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Insights into malignant mitral valve degenerative disease from a sudden cardiac death cohort highlighting significant measurement differences from normal

Joseph Westaby, Luciana Bicalho, Emelia Zullo & Mary N Sheppard

CRY Cardiovascular Pathology Unit, Cardiovascular Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK

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Aims: Mitral valve prolapse (MVP) is an accepted cause of sudden cardiac death (SCD) in most autopsy series. Diagnosis at autopsy relies upon subjective assessment with no established objective pathological criteria. This study set out to establish objective measurements to help pathologists dealing with SCD.
Methods: We diagnosed 120 (1.5%) cases of MVP in 8108 cases of SCD. We measured the mitral annulus, anterior and posterior leaflets, rough zone and mitral annular disjunction (MAD) in 27 MVP cases and compared them to 54 age- and sex-matched normal mitral valves.
Results: Age of death was 39 ± 16 years, with 59 females and 61 males. History of mild MV disease was present in 19 (16%). Eleven (9%) died associated with exertion. Left ventricular hypertrophy was present in nine (15%) females and 10 (16%) males. Both MV leaflets showed thickening and ballooning in all individuals. MVP showed highly significantly increased annular circumference, elongation and thickening of both leaflets as well as increased MAD (all $P < 0.001$). Left ventricular fibrosis was present in 108 (90%), with interstitial fibrosis in the posterolateral wall and papillary muscle in 88 (81%) and coexisting replacement fibrosis in 40 (37%).
Conclusion: This is the largest MVP associated with SCD series highlighting a young cohort with equal representation of males and females. There is involvement of both leaflets with significant annular dilatation, elongation and thickening of both leaflets with MAD. Left ventricular fibrosis explains arrhythmia. Our quantitative measurements should serve as a reference for pathologists assessing post-mortem hearts for MVP.

Keywords: anatomy, autopsy, mitral valve prolapse, pathology, sudden cardiac death

Introduction

Most mitral valve (MV) mortality is associated with rheumatic disease in developing countries, but in developed countries mortality is predominantly due to degenerative mitral valve disease known functionally as MV prolapse (MVP).[1,2] Based upon functional echocardiography studies in living patients, MVP disruption of the MV apparatus and mechanical integrity is associated with progressive alteration of valve structure leading to bulging of the leaflets into the left atrium during systole with thickening and lack of coaptation of the leaflets, together with thickening, elongation and rupture of the cords.[3] The disease in its advanced state is also known as Barlow's disease. Complications include significant valve regurgitation,

Address for correspondence: M N Sheppard, CRY Department of Cardiovascular Pathology, Cardiovascular Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, London SW17 0RE, UK.
e-mail: msheppar@sgul.ac.uk

atrial dilatation, arrhythmias, endocarditis, cardiac failure and sudden death.[4,5]

MV annular abnormalities are present in MVP and are thought to be the primary pathology, with stress on the MV apparatus, resulting in leaflet thickening and cordal lengthening. MV leaflet length, thickness, billowing height and annular diameter are all increased in patients with Barlow's disease on imaging. Increased mitral annular disjunction (MAD) length, where the posterior mitral leaflet abuts the atrial wall above the left ventricle muscle, is reported in detail in echocardiographic studies and is considered a useful diagnostic measurement.[6]

While there are many detailed echocardiogram (ECHO) studies, autopsy studies are few and vary considerably in descriptive changes with the presence or absence of prolapse up into the left atrium, leaflet expansion and cordal rupture and fusion.[7,8] Histological studies emphasise the expansion of the zona spongiosa, destruction of the zona fibrosa and extensive fibrous overlays, but this is non-specific and seen with increasing age, with no histological feature diagnostic of pathological degenerative changes.[9]

Currently, there are no established objective criteria for the diagnosis of MVP at autopsy. ECHO studies during life show bulging into left atrium and lack of coaptation with regurgitant jets, but these may be absent in the inanimate heart at autopsy. While leaflet expansion, thickening, ballooning and bulging are described pathologically, these are subjective and may not be obvious at autopsy (Figure 1). Descriptions rely more upon the texture and thickening of the leaflets with wide variation and interpretation regarding the significance of these findings, especially as the mitral valve, like all heart valves, thicken and become more rigid with age. Detailed measurements of the normal MV at autopsy and comparison to what are labelled as 'prolapsed valve leaflets' has not been reported previously. We recently published a cohort of 63 cases of MVP presenting with sudden cardiac death (SCD)[10] and decided to expand upon this study with detailed objective measurements, comparing MVP to a cohort of age- and sex-matched morphologically normal hearts without MV abnormality. To our knowledge, this has not been conducted previously.

Methods

The study was conducted in the Cardiac Risk in the Young Cardiovascular Pathology centre based in St George's University of London, where more than 600 cases of suspected SCD from throughout the United Kingdom are referred annually. Ethical approval was granted by the London Stanmore NHS Research Ethics Committee (10/H0724/38). A total of 8108 referrals of SCD were received from throughout England and Wales between 1994 and 2023. SCD was defined as witnessed death taking place within 1 h of the development of symptoms or an unwitnessed death taking place within 24 h of last being seen alive. Formalin-fixed hearts were assessed according to the guidelines of the Royal College of Pathologists, Association for European Cardiovascular Pathology and M.N.S.[11–13]

SPECIALIST CARDIAC EXAMINATION

All hearts were weighed and considered to have left ventricular hypertrophy if weighing more than 550 g in males and 450 g in females. Postoperative cases, specimens with significant coronary artery disease, cardiomyopathies, congenital heart disease and aortic dissection were excluded from this study.

The MV was assessed by opening the left atrium between the superior pulmonary veins and examined directly for evidence of bulging/prolapse of the mitral leaflets above the atrioventricular junction into the left atrium with ballooning (Figure 1). Following a mid-ventricular slice, a lateral cut was then made through the left atrium and ventricle to expose the anterior and posterior leaflets for further examination (Figure 2). Macroscopically, the MV was assessed for evidence of MVP, including prolapse into the left atrium, ballooning between cords, thickening of the leaflets and annular dilatation, with thinning and rupture of the cords. MVP was diagnosed macroscopically based on bulging of the valve leaflets into the atrium, expansion and thickening of the leaflets, increase in the rough zone of the anterior leaflet, ballooning of leaflet segments between the cords, cordal thinning and annular dilatation (Figure 1).

Histopathology was taken in all cases to exclude other pathology and to look for microscopic ventricular fibrosis. Ten blocks were routinely taken for histopathology and stained with haematoxylin and eosin and picrosirius red to identify fibrosis.

MITRAL VALVE MEASUREMENTS

In a subcohort of 27 cases macroscopically considered as MVP, detailed measurements were taken including the mitral annulus circumference; the thickness of both leaflets; the length of the anterior leaflet; the anterior scallop of the posterior leaflet

Figure 1. The continuum of mitral valve changes. There is a continuum of change which occurs in the mitral valve ranging from completely normal on the left, to mild ballooning and thickening of the leaflets in the middle to pronounced ballooning and thickening of the leaflets on the right.

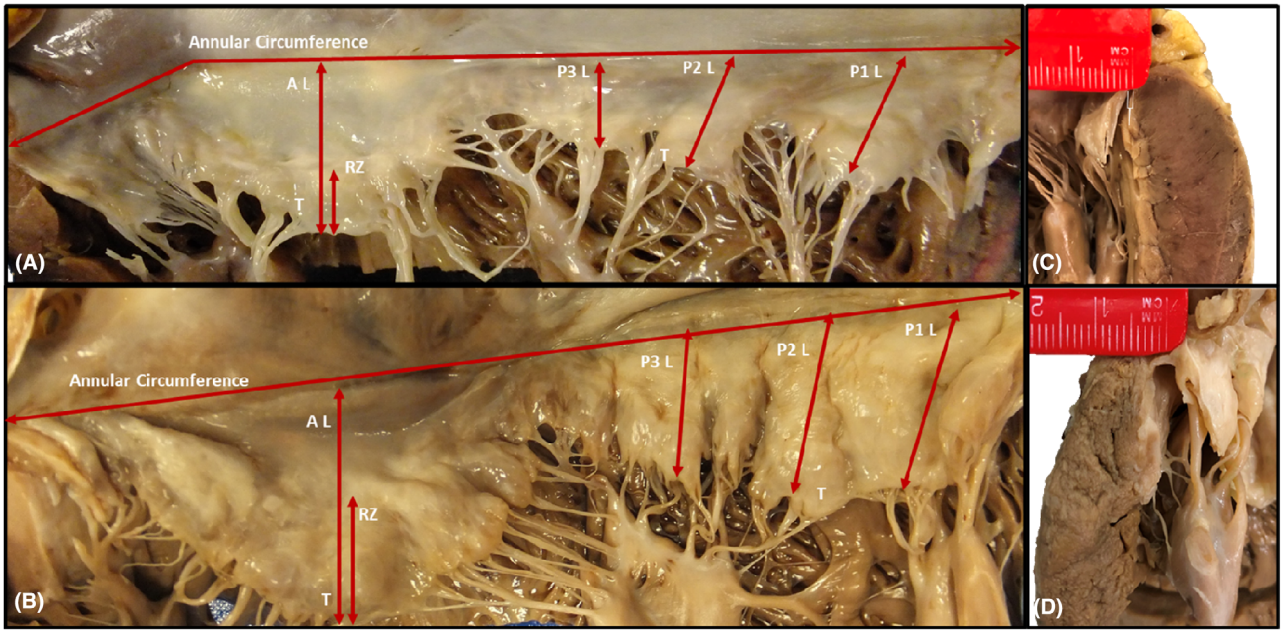

Figure 2. A, The normal mitral valve and the circumference measurement. Positions to take the anterior length (AL) leaflet, roughened zone of the anterior leaflet (RZ), the lengths of the posterior leaflet scallop 1 (P1L), posterior leaflet scallop 2 (P2L) and posterior leaflet scallop 3 (P3L) are demonstrated. **B,** The prolapsing mitral valve and the measurements for the annular circumference, the AL, RZ of the AL, the lengths of the posterior leaflet P1L, P2L and P3L and leaflet thickness (T) are demonstrated. **C,** The measurement for disjunction (demarked by a white bracket) was taken from a transection through the left atrium, mitral valve and left ventricle on a normal mitral valve. The measurement is taken from the tip of the muscle of the left ventricle closest to the mitral valve to the surface of the valve. **D,** The measurement for disjunction taken from a transection through the left atrium, mitral valve and left ventricle on a prolapsing mitral valve, which shows clear disjunction.

(P1); the middle scallop of the posterior leaflet (P2); and the posterior scallop of the posterior leaflet (P3); the rough zone of the anterior leaflet, corresponding to the area that presses together with the posterior leaflet at the zone of coaptation[14]; and MAD, which is the distance between the attachment of the

posterior MV leaflet to the atrioventricular junction and left ventricular myocardium. These measurements were taken in the prolapsing MV and compared to the normal valve in age- and sex-matched controls with a morphologically normal heart at a 2:1 ratio (Figure 2). Measurements of the cords and papillary muscles were beyond the scope of this study.

STATISTICAL ANALYSIS

Categorical and binary data are presented as frequencies and percentages and continuous data are presented as means and standard deviations.

The McNemar test was used to compare paired nominal data with two categories. Paired-samples *t*-tests were used to compare normally distributed continuous variables between two matched groups. The statistical software package SPSS package version 27 was used to perform these tests.

Results

Of 8108 referrals of SCD to our centre, there were 120 (1.5%) cases of MVP as the cause of death. Age of death was 39 ± 16 years, with 59 females and 61 males (1:1). There was a history of mild MV disease in 19 (16%) and connective tissue disease in nine (8%). There was a family history of MVP in three (3%), and two (2%) of these had relatives who died suddenly with MVP. Eleven (9%) died on or immediately following exertion.

MACROSCOPIC FINDINGS

Heart weight for 120 cases of MVP was 424 ± 144 g. Heart weight in females was 370 ± 116 g and 470 ± 153 g in males . Left ventricular hypertrophy was present in nine (15%) females and 10 (16%) males. Both leaflets of the MV showed thickening and ballooning in all individuals. Cordal rupture was present in two (2%) individuals, with rupture occurring to a cord attached to the anterior leaflet in one (1%) and a cord attached to the posterior leaflet in another (1%) (Figure 3). There were no vegetations or perforations identified in any case.

MICROSCOPIC FINDINGS

Mitral leaflet histopathology showed expansion of the spongiosa and destruction of the fibrosa in all MVP cases. Histological changes varied widely, with normal valve areas admixed with abnormal areas and fibrous overlays in all cases. No inflammation or neovascularisation was noted in any of the leaflets. Left ventricular fibrosis was present in 108 (90%) individuals with interstitial fibrosis in the posterolateral wall and papillary muscle in 88 (of 108, 81%) individuals, with coexisting replacement fibrosis in 40 (of 108, 37%) cases (Figure 3).

SUBCOHORT ANALYSIS WITH DETAILED MEASUREMENTS OF THE MITRAL VALVE

The prolapsing MV was analysed in detail in 27 cases and compared to the normal MV in 54 age- and sex-matched individuals with morphologically normal hearts. Age was 36 ± 13 years in both cohorts; there were 13 females and 14 males in the prolapsing MV cohort and 26 females and 28 males in the control cohort.

MV circumference, anterior leaflet, roughened zone, P1, P2 and P3 heights, as well as anterior and posterior leaflet thickness and MAD, were all increased (all $P < 0.001$, Table 1).

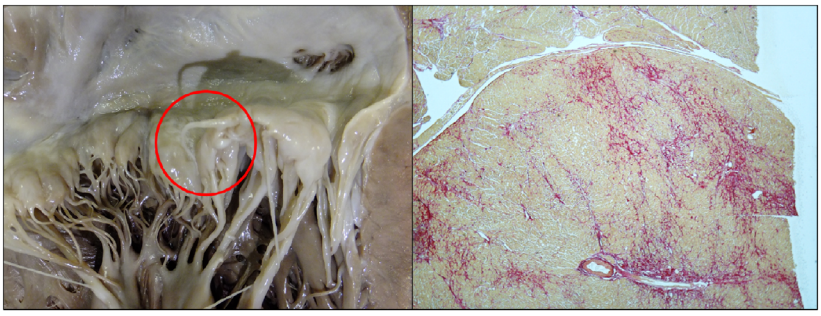

Figure 3. The left-hand panel shows rupture of a tendinous cord (red circle) associated with a ballooning thickened mitral valve. The right-hand panel shows a picrosirius red-stained section demonstrating interstitial and replacement fibrosis, which is highlighted in red and occurs in the posterolateral wall.

Table 1. Demographics and mitral valve measurements for malignant mitral valve prolapse and age- and sex-matched controls

Variable	Summary statistic	MVP (n = 27)	Controls (n = 54)	P-value
Demographics				
Age (years)	Mean ± SD	36 ± 13	36 ± 13	0.957
Sex (male: female)	Numbers Ratio	14:13 1:1	28:26 1:1	1.000
Mitral valve measurements				
Circumference (mm)	Mean ± SD	91 ± 16	75 ± 14	< **0.001**
Anterior leaflet length (mm)	Mean ± SD	26 ± 6	21 ± 4	< **0.001**
Anterior leaflet roughened zone (mm)	Mean ± SD	14 ± 4	9 ± 2	< **0.001**
Anterior leaflet thickness (mm)	Mean ± SD	3 ± 1	1 ± 1	< **0.001**
Posterior leaflet scallop 1 (mm)	Mean ± SD	16 ± 5	11 ± 3	< **0.001**
Posterior leaflet scallop 2 (mm)	Mean ± SD	17 ± 6	11 ± 3	< **0.001**
Posterior leaflet scallop 3 (mm)	Mean ± SD	13 ± 4	9 ± 3	< **0.001**
Posterior leaflet thickness (mm)	Mean ± SD	2 ± 1	1 ± 0	< **0.001**
Annular disjunction (mm)	Mean ± SD	3 ± 2	1 ± 1	< **0.001**

MVP, malignant mitral valve prolapse; SD, standard deviation. Significant values ($p < 0.05$) are highlighted in bold.

Discussion

To our knowledge, this is the largest series of MVP cases associated with SCD ever published. We are the first to take objective quantitative measurements of the MV annulus, both leaflets' length and thickness and MAD. We highlight that annular circumference, both leaflet height and thickness and MAD are highly significantly increased in the MVP. Ventricular fibrosis was identified in the vast majority of cases (90%), which may explain lethal arrhythmia.

A recent autopsy series from the San Francisco County, CA, USA showed that 4% of cases of SCD were due to MVP (13 cases in total). In this study, the valve is described as thickened with elongated cords with no measurements made.[15] A similar study in Australia by Han found an increase in annular circumference and ventricular fibrosis in 79% of their 71 cases, but did not measure the leaflet length, leaflet-thickening or MAD[16].

MVP and SCD are reported in many case reports and series,[10,17–20] and have also been referred to as malignant MV syndrome or arrhythmogenic MV prolapse. Waller measured annular circumference (> 10 cm) and both leaflet areas (> 11 cm^2)[21] in surgically removed MVs, but no autopsy cases were included in the setting of SCD. Davies[8] graded floppy MV according to expansion of the leaflets and cordal abnormalities. Grades 3 and 4, cordal rupture and fusion to the ventricular wall, respectively, were direct causes of death with bacterial endocarditis and/or severe mitral regurgitation.[8] However, he did not mention prolapse into the atrium or take measurements.

We highlight the absence of a clinical history of severe MVP, arrhythmias or cardiac failure in all our cases. The link to connective tissue disease (9%) and a family history (3%) is highlighted in a minority of cases so genetic factors play a role, especially in the younger patients. This has been noted in other autopsy studies.[10] Clinically annular dilatation, increased length and thickness, billowing and MAD have been described by echocardiography.[6] It is postulated that annular dilatation with increased MAD precedes the leaflet changes with regurgitation. MAD in MVP is reported at autopsy[22] and has been put forward as one of the causes of arrhythmias and SCD in MVP.[23,24] However, it is also seen in ischaemic heart disease and in those without MVP.[23,25]

Myocardial fibrosis has been suggested as a substrate for ventricular arrhythmias at both autopsy[10,24] and imaging.[26] Our study confirms ventricular fibrosis in a vast majority of cases (90%), so magnetic resonance imaging (MRI) of the heart in the living may add to the risk profile for SCD. However, a small proportion of MVP cases (10%) do not have fibrosis, so other factors may also contribute to SCD.

The role of MVP in SCD is gaining prominence, with controversy surrounding the role of the valve leaflets, MAD and myocardial fibrosis causing either haemodynamic change or lethal cardiac arrhythmias.[26] MVP is responsible for 0.3–6% of SCD,[15,27] so it is an important condition for future study. Delling's study highlighted that cases with single-leaflet involvement detected premortem by echocardiography can be missed at autopsy.[15] MVP in SCD is probably underdiagnosed due to subjectivity and lack of established pathological guidelines for diagnosis. Our measurements should serve as a

reference for pathologists assessing postmortem hearts for MVP in future studies.

Limitations

We have limited clinical investigations of our cases with no electrocardiogram or ECHO in the majority, as they presented with SCD with no preceding symptoms. This study was performed on formalin-fixed hearts and measurements may vary in fresh hearts, which merits further study. All cases had bi-leaflet involvement, and therefore the role of single-leaflet MVP cannot be established. We did not study the cords or papillary muscles in these cases, which will be the subject of a future study.

Conclusions

The quantitative measurements from our present study indicate that MVP associated with SCD shows annular dilatation, bi-leaflet elongation and thickening, roughened zone elongation and MAD. There is left ventricular fibrosis in most cases. Our measurements should serve as a reference for pathologists assessing post-mortem hearts for MVP.

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Conflicts of interest

We have no conflicts of interest to declare.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Boudoulas KD, Borer JS, Boudoulas H. Etiology of valvular heart disease in the 21st century. *Cardiology (Switzerland)* 2013; **126**; 139–152.
2. Shah PM. Current concepts in mitral valve prolapse-diagnosis and management. *J. Cardiol.* 2010; **56**; 125–133.
3. Lester WM. Myxomatous mitral valve disease and related entities: the role of matrix in valvular heart disease. *Cardiovasc. Pathol.* 1995; **4**; 257–264.
4. Cooper STE, Westaby JD, Griffin KJ, Sheppard MN. The role of endocarditis in sudden cardiac death: highlighting the value of the autopsy, pathological features and cardiac complications. *Cardiovasc. Pathol.* 2021; **50**; 107292.
5. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N. Engl. J. Med.* 2001; **345**; 1318–1330.
6. Hiemstra YL, Tomsic A, Gripari P *et al.* Evolution from mitral annular dysfunction to severe mitral regurgitation in Barlow's disease. *Interact. Cardiovasc. Thorac. Surg.* 2021; **32**; 506–514.
7. Hill DG, Davies MJ, Braimbridge MV. The natural history and surgical management of the redundant cusp syndrome (floppy mitral valve). *J. Thorac. Cardiovasc. Surg.* 1974; **67**; 519–525.
8. Davies MJ, Moore BP, Braimbridge MV. The floppy mitral valve. Study of incidence, pathology, and complications in surgical, necropsy, and forensic material. *Br. Heart J.* 1978; **40**; 468–481.
9. Yutani C, Imakita M, Ueda H. Pathoetiological aspects of mitral valve prolapse. *J. Cardiol. Suppl.* 1989; **21**; 21–37, discussion 38–41.
10. Garbi M, Lancellotti P, Sheppard MN. Mitral valve and left ventricular features in malignant mitral valve prolapse. *Open Heart* 2018; **5**; e000925.
11. Basso C, Aguilera B, Banner J *et al.* Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arch.* 2017; **471**; 691–705.
12. Osborn, M; Lowe J; Sheppard M; Suvarna K. Guidelines on autopsy practice: sudden death with likely cardiac pathology July 2015. 2015:1–16.
13. Sheppard MN. *Practical cardiovascular pathology*. Florida, USA: CRC press, 2022. https://doi.org/10.1201/9780429186530.
14. McCarthy KP, Ring L, Rana BS. Anatomy of the mitral valve: understanding the mitral valve complex in mitral regurgitation. *Eur. J. Echocardiogr.* 2010; **11**; i3–i9.
15. Delling FN, Aung S, Vittinghoff E *et al.* Antemortem and postmortem characteristics of lethal mitral valve prolapse among all countywide sudden deaths. *JACC Clin. Electrophysiol.* 2021; **7**; 1025–1034.
16. Han HC, Parsons SA, Teh AW *et al.* Characteristic histopathological findings and cardiac arrest rhythm in isolated mitral valve prolapse and sudden cardiac death. *J. Am. Heart Assoc.* 2020; **9**; e015587.
17. Basso C, Perazzolo Marra M, Rizzo S *et al.* Arrhythmic mitral valve prolapse and sudden cardiac death. *Circulation* 2015; **132**; 556–566.
18. Narayanan K, Uy-Evanado A, Teodorescu C *et al.* Mitral valve prolapse and sudden cardiac arrest in the community. *Heart Rhythm* 2016; **13**; 498–503.
19. Han H-C, Ha FJ, Teh AW *et al.* Mitral valve prolapse and sudden cardiac death: a systematic review. *J. Am. Heart Assoc.* 2018; **7**; e010584.
20. Nalliah CJ, Mahajan R, Elliott AD *et al.* Mitral valve prolapse and sudden cardiac death: a systematic review and meta-analysis. *Heart* 2019; **105**; 144–151.
21. Waller BF, Howard J, Fess S. Pathology of mitral valve stenosis and pure mitral regurgitation-part II. *Clin. Cardiol.* 1994; **17**; 395–402.
22. 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**; 535–540.

23. Dejgaard LA, Skjølsvik ET, Lie ØH *et al*. The mitral annulus disjunction arrhythmic syndrome. *J. Am. Coll. Cardiol.* 2018; **72**; 1600–1609.
24. Basso C, Iliceto S, Thiene G, Perazzolo Marra M. Mitral valve prolapse, ventricular arrhythmias, and sudden death. *Circulation* 2019; **140**; 952–964.
25. Zhou N, Zhao Q, Zeng X *et al*. Association of mitral annular disjunction with premature cardiac mortality in a large series of autopsies. *J. Am. Coll. Cardiol.* 2021; **77**; 102–104.
26. Reinier K, Chugh SS. Sudden death associated with mitral valve prolapse: structural and functional components of risk. *JACC Clin. Electrophysiol.* 2021; **7**; 1035–1037.
27. Sheppard MN, Westaby J, Zullo E, Fernandez BVE, Cox S, Cox A. Sudden arrhythmic death and cardiomyopathy are important causes of sudden cardiac death in the UK: results from a national coronial autopsy database. *Histopathology* 2023; **82**; 1056–1066.