). To achieve this, longitudinal sections were made at the midpoint of each detected leaflet scallop (inclusive of any accessory scallops) and at each mural leaflet indentation, as well as at both commissure levels. In total, each heart had at least nine locations where MAD's presence was evaluated through longitudinal sections. Subsequently, the mutual relationships between atrial myocardium, ventricular myocardium and mitral valve annulus were macroscopically assessed in search of MAD. In the classical arrangement (MAD not present), the mitral annulus insertion point should be located at the border between atrial wall and ventricular wall, without significant displacement of the mitral leaflet hinge line (in mural leaflet and commissures) towards the left atrium (figure 1A,C). When a spatial displacement of the mitral leaflet hinge line (be it mural or commissural) towards the left atrial wall (a disjunction of ≥2 mm) was observed, it was classified as MAD (figure 1B,C). If MAD was detected, its location within the mural mitral valve leaflet was meticulously described. Additionally, we noted MAD presence in both commissures. The height of the MAD was measured as the maximal distance between the left atrial wall-mitral leaflet junction and the top of the left ventricular myocardium along the endocardial surface. Macroscopic measurements were performed using 0.03 mm precision electronic callipers (YT-7201, YATO, Poland). To mitigate human bias, measurements were performed by two independent investigators, and the mean of two values was calculated and reported as the final value.

Microscopic assessment

Following macroscopic evaluation, histological assessment ensued. Representative samples from MAD (n=18) and classical (no-MAD arrangement) (n=18) hearts underwent standard histological procedures. Tissue blocks were embedded in paraffin before sectioning. Sections (4 μm thick) were cut from each block and mounted on super adhesive glass (SuperFrost Plus White Adhesion Slides, Epredia). Serial sections were stained with H&E and concurrently with the Masson Trichrome Staining Kit (Trichrome Stain (Masson) Kit, HT-15, Sigma-Aldrich) for collagen and muscle cell visualisation. The microscopic structure of the MAD types was depicted by scanning the whole stained slides with SLIDEVIEW vs200 (Olympus) and retrieving the images using OlyVIA V.3.4.1 software (Olympus).

Statistical analysis

Data were analysed using IBM SPSS Statistics V.28.0 (Predictive Solutions). Categorical variables were presented as number (n) or percentages, and quantitative variables as mean (SD) or median (IQR). Normal distribution was assessed with the Shapiro-Wilk

Table 2 Characteristic and comparisons of the study groups with and without mitral annular disjunction (MAD)

Parameter	All (n=224)	MAD not present (n=180)	MAD present in mural leaflet or commissures (n=44)	P value MAD present versus not present
Age (years), mean (SD)	47.9 (17.6)	47.8 (18.1)	48.4 (15.3)	0.85
BMI (kg/m^2), mean (SD)	26.6 (4.5)	26.7 (4.6)	25.7 (3.4)	0.37
BSA (m^2), mean (SD)	1.9 (0.3)	1.9 (0.2)	1.8 (0.5)	0.34
Heart weight (g), mean (SD)	440.0 (99.6)	439.8 (101.3)	441.0 (94.2)	0.84
Heart perimeter (mm), mean (SD)	244.7 (22.3)	243.5 (20.4)	249.6 (12.2)	0.38
Aortomural diameter (mm), mean (SD)	19.7 (4.8)	19.8 (4.8)	19.2 (4.3)	0.62
Intercommissural diameter (mm), mean (SD)	28.3 (5.4)	28.1 (4.9)	29.7 (4.8)	0.06
Classic mitral valve, n (%)	158/224 (70.5)	130/180 (72.2)	28/44 (63.6)	0.26
One accessory scallop in ML, n (%)	33/224 (14.7)	25/180 (13.9)	8/44 (18.2)	0.47
Connections of two scallops in ML, n (%)	24/224 (10.8)	19/180 (10.6)	5/44 (11.4)	0.88
Two accessory scallops in ML, n (%)	5/224 (2.2)	4/180 (2.2)	1/44 (2.3)	0.98
One accessory scallop in AML, n (%)	4/224 (1.8)	2/180 (1.1)	2/44 (4.5)	0.12

AML, aortic mitral valve leaflet; BMI, body mass index; BSA, body surface area; ML, mural mitral valve leaflet.

test. Differences between normally distributed quantitative parameters were evaluated with Student's t-test, while non-normally distributed quantitative data were analysed using the Mann-Whitney U test. Differences between categorical variables were determined using the χ^2 test of independence or Fisher's exact test if the number of observations in one category was below 5. For multiple comparisons, the non-parametric Kruskal-Wallis test with post hoc Dunn test and Bonferroni correction were applied to compare values between groups. Correlation coefficients were calculated to assess statistical dependence between measured parameters. A p value <0.05 was considered statistically significant.

RESULTS

In 19.6% of all studied hearts, we have discovered a presence of MAD located either within the mitral mural leaflet or commissures. The MAD was noted in 12.1% of all mural leaflets (figure 2A–C). There was an uneven distribution of MAD along the mitral annulus circumference, with disjunctions seldom appearing along the entire mural mitral leaflet (table 1, figure 3). Among mural leaflets, the MAD was situated within a single scallop in 55.6% of cases, while in the remaining cases disjunctions were either distributed across two scallops of the same heart (33.3%) or extended through the entire mural mitral leaflet (11.1%). Disjunctions were most prevalent in the P1 scallop (8.9% with MAD), followed by the P2 scallop (5.4%) and P3 scallop (4.5%) (figure 3). Notably, no MADs were identified in any accessory scallops of the mural leaflet. The average MAD height measured was 3.0±0.6 mm, and the height was consistent across the different scallops (P1: 2.9±0.6 mm vs P2: 3.3±0.7 mm vs P3: 3.0±0.9 mm; p=0.21).

When investigating commissures, the MAD may be found in 9.8% of all superolateral commissures and in 5.8% of all inferoseptal commissures (figure 1D, figure 2D and figure 3), among which in 1.3% of studied hearts, MAD was found coexisting in both commissures (table 1). A strong coexistence of mural leaflet and commissural MAD was noted (table 1). In more than half of the cases (15/27) where MAD occurred in the leaflet, it was accompanied by MAD present in one of the commissures. The mean height of MAD was similar for those located in superolateral and inferoseptal commissures (2.1±0.7 vs 2.1±0.5 mm). However, these commissural MADs were significantly smaller in comparison to the MADs found in the mural leaflet ($p<0.0001$).

Histological examination delineated a consistent microscopic structure of MAD across the mural leaflet and both commissures (figure 1E–H). Typically, in the absence of MAD (classical arrangement), the atrial myocardium and ventricular myocardium are situated adjacent to each other, only separated by a thin connective tissue layer (epicardial adipose tissue). The atrioventricular junction is covered with a rich fibrocollagenous layer of tissue (mitral valve annulus) (figure 1E,G). In contrast, heart with MAD displayed a noticeable spatial displacement between the atrial myocardium and ventricular myocardium. This disjunction, leaning towards the left atrial aspect, is filled with connective tissue and lacks leaflet, atrium and ventricle-specific cells. Furthermore, the disjunction is covered by the elongated valve annulus (fibrocollagenous layer), suggesting the disjunction tissue is part of annulus (figure 1F,H).

There were no significant correlations between cadaver characteristics (such as sex, age, weight, height, body mass index, body surface area and heart weight) and the presence or height of MAD (all $p>0.05$). Additionally, intercommissural and aortomural diameter did not significantly differ between valves with and without MAD (all $p>0.05$) (table 2). The identified anatomical variations in mitral valve leaflet scallops are listed in table 2. The classic mitral valve type (a single aortic mitral leaflet and mural mitral leaflet composed of three scallops) was found in 70.5% of the samples. Other identified variations included: one accessory scallop in mural mitral valve leaflet (14.7%), connections of two scallops in mural mitral leaflet (10.7%), two accessory scallops in mural leaflet (2.2%) and one accessory scallop in aortic mitral valve leaflet (1.8%). There were no specific morphological variations in the mitral valve leaflet associated with the presence of MAD.

DISCUSSION

Our study is the first to provide comprehensive morphometric analysis of MAD within the mitral mural leaflet and both mitral commissures. Additionally, we have provided histological image and descriptions of the atrial wall-mitral annulus-ventricular wall junction (figure 1). Our findings indicate that an annular displacement towards the atrial wall may be found in either the mitral leaflet or commissures in about 20% of cases.

The mitral valve annulus, a complex D-shaped fibrous tissue structure, is portioned into two distinct parts: the aortic (or anterior), which is relatively straight, and the mural (or posterior), characterised by its curvature. Contrary to the term 'annulus',

suggesting a solid ring-like structure, the true anatomy is more intricate.[23] The mural part of mitral annulus consists of four components: the atrial wall, leaflet hinge line, crest of the free wall of the left ventricle and epicardial adipose tissue.[24] It is discontinuous, exhibiting variable consistency and robustness even within the same heart.[8] The mural leaflet may be hinged to the atrial wall or to the ventricular wall or exactly at the junction of atrial myocardium and ventricular myocardium.[25] The aortic part of the mitral annulus extends seamlessly into a strip of fibrous tissue called mitral-aortic curtain. This curtain is marked by dense connective tissue bumps, known as the right and left fibrous trigones. This band then transitions into the left inter-leaflet triangle, located between the non-coronary sinus and left coronary sinus. As a result, the aortic part of mitral valve annulus lacks well-defined boundaries.[24] Describing the arrangement of fibrous continuity to the base of the left ventricular wall accurately poses a significant challenge.[3] Pinpointing the locations of these fibrous anchors on the border between the left atrium and the left ventricle is not practical; thus, the displacement of the leaflet hinge line in this region might be a common occurrence.

A preceding systematic review evaluating MAD across various patient groups reported an 8.7% prevalence of MAD in the general population and a heightened 30.1% prevalence among patients with mitral valve prolapse and/or Barlow's disease. Nevertheless, the definitions of MAD exhibited inconsistencies across these studies.[10] It is crucial to underscore that our study is the first to show the prevalence and morphological characteristic of the MAD within mitral valve commissures (figure 3, table 1). The distribution of the disjunctions among the mitral valve components does not show much differentiation (mural leaflet vs commissures) (table 1, figure 3). Such observations contradict recent findings from imaging-centric research. For instance, a study by Toh *et al* using CT revealed a 96.0% prevalence of MAD in patients with structurally normal hearts, showing double peaks at bilateral sides of the mural mitral leaflet (commissural region) on the prevalence distribution map.[20] Likewise, a large-scale study using MRI showed disjunction in 1990 (76%) cases, demonstrating a comparable bimodal distribution.[21] We can identify several factors that may have led to the overdiagnosis of MAD in commissural regions. First, in the above-mentioned studies a cut-off value of only 1 mm was used to define the disjunction, which, in our opinion, is significantly too small, especially for imaging studies (de facto at the limit of imaging resolution). Considering the anatomical structure of the mitral annulus and based on our experience a cut-off value of ≥2 mm should be preferred. Moreover, when evaluating MAD in the commissural region, it is crucial to ensure that we are not assessing the aortic leaflet instead. It is important to note that the base of both commissures measures approximately 6.5 mm according to autopsied research and their proper identification in the clinical imaging may be challenging.[1] Due to the presence of aortomitral continuity and the fibrous trigones the attachment line of the lateral aspects of the aortic leaflet may mimic the MAD and thus be the cause of the over-recognition of the disjunction within the commissures. Lastly, the clinical studies cited above were executed either in the end-systolic or best systolic phase, which introduce errors related to phase-dependent MAD overdiagnosis.[20 21] When assessing the presence of MAD in clinical imaging, it is crucial to evaluate the diastolic phase to avoid potential misdiagnosis. Especially, a potential mistake is so-called pseudo-MAD, when the insertion of the leaflet is normal, but the pseudo-MAD is visible as a juxtaposition of the part of the mural leaflet and atrial wall. The true MAD should only be identified in the diastolic phase, where the hinge of the leaflet is actually visible and is projected to its actual position on the atrioventricular junction.[25] Both the lack of a clear definition of disjunction and the use of an unsuitable imaging phase could result in potential bias of misdiagnosed MADs. Additionally, since MAD is typically interspersed around the mural leaflet circumference, 3D imaging modalities should be used to accurately examine the entire mural mitral leaflet.

The MAD can be considered both as an anatomical variant and a potential risk factor for adverse events. The relatively high prevalence of MAD in patients with structurally normal hearts suggests that it is a variant of the anatomical norm. However, associations between MAD and mitral valve prolapse, ventricular arrhythmias and/or sudden cardiac death have been established.[10–13 22 26 27] MAD regions may be susceptible to long-term mechanical stress, potentially leading to mitral valve prolapse,[13] and subsequent degeneration and fibrosis of the mitral valve apparatus. These may further be associated with an increased risk of arrhythmia.[13 28 29]

Several limitations of this study warrant mention. Our morphological and morphometric evaluations were conducted on formaldehyde-fixed autopsied material, which may affect the obtained measurements even though previous studies have demonstrated that paraformaldehyde fixation does not significantly affect the dimensions of human heart tissue.[30] Furthermore, due to the nature of the autopsied tissue, we were unable to assess the dynamic behaviour of the studied area during the cardiac cycle. Future functional anatomical studies are needed to visualise the behaviour of the mural mitral leaflet hinge line complex throughout the heart cycle. Additionally, our study population comprised solely Caucasian individuals, which may limit the generalisability of our findings to other ethnicities. Finally, our analysis was focused on donors without significant mitral valve diseases, which could restrict the applicability of our results to cases with such diseases. Moreover, without access to premortem echocardiography and other imaging data, we cannot confirm the absence of asymptomatic, minor and insignificant mitral valve prolapse in our study population, and can only able to assure that there were no observable macroscopic alterations in the mitral valve complex. Despite these limitations, our study offers a comprehensive morphometric description of MAD, which carries significant clinical implications.

CONCLUSIONS

Our study reveals that among patients with healthy hearts, MAD is morphologically evident in 12.1% of mural mitral leaflets, 9.8% of superolateral commissures and 5.8% of inferoseptal commissures. The identified MADs are typically sectional, with disjunctions that usually do not extend beyond one of the scallops. Commissural MADs are smaller than those located within the mural leaflet. This study is the first to provide an in-depth morphometric (macroscopic and microscopic) analysis of MAD. Further research should focus on establishing definitions of clinically significant MAD to enhance diagnostic accuracy and patient care.

Contributors AK-O: concept/design, data acquisition, data analysis and interpretation, drafting of the manuscript, guarantor. JB, AD: data analysis/interpretation, critical revision of the manuscript. BZ: data analysis/interpretation. KT: data acquisition. FB, PK, MS: collection of samples, data acquisition. KG: histological processing and analysis. JH: design, data acquisition, critical revision of the manuscript. MKH: data acquisition, histological analysis, critical revision of the manuscript. All authors approved the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Bioethical Committee of the Jagiellonian University, Krakow, Poland (No 1072.6120.169.2022). It is an autopsied study. Samples were obtained during routine forensic medical autopsies performed at the Department of Forensic Medicine, Jagiellonian University Medical College, Krakow, Poland. Our Bioethical Committee waived the need for consent from donors. We collected hearts only from deceased persons who did not express objection, when alive, and only if the family did not also express objection.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD
Agata Krawczyk-Ożóg http://orcid.org/0000-0001-7691-8174

REFERENCES

1 Krawczyk-Ożóg A, Hołda MK, Sorysz D, *et al*. Morphologic variability of the mitral valve leaflets. *J Thorac Cardiovasc Surg* 2017;154:1927–35.
2 Krawczyk-Ożóg A, Hołda MK, Bolechała F, *et al*. Anatomy of the mitral Subvalvular apparatus. *J Thorac Cardiovasc Surg* 2018;155:2002–10.
3 Anderson RH, Garbi M, Zugwitz D, *et al*. Anatomy of the mitral valve relative to controversies concerning the so-called Annular Disjunction. *Heart* 2023;109:734–9.
4 Anderson RH, Mori S, Tretter JT, *et al*. The anatomy of the mitral valve. *Mitral Valve Dis* 2021;2021:39–58.
5 Henle J. *Handbuch der Systematischen Anatomie des Menschen*. London: Williams & Norgate. Braunschweig, 1871.
6 Zimmerman JJ. The functional and surgical anatomy of the heart. *Ann R Coll Surg Engl* 1966;39:348–66.
7 Hutchins GM, Moore GW, Skoog DK. The Association of floppy mitral valve with Disjunction of the mitral Annulus Fibrosus. *N Engl J Med* 1986;314:535–40.
8 Angelini A, Ho SY, Anderson RH, *et al*. A histological study of the atrioventricular junction in hearts with normal and Prolapsed leaflets of the mitral valve. *Heart* 1988;59:712–6.
9 Wu S, Siegel RJ. Mitral Annular Disjunction: A case series and review of the literature. *Front Cardiovasc Med* 2022;9:2205.
10 Bennett S, Tafuro J, Duckett S, *et al*. Definition, prevalence, and clinical significance of mitral Annular Disjunction in different patient cohorts: A systematic review. *Echocardiography* 2022;39:514–23.
11 Essayagh B, Sabbag A, Antoine C, *et al*. The mitral Annular Disjunction of mitral valve Prolapse: presentation and outcome. *JACC: Cardiovascular Imaging* 2021;14:2073–87.
12 Konda T, Tani T, Suganuma N, *et al*. The analysis of mitral Annular Disjunction detected by echocardiography and comparison with previously reported pathological data. *J Echocardiogr* 2017;15:176–85.
13 Dejgaard LA, Skjølsvik ET, Lie ØH, *et al*. The mitral Annulus Disjunction arrhythmic syndrome. *J Am Coll Cardiol* 2018;72:1600–9.
14 Drescher CS, Kelsey MD, Yankey GS, *et al*. Imaging considerations and clinical implications of mitral Annular Disjunction. *Circ Cardiovasc Imaging* 2022;15:e014243.
15 Wunderlich NC, Ho SY, Flint N, *et al*. Myxomatous mitral valve disease with mitral valve Prolapse and mitral Annular Disjunction: clinical and functional significance of the coincidence. *J Cardiovasc Dev Dis* 2021;8:9.
16 Konda T, Tani T, Suganuma N, *et al*. Mitral Annular Disjunction in patients with primary severe mitral regurgitation and mitral valve Prolapse. *Echocardiography* 2020;37:1716–22.
17 Eriksson MJ, Bitkover CY, Omran AS, *et al*. Mitral Annular Disjunction in advanced Myxomatous mitral valve disease: echocardiographic detection and surgical correction. *J Am Soc Echocardiogr* 2005;18:1014–22.
18 Mantegazza V, Volpato V, Gripari P, *et al*. Multimodality imaging assessment of mitral Annular Disjunction in mitral valve Prolapse. *Heart* 2021;107:25–32.
19 Tsianaka T, Matziris I, Kobe A, *et al*. Mitral Annular Disjunction in patients with severe aortic stenosis: extent and reproducibility of measurements with computed tomography. *Eur J Radiol Open* 2021;8:100335.
20 Toh H, Mori S, Izawa Y, *et al*. Prevalence and extent of mitral Annular Disjunction in structurally normal hearts: comprehensive 3d analysis using cardiac computed tomography. *Eur Heart J Cardiovasc Imaging* 2021;22:614–22.
21 Zugwitz D, Fung K, Aung N, *et al*. Mitral Annular Disjunction assessed using CMR imaging: insights from the UK Biobank population study. *JACC Cardiovasc Imaging* 2022;15:1856–66.
22 Lee A-W, Jin C-N, Fan Y, *et al*. Functional implication of mitral Annular Disjunction in mitral valve Prolapse: A quantitative dynamic 3d echocardiographic study. *JACC Cardiovasc Imaging* 2017;10:1424–33.
23 Ho SY. Anatomy of the mitral valve. *Heart* 2002;88 Suppl 4(Suppl 4):iv5–10.
24 Faletra FF, Leo LA, Paiocchi VL, *et al*. Anatomy of mitral Annulus insights from non-invasive imaging techniques. *Eur Heart J Cardiovasc Imaging* 2019;20:843–57.
25 Faletra FF, Leo LA, Paiocchi VL, *et al*. Morphology of mitral Annular Disjunction in mitral valve Prolapse. *J Am Soc Echocardiogr* 2022;35:176–86.
26 Perazzolo Marra M, Basso C, De Lazzari M, *et al*. Morphofunctional abnormalities of mitral Annulus and arrhythmic mitral valve Prolapse. *Circ: Cardiovascular Imaging* 2016;9:e005030.
27 Clavel M, Hourdain J, Deharo J, *et al*. Mitral valve Prolapse phenotypes associated with sudden cardiac death. *Canadian Journal of Cardiology* 2015;31:S159–60.
28 van Wijngaarden AL, de Riva M, Hiemstra YL, *et al*. Parameters associated with ventricular arrhythmias in mitral valve Prolapse with significant regurgitation. *Heart* 2021;107:411–8.
29 Yang M, Zhong L, *et al*. Ventricular premature contraction associated with mitral valve Prolapse. *Int J Cardiol* 2016;221:1144–9.
30 Hołda MK, Klimek-Piotrowska W, Koziej M, *et al*. Influence of different fixation protocols on the preservation and dimensions of cardiac tissue. *J Anat* 2016;229:334–40.