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THE ASSOCIATION BETWEEN MITRAL VALVE PROLAPSE WITH VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

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Abstract

The mitral valve is one of four heart valves, and is situated between the left atrium and left ventricle. Its role is to facilitate the unidirectional flow of blood through the left atrium and ventricle by opening in diastole and closing in systole. Mitral valve prolapse (MVP) involves the atrial displacement of the mitral valve during ventricular systole. While MVP has been linked to the development of sudden cardiac death (SCD) through the development of malignant ventricular arrhythmias (VAs), this association remains controversial. This thesis examines the relationship between MVP, VAs and SCD.

Chapter 1 reviews the published literature surrounding MVP, VAs and SCD. A historical context and contemporary link between MVP and SCD are discussed. Various histopathological, cardiac imaging and electrophysiological findings in MVP and VAs or SCD are explored. The current pathophysiological understanding of SCD in MVP is highlighted, and provides a premise for subsequent chapters.

Chapter 2 systematically reviews all cases of MVP and SCD reported in the literature. The cases in the literature describe a predominantly young, female population with frequent premature ventricular complexes (PVCs) and prolapse involving both mitral valve leaflets. Cardiac arrest usually occurs as a result of ventricular fibrillation. Leaflet redundancy (defined as thickness ≥5mm) is the only independent predictor of SCD.

Chapter 3 describes histopathological findings and cardiac arrest rhythm in individuals with isolated MVP (iMVP, whereby other potential causes of death are excluded) and

SCD. Individuals with iMVP-SCD have increased cardiac mass, mitral annulus size and left ventricular fibrosis compared to a control group matched for age, sex, height and weight. In those with iMVP and witnessed cardiac arrest, ventricular fibrillation is the predominant cardiac arrest rhythm. These findings suggest that histopathological changes in MVP may provide the substrate necessary for the development of VAs leading to SCD.

Chapter 4 comprehensively and systematically quantifies left and right ventricular fibrosis in individuals with iMVP-SCD compared to a matched control group. Individuals with iMVP-SCD have more left ventricular and interventricular septum fibrosis but similar degree of right ventricular fibrosis compared to the control group. In those with iMVP-SCD, there is more fibrosis in the lateral and posterior walls of the left ventricle with an endocardial-epicardial gradient of fibrosis, which is similar to other conditions that cause cardiac remodelling. These findings indicate that non-uniform left ventricular remodelling with both localised and generalised fibrotic changes are important in the pathogenesis of SCD in MVP.

Chapter 5 compares the incidence of VAs detected with continuous cardiac rhythm monitoring in patients with MVP and controls, and examines whether certain factors predicted for the development of VAs within the MVP group. Over a 24-month follow-up period, those with MVP had a significantly higher overall incidence of VAs compared to control groups. Within the MVP group, the presence of late gadolinium enhancement on cardiac magnetic resonance imaging was predictive for the development of VAs.

Chapter 6 evaluates the role of mitral regurgitation and mitral valve surgery with regards to VAs in patients with redundant leaflet MVP. In patients with redundant leaflet MVP, severity of mitral regurgitation does not affect PVC burden while mitral valve surgery does not reduce PVC burden in unselected patients with MVP. Based on the significant change in PVC burden in two patients, the role of mitral valve surgery in selected patients with MVP warrants further investigation.

Declaration

This is to certify that:

i. The thesis comprises only my original work towards the Doctor of Philosophy except where indicated in the Preface;

ii. Due acknowledgement has been made in the text to all other material used; and

iii. The thesis is fewer than 100,000 words in length exclusive of tables, figures, bibliographies and appendices.

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Preface

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CHAPTER 1

LITERATURE REVIEW

1.1 Introduction

Mitral valve prolapse (MVP) is a condition characterised by the atrial displacement of the mitral valve leaflet(s) during ventricular systole (Figure 1.16.1).[1] Two forms of MVP are generally recognised – that which is associated with thick and gelatinous leaflets, often described as myxomatous or redundant MVP;[2, 3] and that which is associated with thin and translucent leaflets, often described a fibroelastic deficiency.[2] The overall prevalence of MVP in the general population is 2.4%, whilst the prevalence of redundant MVP is approximately 1.3%.[4]

Although recognised as a generally benign condition, reported complications of MVP include mitral regurgitation necessitating mitral valve surgery, stroke and infective endocarditis.[1, 5] MVP has also been associated with sudden cardiac death (SCD). While the proposed mechanism of SCD in MVP is thought to be due to malignant ventricular arrhythmias,[6-8] this link remains controversial due in part to low overall event rates.[1, 4] Nevertheless, within certain SCD populations, there appears to be an over-representation of MVP at autopsy.[9, 10] Although far from completely understood, recent advances have suggested histopathological, cardiac structural and electrophysiological changes in MVP patients which provide plausible explanations for the apparent increase in SCD risk within the MVP population.

1.2 Sudden cardiac death – definition, prevalence and aetiology

Sudden cardiac death is generally defined as a non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in an apparently healthy subject or if death is not witnessed, the definition applies when the victim was in good health 24 hours before the event.[11-13] However, variations to the definition have been implemented by individual studies as a result of varying data collection processes.[14-16] Pragmatically, SCD can also been defined as the instantaneous death in a previously stable patient occurring with or without preceding signs or symptoms including sudden dyspnea, lightheadedness or palpitations (if witnessed) or a patient found dead who at the time of last witnessed contact was in a usual state of health without medical complaints or obvious difficulty including during sleep.[17]

The overall incidence of SCD is difficult to determine for various reasons. Overall improvements in emergency responses to cardiac arrests in the community has resulted in a decline in SCD rates over time.[15] Contemporary estimates of SCD incidence are influenced by SCD definition, geographic location, case identification methods and population demographics such as age and gender.[18, 19] For example, a review of SCD found the estimated incidence to range between 14.9 to 110.8 per 100,000 per year.[20]

The underlying aetiology of SCD is also variable. While autopsy determination is the gold standard for underlying aetiology, autopsy methods (for example single expert adjudication, retrospective examination of reports or panel adjudication) employed in individual studies may affect the determination of underlying causes.[11, 12, 21, 22]

Nevertheless, coronary artery disease (acute or chronic) is the most common cause of SCD in the general population with other significant causes being cardiomyopathy (including dilated, hypertrophic, alcohol, drug related, arrhythmogenic right ventricular, non-compaction and stress induced), valvular (including aortic stenosis and MVP), coronary artery anomalies or dissection, myocarditis, cardiac sarcoid, congenital, primary arrhythmia and aortic dissection.[11, 12, 21-25]

1.3 Historical context of mitral valve prolapse

The characteristic cardiac auscultatory finding in MVP is the mid-systolic click with or without an accompanying late systolic murmur. While these auscultatory findings have been described since the 19th century,[26, 27] it wasn't until the 1960s that physicians gained an understanding as to the cause of the murmur. Prior to the 1960s, an auscultatory finding of a mid-systolic click was commonly ascribed to having an extra-cardiac cause such as pneumothorax or pleuropericardial adhesions.[28] However, in a review of mid-systolic clicks, Dr. John Reid postulated that mid-systolic clicks were due to the "snapping taut of a chorda tendinea during the later high-pressure phase of ventricular systole which, when resulting in mitral incompetence, is followed by a murmur that continues … at least to the second heart sound."[28] The accuracy of this postulation was confirmed a few years later by Dr. John Barlow's observation at autopsy of a single fibrosed mitral valve chorda in a patient who had an isolated mid-systolic during life.[29]

These findings along with cine-angiography findings of ballooned mitral leaflets in

patients with mid-systolic clicks led to increased interest in the association of the mid-systolic click and MVP. Further anatomical evidence regarding the association between mitral valve pathology and mid-systolic clicks was demonstrated in 13 patients along with the now pathological finding of voluminous or redundant mitral valve leaflets (Figure 1.16.2).[30]

1.4 Possible link between mitral valve prolapse and sudden cardiac death

Perhaps, the histopathological description of a condition which had perplexed physicians for over half a century led to an abundance of case series and case reports describing the presence of MVP at autopsy.[30-47] A clinical finding which was considered benign for many decades had now been correlated with pathological changes in individuals during autopsy and this led to significant research efforts to try and establish causality.

1.5 Prevalence of mitral valve prolapse in sudden cardiac death population

The prevalence of MVP in patients with SCD is difficult to quantify.[7] Inherent publication and reporting biases from case reports and series potentially distort the true prevalence of MVP within a SCD population. Larger scale autopsy studies sought to provide some clarification on this issue. A recent systematic review and meta-analysis suggested an overall prevalence of 1.9% based on 14 studies,[6] although individual study estimates varied between 0.1-10.4%.[10, 48]

For example, Fragkouli et al.[48] found only 1 case (0.15%) of MVP in a consecutive autopsy series of 688 cases (mean age 60±14 years; 139 females [20%]) with SCD within a region of Greece. The majority of cases in this older, predominantly male cohort were deemed to have coronary artery disease (82%).

Additionally, de Noronha et al.[49] found the overall prevalence of MVP in a national (United Kingdom) SCD population of 720 cases (median age 32 years, range <1-98 years; 245 females [34%]) to be 1.9% (14 cases). The majority of cases in this cohort were assessed as having morphologically a normal heart (45%) followed by cardiomyopathy (29%) and coronary artery disease (10%).

Conversely, Chugh et al.[10] retrospectively reported on cardiac findings in 270 hearts (mean age 42±14years; 80 females [30%]) from an American state-wide registry of SCD. MVP was identified in 28 cases (10.4%). Interestingly, the presence of MVP was classified as a non-specific finding rather than as a cause of SCD in this cohort probably reflecting the unresolved link between MVP and SCD.

Similarly, Basso et al.[9] reported MVP to be present in 43 (median age 32 years, range 19-40 years; 26 females) out of 650 (6.6%) consecutive autopsy hearts of patients ≤40 years from an Italian state-wide registry of SCD. The 26 female cases of MVP accounted for 13% of females who died suddenly in their registry.

The above autopsy studies present quite discrepant estimates about the prevalence of MVP in the SCD cohort. This may reflect true differences in prevalence, regional

variations in practice with regards to assigning a diagnosis at autopsy,[50] differences in practice over time or possibly clinician bias.[51] Additionally, the prevalence of MVP within a SCD population will be subject to the differences in inclusion criteria used and its subsequent effect on the age and gender distribution of the studied population.[9, 48]

The prevalence of MVP within cardiac arrest registries has been estimated to be between 2-2.5%. Sriram et al.[52] reported MVP to be present in 24 (mean age 32±15 years; 16 females) out of 1200 (2%) cardiac arrest survivors within a longitudinal registry. Similarly, Narayanan et al.[53] sought to investigate the prevalence of MVP within a general cardiac arrest population. Utilising an American regional registry of 3040 cardiac arrest patients, echocardiogram data was available in 729 cases (mean age 69.5±14.8 years; 258 females [35%]). The prevalence of MVP in this cohort was 2.3% (17 cases).

1.6 Incidence of sudden cardiac death in mitral valve prolapse population

1.6.1 *Retrospective studies*

Mills et al.[36] presented the first long term follow-up study investigating the complications of patients with MVP. They retrospectively identified 53 patients who had phonocardiographic evidence of a mid-systolic click and/or late-systolic murmur a minimum of 10 years earlier (mean 13.7 years). Confirmation of MVP through echocardiography was achieved in all but 2 patients. At follow-up, 7 patients died of non-MVP related conditions, 38 were alive without serious complications, and 8 had

serious complications related to MVP. Of the 8 who had MVP related complications, there was 1 case of MVP related SCD and 1 case of cardiac arrest due to ventricular fibrillation resulting in an event rate of 275 per 100,000 person-years.

Data regarding the incidence of SCD in MVP from other retrospective studies are limited. Utilising a regional United States registry, Avierinos et al.[54] found 31 deaths related to MVP in 4581 person-years-worth of follow-up. However, additional classification regarding the number of sudden cardiac deaths was not provided. In a study of MVP in military aviators, Osswald et al.[55] found only 1 case of SCD out of 404 subjects with a mean follow-up period of 8.6 years. However, this was a young and very male predominant cohort. Finally, preliminary data from a tertiary Italian cardiovascular institution indicates a SCD event rate of 145 events per 100,000 person-years.[56]

1.6.2 *Prospective studies*

A handful of studies have prospectively detailed the long-term outcomes of patients with MVP.

Bissett et al.[57] documented the long term follow up on 119 children with MVP evident on cardiac auscultation. Over the follow-up period, one patient developed infective endocarditis, and one had a stroke. There were no SCD events in this paediatric cohort.

Possibly the most insightful study into the long-term outcomes of patients with MVP

was reported by Nishimura et al.[5] which provided follow-up information on 237 patients with MVP on echocardiography who had no or minimal symptoms, and did not have other congenital or valvular heart disease. In total, there were 10 patients who experienced cardiac death with 4 due to coronary artery disease and 6 due to SCD with a resultant event rate of 408 per 100,000 person-years. The presence of mitral valve leaflet redundancy (defined by leaflet thickness ≥5mm) in this cohort of patients was independently associated with the occurrence of SCD. Additionally, 10 out of 97 patients who had MVP and redundant leaflets developed adverse outcomes (6 had SCD, 3 had endocarditis, and 1 had an isolated stroke) compared to only 1 out of 140 patients without redundant leaflets developing an adverse outcome (1 isolated stroke), thus implicating a strong association between myxomatous MVP and adverse outcomes.

Further long term follow-up was described by Duren et al.[58] for 300 patients with MVP diagnosed on echocardiography and without other significant cardiac disease. During the follow-up period, there were 2 non-cardiac deaths, 3 with SCD and 1 patient with cardiac arrest due to ventricular fibrillation with a SCD event rate of 219 per 100,000 person-years. Additionally, Zuppiroli et al.[59] reported follow-up data on 316 patients with MVP diagnosed on echocardiography. During the follow-up period, there were 6 patients who experienced cardiac death with 1 due to coronary artery disease, 1 due to congestive cardiac failure, 1 during cardiac surgery and 3 due to SCD (event rate 112 per 100,000 person-years).

Excluding the studies which were comprised of highly selected patient populations,[55,

[57] overall population studies estimate the SCD event rate in patients with MVP to be between 112 to 408 per 100,000 person-years (Table 1.15.1). Compared with unmatched population estimates, the rate of SCD in an unselected MVP cohort is at least 1.7 times greater.[6] However, when considering that all 6 SCD events from Nishimura et al.[5] occurred in patients with evidence of redundant leaflets, a potentially more malignant subset of patients may exist.

1.7 Echocardiographic diagnosis and the mitral valve prolapse 'epidemic'

The introduction of echocardiography for the non-invasive diagnosis of MVP served to complicate matters.

Initial studies in the early-mid 1970s using M-mode and 2-dimensional echocardiography for the diagnosis of MVP delineated prolapse in the anterior and posterior plane using a parasternal long-axis view (Figure 1.16.3).[60-65] Further work published in the early 1980s suggested that a diagnosis of MVP could be reliably obtained utilising either a parasternal long axis or apical 4-chamber view[66, 67] (Figure 1.16.4) and this approach was adopted in many studies, including the aforementioned prospective studies into the natural history of MVP.[5, 58, 59]

In the late 1980s, Robert Levine and colleagues published a series of groundbreaking papers detailing the saddle-shaped nature of the mitral valve annulus leading to the appearance of valvular prolapse in the apical 4-chamber view without actual leaflet distortion (Figure 1.16.5).[68-70] Through their work, they demonstrated that the annular

plane of the mitral valve in normal subjects deviated by up to 1.4cm (±0.3cm).[70] Most importantly, the group showed that patients with leaflet displacement confined to the apical 4-chamber view, were no more likely than normal subjects to have other echocardiographic abnormalities specified as leaflet thickening, left atrial enlargement or mitral regurgitation whereas those with leaflet displacement in the parasternal long-axis view were significantly more likely to have other associated abnormalities.[69]

In line with shifts in diagnostic criteria, there have been significant shifts in the estimated prevalence of MVP. Early estimates had suggested a prevalence as high as 17% in young adult females,[71] and as high as 34% in adolescent females when utilizing either a long axis or apical echocardiographic view.[72] Courtesy of Framingham cohort studies, the overall population estimate of MVP prevalence was 5.3%, which was higher in females (7.6%) than males (2.5%).[71] Since the implementation of the refined diagnostic criteria, the overall population estimate of MVP has decreased to 2.4%, with the diagnostic frequency in females (2.7%) being affected more than that in males (2.1%).[4] Importantly, within the same cohort, the prevalence of redundant leaflet MVP was 1.1% (1.3% in females and 0.8% in males).[4]

Consequently, results from certain studies in which patients were recruited where MVP was diagnosed using an apical 4-chamber view on echocardiography requires cautious interpretation. Studies which more liberally included patients with milder forms of MVP or possibly no MVP whatsoever may have given rise to weakened risk estimates for clinical complications. Perhaps the best example for this was provided by Nishimura et al.[5] as the authors found significantly more adverse clinical events in

patients with evidence of leaflet redundancy (and therefore more likely to have true MVP) than those without leaflet redundancy.

1.8 Mitral valve anatomy – structure and function

The mitral valve is situated between the left atrium and left ventricle (Figure 1.16.6). Its function is to facilitate the unidirectional flow of blood from the left atrium to the left ventricle through opening in diastole and closure during systole. The mitral valve apparatus is composed of the left atrial wall, mitral valve annulus, mitral valve leaflets (an anterior leaflet also referred to as the aortic leaflet and a posterior leaflet also referred to as the mural leaflet), chordae tendineae and papillary muscles attached to the left ventricular wall.[73]

The left atrium is situated above the mitral valve and the atrial myocardium lies in continuity with the posterior mitral leaflet.[74] This renders the mitral valve susceptible to regurgitation in the event of left atrial enlargement.[74, 75]

The mitral valve annulus lies in the junctional zone between the left atrium and ventricle.[76] It is 'D' shaped with a straight border in continuity with the interventricular septum and adjacent to the aortic valve from which the anterior leaflet is attached and a free border in continuity with the left ventricular free wall from which the posterior leaflet is attached.[74] Fibrous tissue is found along the straight border and non-uniformly interspersed along the free border allowing the annulus to conform and change shape

during the cardiac cycle.[74, 76, 77] Owing to the non-uniform distribution of fibrous tissue, the free border is susceptible to pathological dilatation.[74]

There are two mitral valve leaflets. An anterior leaflet is attached to the straight border of the annulus, has a rounded free edge and occupies approximately 1/3 of the mitral valve orifice.[3, 74, 76] The anterior leaflet – while not necessarily separated by clefts – can be divided into A1, A2 and A3 corresponding to the adjacent regions of the posterior leaflet.[78] A posterior leaflet is attached to the free border of the annulus, is crescent shaped and occupies approximately 2/3 of the mitral valve orifice.[3, 74, 76] The posterior leaflet has 3 scallops formed by clefts along the free edge. The scallops as situated from lateral to medial are identified as P1 (lateral), P2 (middle) and P3 (medial) respectively.[78, 79] During leaflet coaptation, the free edges of the leaflets form an arc shaped closure line.[74] The ends of the closure line are designated commissures – an anterolateral commissure and a posteromedial commisure.[79, 80] Histologically, the mitral valve leaflets are composed of 3 layers when viewed in cross section – atrialis, spongiosa and fibrosa (or ventricularis).[3, 76] The atrialis layer lies adjacent to the left atrium and is lined with endothelium. The spongiosa layer is composed of extracellular matrix, proteoglycans and glycosaminoglycans.[81] It is the major component of the leaflet free edge. The hydrophilic nature of this layer allows for buffering during leaflet closure.[81] The fibrosa layer lies adjacent to the ventricular surface and is thickest near the annulus.[76] Normal mitral valve leaflet morphology is thin and translucent.

Chordae tendineae are fan shaped string-like structures connecting the ventricular aspect of the mitral valve leaflets to the apices of the papillary muscles.[82, 83] Their branching

nature results in more chordae at the valve aspect than at the papillary muscle aspect. Chordae generally attach to either the free edge of leaflets (primary chordae) or the ventricular surface of leaflets (secondary chordae).[74, 84]

Two papillary muscles are found in the mid to apical region of the left ventricular wall.[74] The anterolateral papillary muscle lies in the lateral portion of the left ventricular wall below the anterolateral commissure. The anterolateral papillary muscle gives rise to chordae tendineae of the lateral half of both mitral valve leaflets (P1/A1 and the lateral half of P2/A2). The posteromedial papillary muscle lies in the posterior portion of the left ventricular wall below the posteromedial commissure. The posteromedial papillary muscle gives rise to chordae tendineae of the medial half of both mitral valve leaflets (P3/A3 and medial half of P2/A2).[76]

1.8.1 *Mitral valve anatomy in MVP*

Significant anatomical changes within the mitral valve apparatus occur in patients with MVP. Left atrial enlargement can manifest as a result of mitral regurgitation.[85] The mitral annulus can be dilated,[45, 85] with associated dysfunction or disjunction – separation between the atrial wall-mitral valve junction and the left ventricular attachment (Figures 1.16.7-1.16.9).[86-88] Those with myxomatous MVP also have thick and redundant leaflet(s) in conjunction with characteristic histological changes of disrupted collagen and excess proteoglycans or mucopolysaccharides.[3, 30, 74] By comparison, those with fibroelastic deficiency have thinned leaflets with which are deficient in collagen and proteoglycans.[3] Chordal changes in MVP include elongation

with possible rupture, while those with myxomatous disease may also have associated thickening.[2, 3] The excess stress imparted by prolapsed leaflets are postulated to cause resultant papillary muscle fibrosis in patients with myxomatous MVP.[9, 89]

1.9 Histopathological findings

1.9.1 *Pathological findings*

Given the initial pathological description of MVP,[29] various autopsy studies have provided documentation of gross pathological changes in those with MVP and SCD.

Following on from their initial observation "of a single fibrosed mitral valve chorda in a patient who … had an isolated mid-systolic click",[29] Barlow and colleagues sought to provide further pathological characterisation of mitral valves in patients with systolic murmurs and clicks.[30, 90] By the late 1960s, a clinical entity comprising of a mid-systolic click with late systolic murmur was associated with the presence of both mitral leaflet abnormalities (voluminous, fibrosed and/or calcified leaflets), chordae tendineae abnormalities (thickening or thinning, elongation or shortening, fusion and/or rupture) and mitral annular dilatation.[30, 90]

Additional autopsy studies have attempted to compare clinical and pathological findings of patients with MVP and SCD with various comparator groups. Dollar et al.[45] compared a group with MVP and SCD (n=15) to a group with MVP and other cardiac conditions (n=34). Those with MVP and SCD were younger, predominantly female,

and less likely to have significant mitral regurgitation or ruptured chordae tendineae. Cardiac mass, mitral and tricuspid annular size, mitral leaflet length and presence of endocardial plaques were similar between the groups. Additionally, Farb et al.[85] compared those with MVP and SCD (n=27) to those with clinically significant mitral regurgitation secondary to MVP (n=14) and those with incidental MVP at time of death (n=19). Those with MVP and SCD were younger than both other groups and had lower cardiac mass than those with MVP and mitral regurgitation. Compared to those with incidental MVP, those with MVP and SCD had larger mitral annulus, longer and thicker mitral leaflets and more endocardial plaque. Of note, these studies may not have controlled for influencing factors such as age, sex, height and weight with regards to measurements of cardiac mass and annulus size.[91-93]

In addition to mitral annular dilatation, Hutchins et al.[86] described the presence of mitral annular disjunction (a discrete separation between the atrial wall-mitral valve junction and the left ventricular attachment) in patients with MVP (Figure 1.16.9). In a large series of 900 autopsy hearts, mitral annular disjunction was present in 92% (23/25) of cases with MVP but only 5% (42/905) of cases without MVP leading to the hypothesis that mitral annular abnormalities are equally important in the pathophysiology of MVP as the presence of leaflet distortion.

1.9.2 *Histological findings*

Other studies have investigated histological changes in patients with MVP.

Right ventricular histological changes in living patients with MVP include increased levels of fibrosis in percutaneously obtained endomyocardial samples.[94, 95] Mason et al. demonstrated an increase in endocardial and interstitial fibrosis and mitochondrial degeneration at the right ventricular apical region in a cohort of 14 patients with MVP compared to a control group of patients without MVP.[94] La Vecchia et al. also demonstrated an increase in myocardial fibrosis at the right ventricular septal region in 7 patients with MVP and a history of ventricular tachycardia compared to 21 patients with a history of ventricular tachycardia but no MVP.[95]

Increased levels of left ventricular fibrosis have been found in cases of MVP and SCD based on autopsy studies. Burke et al.[96] showed that those with MVP had significantly higher amounts of basal septum fibrosis in conjunction with atrioventricular nodal artery narrowing compared to control cases. Basso et al.[9] demonstrated increased fibrosis at the papillary muscles and inferobasal wall (in between the papillary muscles) in 43 cases of MVP and SCD compared with a control cohort who had non-cardiac cause of death. Furthermore, evidence suggests that those with MVP and SCD may exhibit diffuse left ventricular fibrosis in conjunction to the focal changes described above,[97] whilst qualitative assessment indicates to a predominant endocardial distribution.[9, 97]

1.10 Cardiac imaging findings

Non-invasive cardiac imaging findings from echocardiography and cardiac magnetic resonance imaging provide certain insights into the link between MVP and SCD.

Echocardiography is a non-invasive cardiac imaging modality based on the use of ultrasonic sound waves and the different responses of human tissue (including cardiac valve motion) to the Doppler effect.[98-102] Modern echocardiography is crucial in the application of diagnostic cardiology allowing for definition of various cardiac structures including valvular morphology and function.[103, 104]

Magnetic resonance imaging relies on the relative difference of water content between tissues within a magnetic field.[105, 106] While initial implementation of magnetic resonance for cardiac imaging predominantly characterised cardiac structure,[107, 108] recent advances have allowed the use of cardiac magnetic resonance in cardiovascular conditions for the determination of focal scarring through detection of late gadolinium enhancement and diffuse fibrosis through the measurement of myocardial T1 time and extracellular volume.[109]

1.10.1 *Abnormalities of the mitral valve leaflets*

Following on from Barlow's initial pathological description of abnormal mitral valve leaflets in MVP,[30] studies have sought to non-invasively characterise mitral leaflet changes in MVP. Both anterior and posterior mitral leaflet thickness and length have been found to be associated with the presence of either non-sustained ventricular arrhythmias or repolarization abnormalities.[110-113] The presence of bileaflet redundant MVP has also been associated with the presence of papillary muscle origin premature ventricular complexes.[114] Importantly, leaflet thickness remains the only independent

predictor for SCD events in MVP thus far.[5]

More recently, the presence of bileaflet redundant MVP was found to be associated with appropriate implantable cardioverter defibrillator discharges in a cohort of cardiac arrest survivors.[52] Conversely however, the same research group also concluded that bileaflet redundant MVP was associated with better overall survival compared to matched control groups despite a higher rate of ventricular tachycardia.[115] In an attempt to resolve the discrepancy, the authors suggested that other factors may be important for the development of SCD rather than isolated bileaflet MVP.

1.10.2 *Abnormalities of the mitral valve annulus*

Studies have also sought to non-invasively characterise the mitral annulus in MVP. Mitral annulus dilatation has been described using echocardiography and cardiac magnetic resonance studies in MVP.[116-118] The presence of mitral annular disjunction has also been extensively reported using 2-dimensional and 3-dimensional echocardiography, trans-oesophageal echocardiography and cardiac magnetic resonance.[87, 88, 118-120] Within these studies, mitral annular disjunction has been associated with the presence of ventricular arrhythmias.[88, 118, 120] Furthermore, there appears to be abnormal physiological function of the mitral valve in MVP with a paradoxical increase in annulus size during ventricular systole.[88, 118] These findings suggest that disorganised mitral annular dynamics may be a critical component in the association between MVP and SCD.

1.10.3 *Mitral regurgitation*

The relationship between MVP, mitral regurgitation and adverse outcomes is contentious. Studies have indicated that the presence or severity of mitral regurgitation in MVP is associated with the presence of ventricular arrhythmias or repolarization abnormalities,[110, 113, 121-124] whereby the assertion is that it is the mitral regurgitation rather than the MVP causes ventricular arrhythmias.[122] Of note, contemporary studies have indicated that the degree of mitral regurgitation is not associated with arrhythmic outcomes in MVP.[52, 125] Quite possibly, this is a result of the shift in MVP diagnostic criteria whereby the presence of mitral regurgitation correlated with 'true' cases of MVP in older studies.[69]

Not surprisingly, worsening mitral regurgitation severity is also linked to increased cardiovascular mortality in MVP.[54] However, it is important to distinguish that the likely pathophysiology of death in those with MVP with severe mitral regurgitation is probably related to haemodynamic cardiac decompensation resulting in clinical heart failure,[126] whereas those with MVP and SCD are likely to have experienced a malignant ventricular arrhythmia.[7, 8, 52]

1.10.4 *Non-invasive detection of cardiac fibrosis*

Non-invasive evaluation of myocardial fibrosis utilizing cardiac magnetic resonance has demonstrated an association between late gadolinium enhancement detected areas of focal ventricular fibrosis with complex ventricular arrhythmias in patients with MVP.[9,

[89, 114, 125] The regions affected appear to be predominantly the papillary muscles and the basal infero-lateral regions of the left ventricle,[9, 89, 114, 125, 127] corresponding to localised areas of premature ventricular complexes.[9, 128] In contrast, there is conflicting evidence for the association between myocardial T1 times (indicating diffuse left ventricular fibrosis) and ventricular arrhythmias.[127, 129]

1.10.5 *Novel cardiac imaging markers*

Novel echocardiography parameters reportedly associated with ventricular arrhythmias in patients with MVP include high velocity systolic signals with tissue Doppler of the medial and/or lateral mitral annulus and the presence of mechanical dispersion of the left ventricle as determined by speckle tracking echocardiography.[130, 131]

1.11 Electrophysiological findings

Electrophysiological findings from 12-lead electrocardiogram (ECG), 24-hour Holter monitoring, continuous long-term cardiac rhythm monitoring, signal averaged ECG and programmed ventricular stimulation provide certain insights into the link between MVP and SCD.

A 12-lead ECG is a non-invasive test for ascertaining information regarding the electrical depolarization and repolarization of the heart.[132] The origins for the modern-day ECG date back to the late 1890s and early 1900s with Einthoven's description of the string galvanometer.[133] Throughout the mid-1900s,[134] the ECG was studied and

developed extensively into an indispensable tool which is used to diagnose various cardiac conditions including those which are associated with SCD.[135-142]

While a 12-lead ECG can provide immediate information regarding the electrical system of the heart, a 24-hour cardiac monitor carries incremental advantages with regards to our understanding of cardiac rate, rhythm and conduction during times of physical exertion, emotional activity and during rest.[143, 144] Ambulatory cardiac rhythm monitoring, predominantly in the form of a 24-hour Holter monitor – named after discoverer Norman J. Holter,[143] can also allow for diagnosis of complex ventricular arrhythmias and occult cardiac rhythm disturbance including those associated with SCD.[145-149]

Continuous long-term cardiac rhythm monitoring may be achieved through the use of insertable cardiac monitors which have a battery life of approximately 3 years.[150-152] Modern day devices are small in size and inserted through a small incision in the left parasternal region, sitting in the subcutaneous space approximately 1cm below the surface of the skin.[151, 152] These devices provide continuous ECG monitoring through a loop memory system and can store ECG information based on predefined arrhythmic triggers (including tachyarrhythmias and bradyarrhythmias) or patient activated triggers.[150-154] The use of insertable cardiac monitors has proven beneficial in the diagnosis of unexplained syncope,[153-155] the detection of atrial fibrillation in patients with cryptogenic stroke[156] and for documenting cardiac arrest rhythm in patients at high risk of sudden death.[152]

Another extension of the 12-lead ECG is signal averaged ECG (SAECG) which utilises high-resolution processing software to record cardiac late potentials which occur at the end of or after a QRS complex.[157, 158] The presence of cardiac late potentials is postulated to represent localised areas of abnormal myocardium with electrical activity described as desynchronised from the rest of the heart – akin to localised ventricular fibrillation.[159] Similar to the 12-lead ECG and a 24-hour Holter monitor, abnormalities identified on SAECG are potentially predictive of malignant ventricular arrhythmias or SCD in certain populations.[160, 161]

Invasive electrophysiological testing by means of programmed ventricular stimulation involves electrode catheters inserted through the femoral vein.[162] Through rapid ventricular pacing with extrastimuli, initiation and termination of ventricular tachycardia may occur in patients with an underlying substrate for myocardial disease.[162-164] Again, inducible ventricular arrhythmia on programmed ventricular stimulation may predict for the occurrence of SCD in certain populations.[165]

1.11.1 *Malignant ventricular arrhythmias*

Multiple case series and case reports have documented ventricular arrhythmias in patients with MVP.[31, 34, 35, 39, 166-193] However, due to the inherent limitations with case series and reports,[194] only isolated cases have been able to describe cardiac arrest rhythm in patients with pathologically diagnosed MVP.[31, 34, 35, 39, 179, 181, 183, 188, 192, 193] Consequently, without the systematic documentation of cardiac arrest rhythm in patients with pathologically confirmed MVP, hence a direct causal relationship

between SCD and MVP is yet to be established.

1.11.2 *Bradycardia*

Case reports have also documented bradycardic events in patients with MVP. Documented conduction abnormalities include both the sinus node and/or the atrioventricular node,[195-203] although this is also seen in individuals experiencing vagal stimuli.[204-207] Given the prevalence of MVP, these isolated cases likely reflect a convergence of patients with MVP with autonomically mediated conduction abnormalities rather than a pathogenic association.

1.11.3 *Electrocardiogram findings*

Based on observations from initial case report descriptions of MVP and SCD, Jeresaty proposed that those with MVP who experience SCD are likely to exhibit "ST-T wave changes in the inferior and left precordial leads".[35] This was supported by qualitative findings of non-specific T-wave changes in 9/10 patients with MVP and recurrent ventricular tachycardia,[169] and inverted or biphasic T-wave changes in 10/12 patients with MVP and SCD.[9] Additionally, in a cohort of patients with idiopathic out-of-hospital cardiac arrest, Sriram et al documented significantly higher rates of inferior T-wave changes (biphasic or inverted) in those with MVP compared to those without MVP.[52]

1.11.4 *Premature ventricular complex morphology*

The underlying pathophysiology of ventricular arrhythmias in patients with MVP is postulated to be related to mechanical stresses imparted by the valve and valve apparatus on the left ventricle.[182, 208] Hence, the site of origin of premature ventricular complexes and ventricular tachycardia in patients with MVP provide clues about an underlying electroanatomical pathogenic process related to the mitral valve apparatus.

For example, Lichstein et al.[209] demonstrated that in 10 patients with MVP and unifocal premature ventricular complexes, 8 were localised to the posterior aspect of the left ventricle while only 2 were from the right ventricle. Similarly, La Vecchia et al.[95] documented that all 7 of their patients with MVP and ventricular tachycardia had a left ventricular focus. Of note, these two studies utilised 12-lead electrocardiography for premature ventricular complex location.

Studies reporting sites of premature ventricular complex ablation in MVP lend further support to the above notion. Syed et al.[128] retrospectively reported on premature ventricular complex ablation procedures in 16 patients with bileaflet redundant MVP. In 15 patients, ablation targeted either one of the left sided papillary muscles or left sided fascicles using invasive electroanatomical mapping.

1.11.5 *Other electrocardiogram abnormalities*

Other cardiac electrical abnormalities have been reported in patients with MVP including the presence of accessory conduction pathways,[210-213] prolongation of the QT or QTc interval[214, 215] and increased QT or QTc dispersion.[112, 216-218] Significantly,

increased QTc dispersion has been shown to be an independent predictor for non-sustained ventricular tachycardia on 24 hour Holter monitoring in MVP.[112]

1.11.6 *Ambulatory 24-hour Holter monitoring*

The estimated incidence of ventricular arrhythmias (including the presence of isolated premature ventricular complexes) in patients with MVP using Holter monitoring vary between 34-88%.[124, 217-223] In a consecutive series of 58 patients with MVP, Turker et al.[124] found 20 (34%) to have evidence of ventricular arrhythmias on Holter monitoring. This was predominantly driven by having 17 patients with isolated PVCs, whilst only 2 had couplets and 1 patient had non-sustained ventricular tachycardia. On the other side of the spectrum, Kulan et al.[217] found premature ventricular complexes in 56 of 64 (88%) patients with MVP undergoing Holter monitoring.

Additionally, studies estimate the prevalence of complex ventricular arrhythmias – as defined by the presence of Lown grade ≥3 premature ventricular complexes[145] on Holter monitoring – to be between 17% to 59%.[111, 123, 217, 218, 224]

Controlled studies involving patients with MVP has shown varying results. Comparisons between patients with MVP and healthy controls suggests that those with MVP have either an increased frequency of premature ventricular complexes or more complex ventricular arrhythmias.[63, 217] In contrast, data from the Framingham cohort showed no statistically significant difference in Lown grade ≥2 ventricular arrhythmia burden between 61 patients with MVP and 179 patients without MVP.[71] Others have

suggested that premature ventricular complex frequency and prevalence of complex ventricular arrhythmias is related to degree of mitral regurgitation rather than MVP,[122] or are related more so to the presence of clinical symptoms rather than MVP itself.[225]

Inconsistencies between these studies likely reflect the evolution of diagnostic criteria used to select patients with MVP.[68-70] Furthermore, while Holter monitoring provides 24-hour cardiac rhythm monitoring, data regarding continuous long-term cardiac rhythm monitoring in MVP is currently lacking.

1.11.7 *Signal-averaged electrocardiogram*

Late potentials on SAECG are more common in patients with symptomatic MVP compared with control cohorts,[95, 226] and in those with MVP the presence of late potentials are associated with episodes of ventricular arrhythmias.[123, 226] Conversely, asymptomatic individuals with MVP diagnosed on routine screening do not exhibit evidence of late potentials,[227] although the reasons for this discrepancy are uncertain.

These findings suggest that the presence of late potentials is intimately related to ventricular arrhythmias, although their clinical utility over the use of Holter monitoring is not well established.

1.11.8 *Programmed ventricular stimulation*

The utility of invasive programmed ventricular stimulation as a SCD risk stratification

tool in MVP lacks supporting evidence. Despite multiple studies having documented successful induction of ventricular arrhythmias – including monomorphic ventricular tachycardia, polymorphic ventricular tachycardia and ventricular fibrillation – during programmed ventricular stimulation,[123, 175, 228, 229] the lack of a therapeutic or clinical endpoint coupled with the absence of adequate control groups limit the clinical applicability of data obtained.

1.12 Current pathophysiological understanding

Certain findings from the various histopathological, cardiac imaging and electrophysiological research outlined above provide mechanistic insights into the potential pathophysiology of SCD in patients with MVP.

Increased cardiac mass and ventricular fibrosis may represent a process of diffuse cardiac remodelling akin to other conditions associated with SCD,[9, 45, 50, 85, 94-96, 230, 231] resulting in myocardial stretch or myofiber disarray and subsequent substrate for generalised electrical instability. Furthermore, focal papillary muscle fibrosis may provide more discrete areas of localised electrical instability in patients with MVP.[9] In addition, mitral annular instability in the form of enlargement and/or disjunction may contribute to areas of electroanatomical instability.[85, 86] These findings of both focal and diffuse cardiac fibrosis along with mitral annular instability are supported by cardiac imaging studies,[9, 89, 114, 118, 120, 127] thus providing a correlation between non-invasive and invasive findings in patients with MVP.

Electrophysiological abnormalities of ventricular repolarization – suggestive of underlying substrate instability – are evident in patients with MVP in the form of inferolateral ST-T wave changes, increased QTc or QTc dispersion and late potentials on signal averaged ECG.[9, 35, 52, 112, 169, 214-218] Furthermore, electrical trigger instability is evidenced by the increased burden and complexity of premature ventricular complexes arising from the left ventricular papillary muscles.[63, 128, 217] Thus, a milieu for electrical instability created by this substrate-trigger interaction may lead to sustained ventricular arrhythmia development and subsequent sudden cardiac death in patients with MVP.[6-8, 232]

Hence, histopathological changes of increased cardiac mass,[9, 45, 50, 85] enlarged mitral valve annulus,[85] mitral annular disjunction,[86] and cardiac fibrosis[9, 50, 96, 97] causing resultant electrophysiological instability as evidenced by premature ventricular complexes and repolarization abnormalities provides a working hypothesis regarding the underlying pathophysiology of SCD in patients with MVP.

1.13 Other abnormalities in mitral valve prolapse

Other structural cardiac findings have been associated with MVP patients including the co-existence of congenital heart defects.[45] Additionally, case reports have described the co-existence of coronary vasospasm, arrhythmogenic right ventricular cardiomyopathy and Takotsubo cardiomyopathy in patients with MVP and cardiac arrests.[176, 183, 187] These findings are unsurprising given the high prevalence of MVP. However, to determine the true relationship between MVP and SCD, it would be prudent to

distinguish between those with isolated MVP (iMVP, whereby other potential causes of death are excluded) and those with non-isolated MVP (whereby the individual has another potential cause of death).

1.14 Contemporary management

1.14.1 *Guideline recommendations*

There is limited data regarding SCD prevention specific to patients with MVP.[7, 8] Medical management with beta-blockers and to a lesser extent amiodarone may be considered in certain circumstances based on current guidelines for the treatment of VAs and prevention of SCD, while a secondary prevention implantable cardioverter defibrillation insertion is recommended for survivors of cardiac arrest.[13, 233] In addition, use of long term continuous cardiac rhythm monitoring (internal or external) would be indicated in patients with MVP with a history of unexplained syncope.[234, 235]

1.14.2 *Electrophysiology studies*

As described above, the role of programmed ventricular stimulation in patients with MVP and ventricular arrhythmias has not been established.[7, 123, 173, 175, 229] Limited evidence does suggest that catheter ablation of premature ventricular complexes may offer symptomatic benefit by reducing their burden in MVP patients with symptomatic premature ventricular complexes and decrease appropriate implantable cardioverter-defibrillator therapies in MVP patients with a secondary prevention device.[128] However,

catheter ablation in this cohort present intraprocedural challenges owing to the high proportion of papillary muscle origin premature ventricular complexes while its effect on survival outcomes is not established.[236, 237]

1.14.3 *Mitral valve surgery*

The role of mitral valve surgery for ventricular arrhythmias in patients with MVP requires further clarification. In patients with flail mitral regurgitation, operative correction has been associated with improved overall survival,[126] although this is likely due to prevention of death associated with acute left ventricular failure and pulmonary oedema rather than the prevention of arrhythmic SCD. A reduction in ventricular arrhythmias has been reported in some patients with MVP and malignant ventricular arrhythmias undergoing mitral valve surgery,[189, 208, 238-240] although findings from these case reports and series are subject to publication bias. Additionally, some patients who undergo mitral valve surgery continue to experience malignant ventricular arrhythmias requiring implantable cardioverter-defibrillator therapy.[240]

1.15 Tables

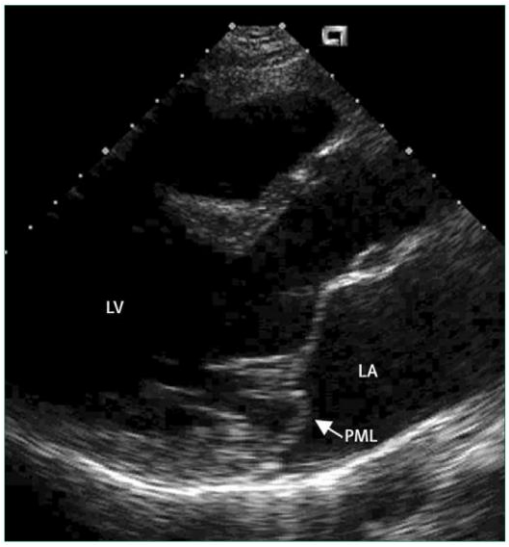
1.15.1 *Incidence of SCD in MVP*

Study	Year	Nature	Patients	Age	Females (%)	Follow-up	SCD events (event rate)
Mills[36]	1977	Retrospective	53	41	34 (64)	13.7	2* (275)
Bissett[57]	1980	Prospective	119	10	82 (69)	6.9	0
Nishimura[5]	1985	Prospective	237†	44	142 (60)	6.2	6 (408)
Düren[58]	1988	Prospective	300	42	164 (55)	6.2	4* (219)
Zuppiroli[59]	1995	Prospective	316	42	220 (70)	8.5	3 (112)
Osswald[55]	2007	Retrospective	404	36	9 (2)‡	8.6	1 (29)
Mecarocci[56]§	2016	Retrospective	250	52	126 (50)	8.3	3 (145)

Age and follow-up presented as means (in years)
SCD event rate presented as SCD events per 100,000 person-years
*One case of documented ventricular fibrillation with cardiac arrest included in overall SCD events
†97 patients with leaflet redundancy
‡Military aviation cohort resulting with a predominantly male cohort
§Study only available in abstract form

1.16 Figures

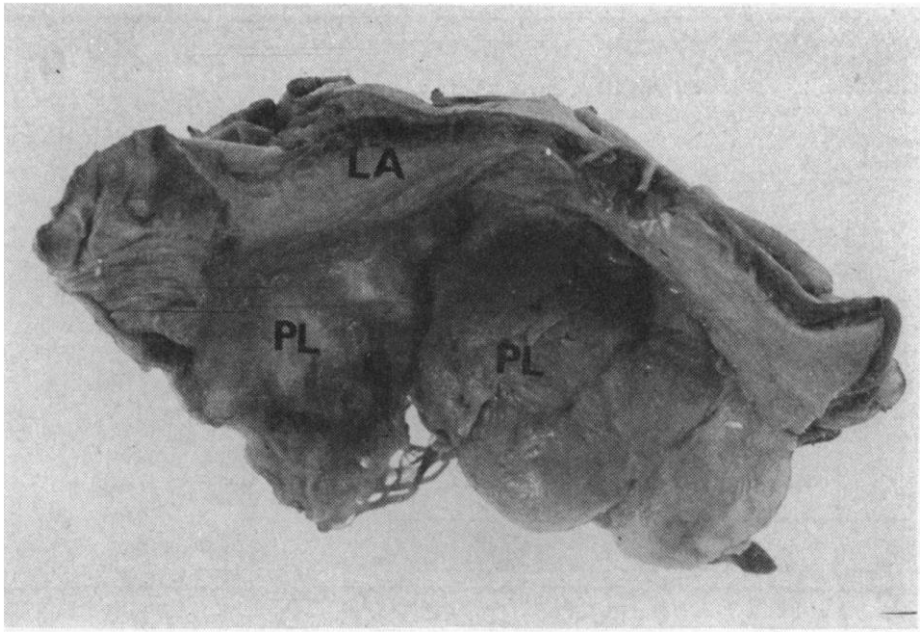
1.16.1 *MVP on echocardiography*



Mitral valve prolapse involving the posterior leaflet. The leaflet prolapses into the left atrium during ventricular systole. LV, LA and PML denotes left ventricle, left atrium and posterior mitral valve leaflet respectively.

Reproduced from Hayek E, Gring CN, Griffin BP. Mitral valve prolapse. Lancet 2005;365:507-18, with permission from Elsevier.

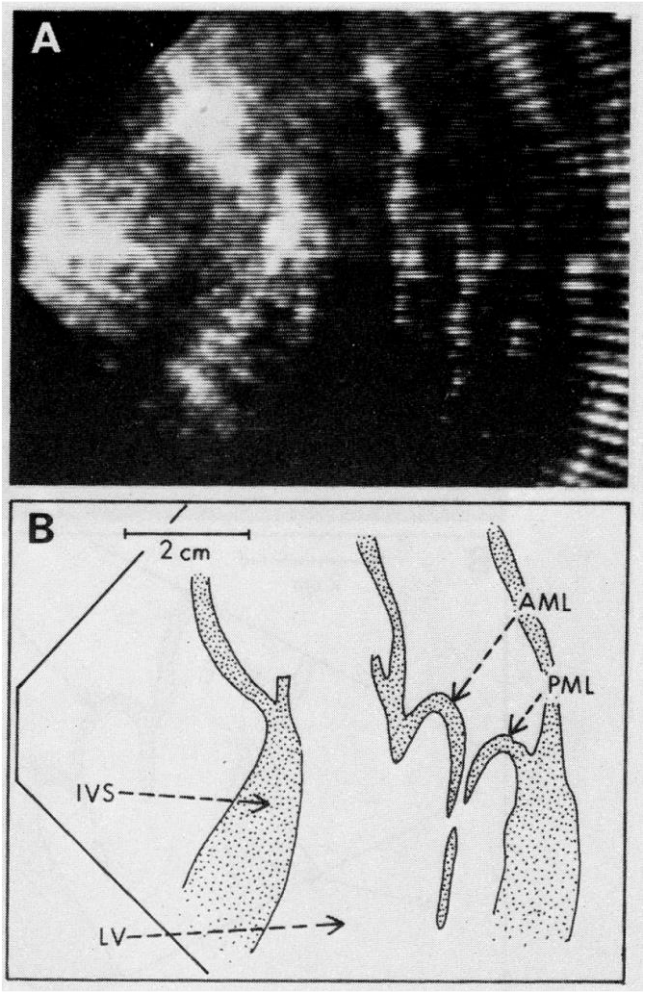
1.16.2 *Pathological assessment of MVP*



Initial pathological assessment of voluminous mitral valve leaflet in a patient with mitral valve prolapse and sudden death. LA and PL denote left atrium and posterior mitral valve leaflet respectively.

Reproduced from Barlow J, Bosman C, Pocock W, Marchand P. Late systolic murmurs and non-ejection ("mid-late") systolic clicks. An analysis of 90 patients. British Heart Journal 1968;30:203-18, with permission from BMJ Publishing Group Ltd.

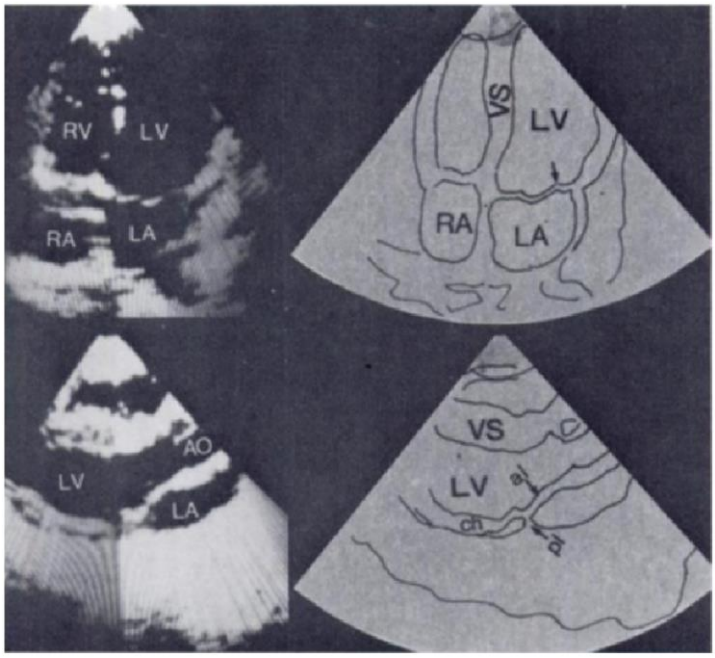
1.16.3 *Initial echocardiography diagnosis of MVP*



Mitral valve prolapse demonstrated on 2-dimensional echocardiography using a parasternal long axis view. Panel A shows prolapse of both leaflets into the left atrium during ventricular systole. Panel B is a schematic representation. IVS, LV, AML and PML denotes interventricular septum, left ventricle (cavity), anterior mitral valve leaflet and posterior mitral valve leaflet respectively.

Reproduced from Gilbert BW, Schatz RA, VonRamm OT, Behar VS, Kisslo JA. Mitral valve prolapse. Two-dimensional echocardiographic and angiographic correlation. Circulation 1976;54:716-23, with permission from Wolters Kluwer Health Inc.

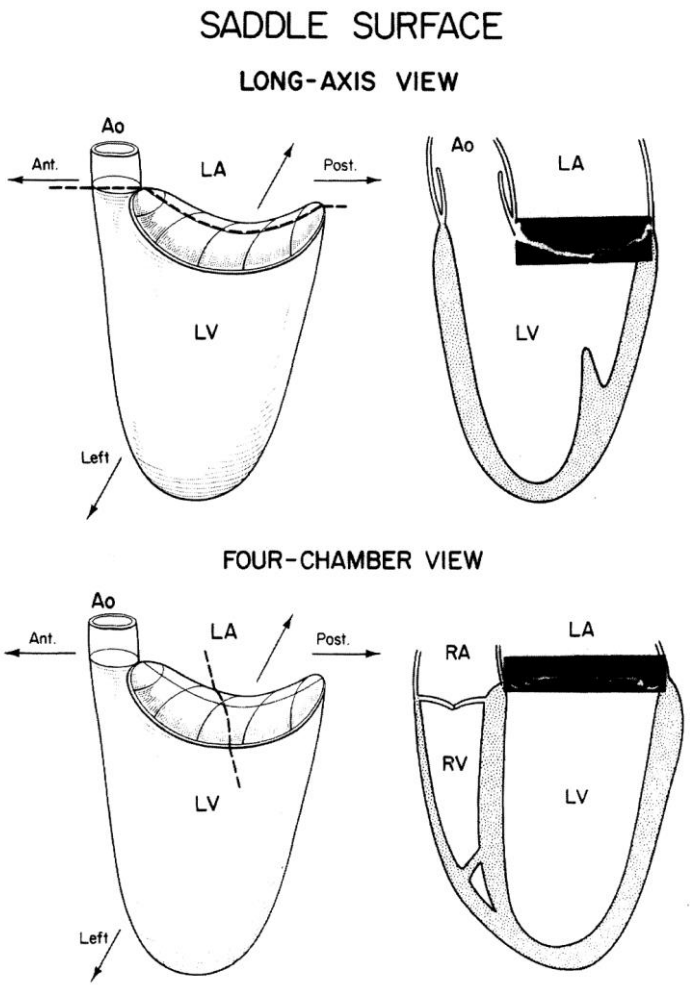
1.16.4 *MVP in apical view*



Images showing apparent mitral valve prolapse using an apical view (top images) with no evidence of mitral valve prolapse using a long-axis view (bottom images). VS, LV, RA and LA denotes ventricular septum, left ventricle (cavity), right atrium and left atrium respectively.

Reproduced from Morganroth J, Mardelli TJ, Naito M, Chen CC. Apical cross-sectional echocardiography. Standard for the diagnosis of idiopathic mitral valve prolapse syndrome. Chest 1981;79:23-8, with permission from Elsevier.

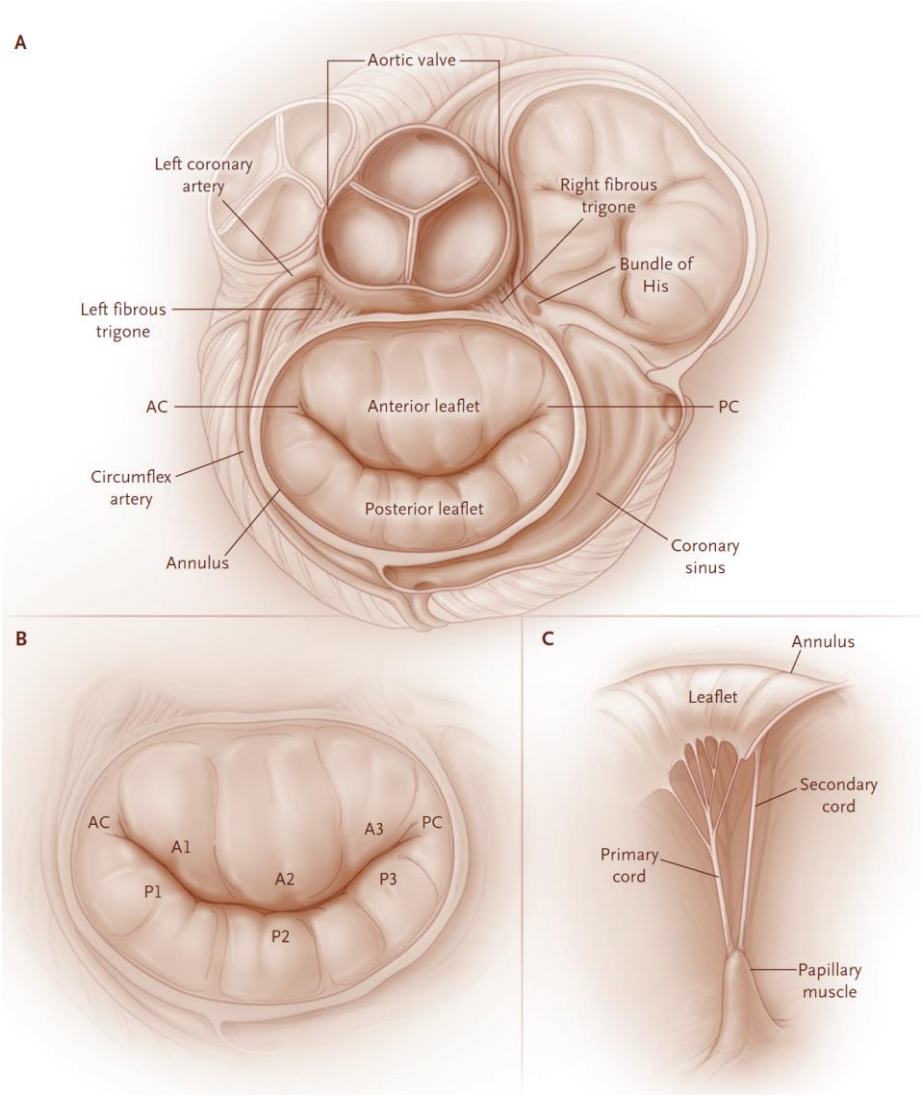
1.16.5 *Saddle shape of mitral valve annulus*



The saddle shaped nature of the mitral valve annulus. The anterior-posterior points of the annulus (dashed line on top image) lie more atrial compared to the medial and lateral points of the annulus (dashed line on bottom image) leading to apparent prolapse in the apical (four-chamber) view but not in the long-axis view. Ant., Post., Ao, LA, LV, RA and RV denotes anterior, posterior, aorta, left atrium, left ventricle, right atrium and right ventricle respectively.

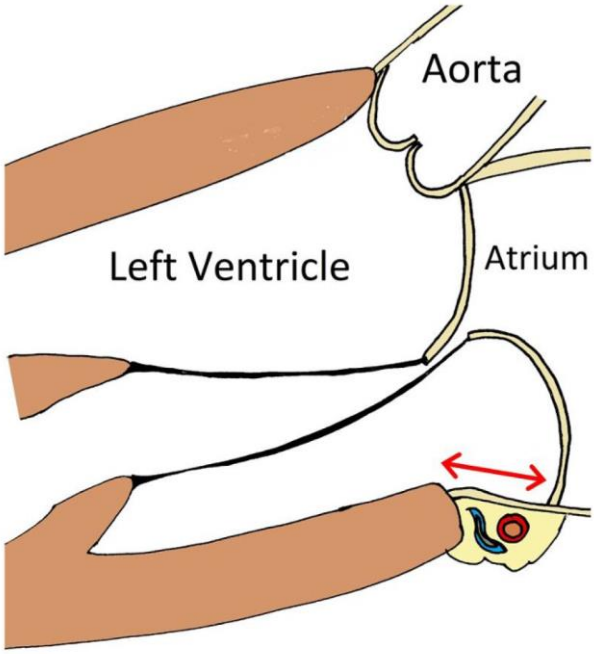
Reproduced from Levine RA, Triulzi MO, Harrigan P, Weyman AE. The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. Circulation 1987;75:756-67, with permission from Wolters Kluwer Health Inc.

1.16.6 *Anatomy of the mitral valve*



Panel A shows the mitral valve (below) in cross section as viewed from the left atrium at the level of the annulus in relation to the aortic valve (above centre), pulmonary valve (above left) and tricuspid valve (above right). The mitral valve annulus is 'D' shaped with a straight border adjacent to the aortic valve. The anterior leaflet is rounded and attached to the straight border of the annulus while the posterior leaflet is crescent shaped and attached to the free border of the annulus. AC and PC denotes anterior commissure and posterior commissure respectively. **Panel B** shows a magnified view of the mitral valve and annulus. The anterior and posterior leaflet are divided into 3 scallops designated as A1, A2, A3 and P1, P2, P3 respectively. **Panel C** show the mitral valve leaflet in relation to chordae tendineae and papillary muscle.

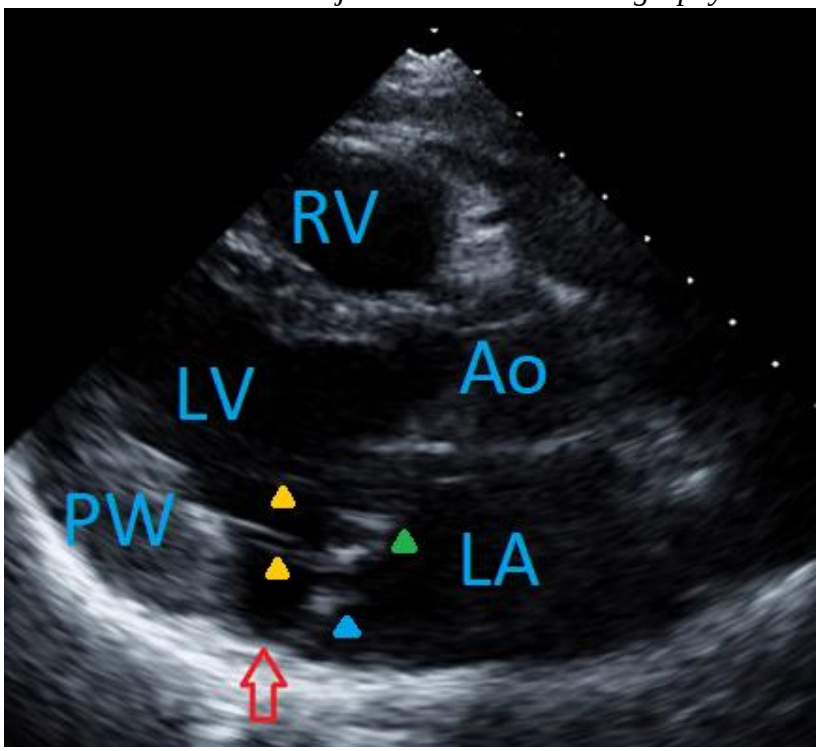
1.16.7 *Schematic representation of mitral annular disjunction*



The red double headed arrow shows separation of the posterior left ventricular wall and posterior mitral valve attachment to the left atrium.

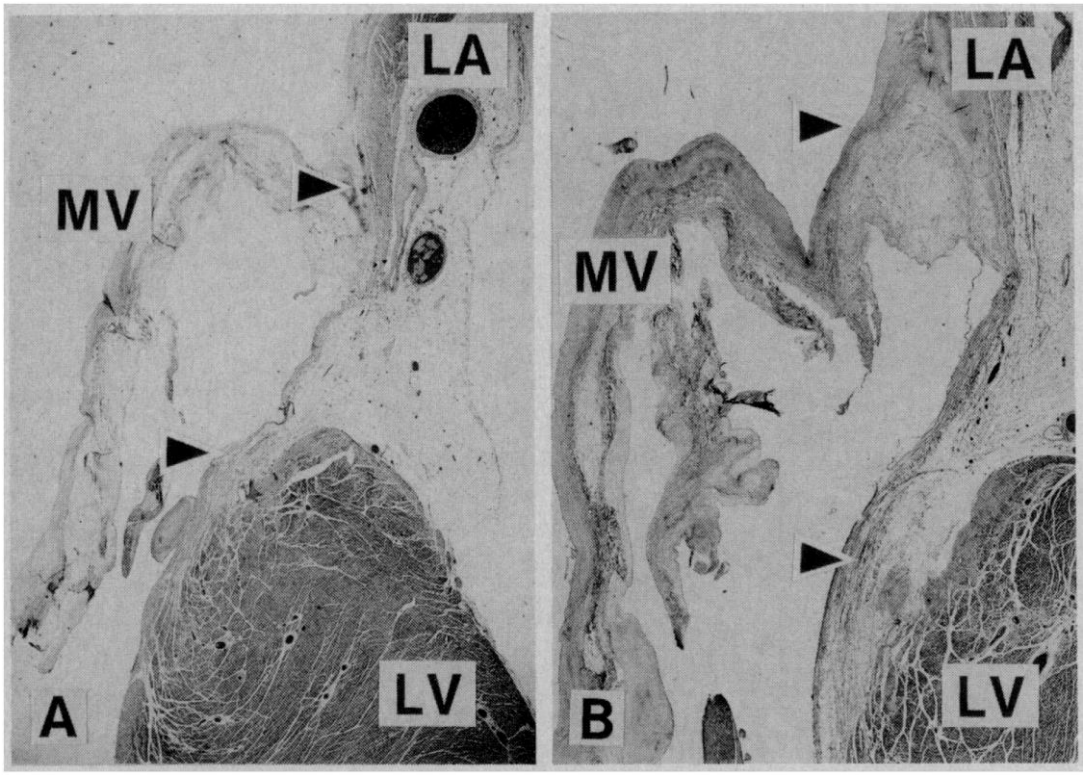
Reproduced from Carmo P, Andrade MJ, Aguiar C, Rodrigues R, Gouveia R, Silva JA. Mitral annular disjunction in myxomatous mitral valve disease: a relevant abnormality recognizable by transthoracic echocardiography. Cardiovascular Ultrasound 2010;8:53, with permission from BioMed Central Ltd.

1.16.8 *Mitral annular disjunction on echocardiography*



Red arrow shows mitral annular disjunction. Yellow, green and blue arrowheads show chordae tendineae, anterior mitral valve leaflet and posterior mitral valve leaflet respectively. RV, LV, PW, Ao, LA denotes right ventricle, left ventricle, posterior wall, aorta and left atrium respectively.

1.16.9 *Mitral annular disjunction on histology*



The distance of disjunction is separated by the top and bottom arrowheads. LA, MV, LV denotes left atrium (wall), mitral valve and left ventricle (wall) respectively.

CHAPTER 2

Mitral Valve Prolapse and Sudden Cardiac Death: A Systematic Review

2.1 Overview

Background: The relationship between mitral valve prolapse (MVP) and sudden cardiac death (SCD) remains controversial. In this systematic review, we evaluate the relationship between isolated MVP and SCD to better define a potential high-risk subtype. Additionally, we determine whether pre-mortem parameters could predict SCD in patients with MVP and the incidence of SCD in MVP.

Methods and Results: Electronic searches were conducted in PubMed and Embase for all English literature articles published between 1960 and 2018 regarding MVP and SCD or cardiac arrest. We also identified articles investigating predictors of ventricular arrhythmias or SCD and cohort studies reporting SCD outcomes in MVP.

From 2180 citations, there were 79 articles describing 161 cases of MVP with SCD or cardiac arrest. Median age was 30 years and 69% of cases were female. Cardiac arrest occurred during situations of stress in 47% and was due to VF in 81%. Premature ventricular complexes on Holter monitoring (92%) were common. Most cases had bileaflet involvement (70%) with redundancy (99%) and non-severe mitral regurgitation (83%). From 22 articles describing predictors for ventricular arrhythmias or SCD in MVP, leaflet redundancy was the only independent predictor of SCD. Incidence of SCD in with MVP was estimated at 217 events per 100,000 person-years.

Conclusions: Isolated MVP and SCD predominantly affects young females with redundant bileaflet prolapse, with cardiac arrest usually occurring due to ventricular arrhythmias. To better understand the complex relationship between MVP and SCD, standardised reporting of clinical, electrophysiological and cardiac imaging parameters with longitudinal follow-up is required.

2.2 Introduction

Mitral valve prolapse (MVP) is characterised by the atrial displacement of the mitral valve (MV) leaflet(s) during ventricular systole. The estimated prevalence of MVP is 2.4% with equal sex distribution.[4]

Although most MVP cases are thought to be benign, reported complications include mitral regurgitation (MR) requiring MV surgery, infective endocarditis, stroke and sudden cardiac death (SCD).[1] The association between MVP and SCD (a potential high-risk MVP subtype) has been reported but the underlying mechanisms remain poorly understood. It is postulated that SCD in individuals with MVP is due to ventricular arrhythmias (VAs),[9, 52] although this association remains controversial.[1, 4, 122] The initial description of MVP involved cardiac auscultation, cineangiography and histopathological examination.[29] This led to an abundance of literature describing MVP at autopsy,[37, 42, 43, 45, 179] provoking discussions about a causal relationship between MVP and SCD.

The application of M-mode and 2-dimensional echocardiography for the diagnosis of MVP posed challenges as the identification of MVP shifted from the long axis view,[60, 61] to either a long axis or apical 4-chamber view,[66] and then back to the long axis view as the gold standard for diagnosing MVP.[70] These changes resulted in a significant rise and fall in the prevalence of MVP,[4, 71] with implications for the estimated incidence of SCD.

We aimed to comprehensively evaluate all reported cases of MVP and SCD in the current literature to better characterise the potential high-risk MVP subtype and to determine whether clinical and diagnostic parameters can predict which patients with MVP were at higher risk of experiencing SCD. Furthermore, based on published studies, we provide an estimated incidence of SCD in MVP.

2.3 Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure as source data for this systematic review are available from web-based medical libraries.

2.3.1 *Case identification and search strategy*

We conducted a literature search for cases of MVP with SCD or cardiac arrest in PubMed and Embase on January 1 2018 using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[241] PubMed search terms were

(“mitral valve prolapse” AND “cardiac arrest”) OR (“mitral valve prolapse” AND “sudden cardiac death”) OR (“mitral valve prolapse” AND “sudden death”) OR (“mitral valve prolapse” AND “arrhythmia”). Embase search terms were (“mitral valve prolapse” AND “heart ventricular fibrillation”) OR (“mitral valve prolapse” AND “heart arrest”) OR (“mitral valve prolapse” AND “sudden death”) OR (“mitral valve prolapse” AND “sudden cardiac death”) OR (“mitral valve prolapse” AND “heart ventricular tachycardia”) OR (“mitral valve prolapse” AND “heart arrhythmia”) OR (“mitral valve prolapse” AND “heart ventricular arrhythmia”).

Titles and abstracts were screened for relevance by two reviewers (HH and FJH) and bibliographies of all included publications were screened to identify additional references. Screening of the above search result was also conducted to identify articles which investigated whether MVP patients had certain clinical, electrophysiological or imaging predictors that were associated with VAs or SCD. Finally, prospective studies of patients with MVP which reported SCD outcomes were included to estimate the incidence of SCD in MVP. Details of the search algorithm are shown in Figure 2.8.1.

Included articles were any cases of MVP with SCD or MVP with cardiac arrest and documented rhythm reported in English. Cases of MVP and SCD were separated into isolated MVP (iMVP) and non-isolated MVP (non-iMVP) depending on whether there was another potential cause of death or cardiac arrest. Reports from case series were included if individual patient age and sex could be determined. Cases were excluded if they described VAs which did not result in cardiac arrest or survived cardiac arrest

without a documented rhythm. Reports were also excluded if published only in abstract form.

Regarding predictors of SCD or VAs, we excluded articles which used normal subjects (as opposed to high versus low risk MVP) as controls. We also excluded articles with non-significant findings or outcomes which were not related to VAs or SCD.

Regarding incidence of SCD in MVP, we included prospective studies, with mean patient age over 18 years, at least 100 patients and minimum follow-up duration of 24 months.

2.3.2 *Statistical analysis*

Continuous data are presented as either medians with inter-quartile range (IQR) or means with standard deviations (SD) as indicated. Categorical data are presented as absolute numbers and percentages.

2.4 Results

In total, 161 cases of MVP with either SCD or cardiac arrest were identified from 79 studies, with 123 cases of iMVP and 38 cases of non-iMVP. A further 22 studies investigated predictors of VAs or SCD. Comprehensive details of all included studies are presented in Tables 2.9.1 and 2.9.2. There were 3 studies which provided long term follow-up data regarding SCD in MVP.[5, 58, 59]

2.4.1 *Clinical characteristics in iMVP and SCD*

Clinical characteristics of the cases are summarised in Table 2.7.1. The age-sex distribution of the index event of cardiac arrest or death is illustrated in Figure 2.8.2.

For those with iMVP, the median age was 30 years (range 6 to 79 years), female sex accounted for 69% of cases and 61% were SCD cases. Median age for female cases was 28 (IQR, 24-41) years and median age for male cases was 39 (IQR, 28-53) years. Two cases occurred in individuals aged under 10 (ages 6 and 7), and a further 6 cases in individuals between 10-18 years. Activity at the time of cardiac arrest included routine daily activities (46%), exertion related (23%), emotional stress (5%), sleeping (7%), driving (5%) and pregnancy related (4%). Seven cases had cardiac arrest while in hospital with 5 occurring in the setting of general anesthesia.

Preceding symptoms included palpitations (58%), syncope (29%), chest pain (31%), dizziness (23%), and fatigue (8%). Only 21% of patients were reported to be asymptomatic prior to the index event. Three cases had a history of cardiac arrest, although none of these cases overlapped with those who had prior syncope.

Prior medication use was reported in 32 cases, of which eight (25%) involved patients taking either a beta blocker or digoxin at the time of cardiac arrest or SCD and 50% who were not taking any medications. One patient was taking multiple psychotropic medications,[242] while another case described MVP and SCD in a patient with markedly elevated concentrations of caffeine (from an energy supplement).[192]

A positive family history for SCD was reported in 14% of cases. One case described a possible familial cluster of malignant MVP involving a 14-year-old female with SCD and MVP, 3 first degree relatives with SCD (mother aged 36, sister aged 11, and brother aged 12 who had thickening of his mitral valve) and 3 of 7 remaining siblings with MVP.[42]

2.4.2 *Electrophysiological findings in iMVP and SCD*

Electrophysiological findings for cases of MVP and SCD or cardiac arrest are shown in Table 2.7.2.

On baseline electrocardiogram (ECG), premature ventricular complexes (PVCs) were frequently reported (51%), while T-wave inversion in the inferior leads (24%) and other T-wave changes (19%) were also common. Seven cases described combined inferior and lateral T-wave changes. Normal baseline ECG was described in 32% of cases.

Among patients who underwent Holter monitoring, PVCs and couplets were the most common finding (63%) followed by non-sustained VT (29%). No abnormalities were recorded in 8%.

The site of origin of VT or PVCs was available (either reported or interpreted based on published ECG) in 6 cases. Both left and right bundle branch morphologies (in V1) were present with regard to VT or PVC origin. Four cases (all VT) published 12-lead

ECGs allowing for interpretation of possible VT origin (Figure 2.8.3).[168, 178, 190, 243] Cardiac arrest rhythm was reported in 53 cases and was due to VF (81%), VT (11%), TDP (4%), and asystole (4%). Six cases documented the initiation of malignant VAs with 5 cases showing PVC triggered polymorphic VT or VF (Figure 2.8.4).[167, 171, 178, 183, 189, 244] In total, there were 10 cases of autopsy confirmed MVP (6 with iMVP and 4 with non-iMVP) with documented cardiac rhythm at time of death – all had VF.[31, 34, 35, 39, 179, 181, 183, 188, 192, 193]

Programmed ventricular stimulation (PVS) was reported for 22 cases utilising various induction protocols. Findings included sustained VT (5%), non-sustained VT (23%), VF (18%), and no induction of VAs (55%).

2.4.3 *Cardiac imaging findings in iMVP and SCD*

Cardiac imaging findings for cases of MVP and SCD or cardiac arrest are shown in Table 2.7.3.

Leaflet involvement was most commonly bileaflet (70%), then posterior leaflet (26%) and anterior leaflet (4%). Severe MR was present in 17% of cases. Six cases reported MV surgery (3 repair and 3 replacement) with 3 cases describing improvement in VAs (follow-up duration ranged from 2 to 3 years), 2 cases describing recurrent VT requiring treatment even after surgery and 1 case with unreported arrhythmia outcomes.

Two cases reported cardiac MRI findings. with one case reporting anteroseptal and posterior wall fibrosis while the other did not demonstrate late gadolinium enhancement.

2.4.4 *Cardiac structural findings in iMVP and SCD*

Cardiac structural findings are summarised in Table 2.7.4.

Autopsy confirmation of MVP was documented in 73 of the 75 SCD cases. In total, 72/73 (99%) cases which commented on the mitral valve described redundant leaflets. Median MV annulus circumference was 126mm based on 15 cases, while another 2 cases reported a dilated annulus. Median anterior and posterior MV lengths were 30mm and 25mm respectively. Leaflet thickness was not reported in cases of iMVP and SCD. Chordae were described in 45 cases and included generalised abnormalities (62%), rupture (33%) and normal appearance (4%).

Histological abnormalities in the left ventricle were described in 12/30 cases (40%) with three cases describing fibrosis involving the papillary muscles. From 27 cases which described other cardiac structural findings, 17 cases (63%) had no other abnormal findings, 5 cases (19%) had right ventricular fibrosis, 3 cases (11%) had tricuspid valve prolapse and 2 cases (7%) had evidence of prior endocarditis

2.4.5 *Non-isolated MVP cases*

For cases of non-iMVP, there were 11 cases with a probable other cause of death or cardiac arrest including anomalous right coronary artery (2), significant left main coronary disease (1), diffuse coronary disease in the setting of pseudoxanthoma elasticum (1), coronary vasospasm (1), previous inferior infarct (1), arrhythmogenic right ventricular cardiomyopathy (1), Brugada syndrome (1), hypertrophic cardiomyopathy (1), dilated cardiomyopathy (1) and post-partum cardiomyopathy (1). There were a further 27 cases with another possible cause of death or cardiac arrest including non-specific left ventricular hypertrophy or cardiomegaly (12), conduction system fibrosis (2), possible side effect from anti-arrhythmic medications (13) and prolonged QTc (3) or a combination of the above. These cases are identified in Table 2.9.1.

2.4.6 *Predictors of ventricular arrhythmias and SCD*

We identified 22 articles which reported a heterogeneous group of clinical, electrical and imaging predictors for MVP and its association to various clinical outcomes. A summary of all studies is presented in Table 2.7.5 and a full list in Table 2.9.2.

Significant multivariate predictors of various outcomes include female sex and anterior mitral leaflet thickness for Lown grade ≥3 complex VAs, QTc dispersion and anterior mitral leaflet length for VT, moderate to severe MR with PVCs for VAs, degree of MVP and anterior mitral leaflet thickness for QT dispersion and leaflet redundancy for SCD.

2.4.7 *Incidence of SCD in MVP*

We identified 3 prospective articles which described SCD events in patients with MVP, shown in Table 2.7.6.[5, 58, 59]

Incidence of SCD ranged from 112-408 events per 100,000 person-years with an aggregate incidence of 217 events per 100,000 patient-years (total 13 event in 5985.4 person-years of follow-up). One additional study described a pediatric cohort (mean age 9.9 years) of patients with MVP with no SCD events during 814 person-years of follow-up.[57]

2.5 Discussion

This systematic review of all identified cases of cardiac arrest in patients with MVP demonstrates the following key features in patients with iMVP and SCD:

1. Clinical characteristics
    a. Median age of 30 years (range 6-79 years) and 69% were female
    b. 47% of cases occurred during physiological or psychological stress
2. Cardiac electrophysiological findings
    a. Frequent PVCs or VAs (92% on Holter monitoring)
    b. VF is the primary rhythm (81%) in cardiac arrest and death
3. Cardiac imaging findings
    a. Predominant (70%) bileaflet MVP
    b. Moderate MR or less in 83%
4. Histopathological findings

    a. Redundant leaflets in 99%
    b. Abnormal chordae in 96%
5. Clinical predictors for SCD in MVP
    a. Lacks robust evidence with heterogenous predictors and endpoints
    b. Leaflet redundancy is the only independent predictor of SCD in patients with MVP
6. Estimated incidence of SCD in MVP is 217 events per 100,000 person-years

2.5.1 *Clinical characteristics*

The median age at time of cardiac arrest or SCD was 30 years although this was 28 years in females and 39 years in males. Age-sex distribution graph for the cases demonstrated a peak in female cases between 20 to 30 years consistent with previous data relating to iMVP and SCD.[52, 111] Cases of MVP related cardiac arrest or SCD in males appeared evenly distributed throughout life.

There appeared to be a disproportionately large number of cases (47%) related to situations of stress (physical, emotional, driving, pregnancy and in-hospital). The association between increased adrenergic state and complex VAs may provide a plausible explanation as to why autonomic fluctuations may be important in the pathogenesis of iMVP related SCD.[224]

2.5.2 *Cardiac electrical findings*

From this large collection of MVP cases with cardiac arrest rhythm, VF appears to be primarily responsible for iMVP related SCD. Where documented, most were PVC triggered. Only 2 cases described cardiac arrest due to asystole, with one patient having exercise induced asystole and another a likely vagal reaction.[202, 245] These findings support a primary arrhythmogenic cause of SCD in patients with iMVP.

Common electrocardiographic changes included the presence of inferolateral T-wave inversion and PVCs on ECG and the presence of PVCs and VAs on Holter monitoring. However, despite the postulation that inferior T-wave changes on ECG are associated with a potentially high-risk MVP subtype,[35, 52] prospective evidence is lacking. Similarly, despite reports of a high incidence of PVCs and VAs on Holter monitoring,[217] these findings have not been prospectively correlated to SCD events in MVP patients.

Inducible VAs on PVS does not appear to predict SCD events in patients with MVP.[175] Two cases in this study reported PVS findings prior to SCD and both cases did not induce VAs.[173, 181] Additionally, only 1/22 cases (5%) had sustained VT during PVS suggesting that arrhythmia initiation is PVC triggered rather than re-entrant scar related. As such, the role of electrophysiological testing in identifying a potential high-risk MVP subtype may be limited.

2.5.3 *Cardiac imaging findings*

The presence of bileaflet prolapse has been associated with an increased rate of VAs and cardiac arrest.[52, 114] This is consistent with our findings where a bileaflet phenotype

was present in 70% of cases of SCD or cardiac arrest. The association between bileaflet prolapse, mitral annular disjunction and VAs indicates that mitral apparatus abnormalities likely plays a contributory role in the development of malignant VAs.[118]

Although prior studies suggest that severe MR is correlated with VAs,[122] we found no association between the two. Where degree of MR was reported, the majority (83%) experienced cardiac arrest in the setting of non-severe MR. Whether surgery on the MV may mitigate risk of cardiac arrest is also unclear. Patients who underwent MV surgery had variable results including 2 cases that experienced recurrent VAs requiring defibrillator therapy post MV surgery.[240] The lack of systematic reporting and long-term follow-up limits our interpretation.

Other cardiac imaging parameters which may be important include degree of redundancy,[5] mitral annular dilatation,[118] mitral annular disjunction,[118] and anterior mitral leaflet thickness and length.[111, 112] Unfortunately, few studies documented findings in regard to these parameters. Furthermore, although previous work has suggested that radiological myocardial fibrosis may be a trigger for complex VAs in MVP,[9, 114] results from cardiac MRI was only available in 2 studies limiting interpretation. Studies which prospectively evaluate cardiac imaging parameters with systematic reporting of longitudinal outcomes are required.

2.5.4 *Cardiac structural findings*

Where reported, 99% of cases described mitral leaflet redundancy and MV annulus diameter was dilated compared with population data.[92] Anterior and posterior mitral leaflet length were also greater than otherwise expected.[85] Abnormal chordal findings were present in 96% of cases. The combination of morphological valve distortion and chordal abnormalities are consistent with other autopsy studies of patients with MVP,[85, 90] and provide further support that mitral apparatus abnormalities have a contributory role in the development of SCD.

There were 30 cases where cardiac histopathological findings were described. Among these, 12 cases reported abnormal left ventricular histological changes including three cases which specifically described histological abnormalities involving the papillary muscles. Left ventricular fibrosis, especially near the papillary muscles, is described in autopsy patients with MVP and may provide a substrate for the development of VAs.[9, 96] These findings suggest that both diffuse and focal changes within the left ventricle occur in patients with MVP which may act as a substrate for the development of VAs.

2.5.5 *Findings in non-iMVP*

As described, there was a subset of patients with SCD and MVP but also other cardiac abnormalities.

SCD is likely attributable to significant coronary artery disease, dilated or hypertrophic cardiomyopathy, Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy in cases with these co-existent conditions.

Other co-existent findings are more contentious. Anatomical findings such as mild left ventricular hypertrophy or cardiomegaly at autopsy have been described in relation to MVP,[10] and could indicate that pathological changes of the ventricle in otherwise "iMVP" is a contributor to SCD events. Additionally, 13 patients were on antiarrhythmic medications. It is prudent to consider that while these medications in themselves may have pro-arrhythmic side effects, these medications were likely administered to treat pre-existing VAs in the cases. Finally, findings of prolonged QTc may also reflect underlying repolarisation abnormalities in patients with MVP which has also been previously described.[112, 113]

2.5.6 *Challenges in predicting SCD in patients with iMVP*

Studies investigating pre-mortem predictors of SCD in MVP are limited. One prospective study demonstrated that leaflet redundancy was an independent predictor of SCD.[5] Some controversy surrounds the risk of bileaflet MVP with one study suggesting that it was associated with appropriate ICD therapies,[52] whilst another suggested that bileaflet MVP was associated with lower all-cause mortality based on registry data.[115]

Pre-mortem predictors of VAs are difficult to validate in the current collection of cases. Some predictors such as leaflet redundancy, bileaflet MVP and inferolateral T-wave inversion on ECG were only available in approximately half the case reports while degree of MR was available for about one-quarter of cases. Other potential predictors such as catecholamine levels, late potentials, QT dispersion, anterior mitral leaflet

thickness and length, mitral annular disjunction, presence of late-gadolinium enhancement and myocardial T1 time were either scarcely reported or not reported.

Additionally, many studies have used VAs or repolarisation abnormalities as surrogate end-points for SCD (Table 2.7.2) due to the relatively low event rates of SCD. These end-points which include NSVT, Lown grade VAs of varying degrees, PVC frequency, exercise induced PVCs, presence of papillary muscle PVCs, PVC reduction post MV surgery, corrected QT interval or QT dispersion are yet to be validated as predictors of SCD in the MVP population.

The heterogeneous nature of these predictors and end-points limits comparisons between studies. As such, despite the numerous cases reporting SCD or cardiac arrest in MVP, there is limited evidence that such outcomes can be reliably predicted.

2.5.7 *Incidence of SCD in MVP*

Our findings suggest that the overall incidence of SCD in MVP was 217 events per 100,000 person-years based on 3 prospective studies, although the presence of leaflet redundancy may signal a higher risk cohort. Extrapolation of data from Nishimura et al. suggests an approximate event rate of 998 per 100,000 person-years in those with evidence of leaflet redundancy.[5]

Comparisons to population data is inherently limited (Figure 2.8.5). More recent population based studies indicate that the incidence of SCD in the general population

has decreased from 94-97 events per 100,000 person-years in the 1990s to 42-53 events per 100,000 person-years in the 2000s,[11, 12, 14-16] although advances in resuscitation methods may account for some of this difference. Framingham data (involving an older and more male predominant cohort) suggests that the SCD risk in the general population was approximately 130 events per 100,000 person-years during the 1980s,[15] around the time of the 3 prospective studies.

2.5.8 *Limitations*

This is the largest systematic review of published cases of MVP and SCD or cardiac arrest. We sought to provide a comprehensive insight into the clinical, electrical, imaging and histopathological characteristics. Our results highlight some significant challenges when attempting to characterise a potential high-risk MVP subtype.

The cases which describe MVP and SCD or cardiac arrest span over 50 years. Our understanding of MVP has evolved significantly over that time. Changes in clinical medicine affect the reproducibility of various diagnostic tests, especially echocardiography for the diagnosis of MVP. Information regarding clinical, electrical, imaging and histopathological characteristics were inconsistently described and are subject to reporting and publication bias. Notably, a lack of systematic reporting regarding these characteristics likely affected their prevalence within this collection of cases.

Further work is required to validate many of the current reported predictors. The disconnect between pre-mortem predictors and available information from SCD cases limits our ability to determine whether these factors may be important in the development of SCD and cardiac arrest.

Finally, despite all the published literature hypothesizing that SCD in MVP is due to malignant VAs, there are only 10 cases describing autopsy proven MVP with documentation of cardiac arrest rhythm. Further correlation of cardiac arrest rhythm and pathological description may be important.

2.6 Conclusion

Our systematic review indicates that iMVP and SCD predominantly affects young females. The MV is frequently redundant with bileaflet prolapse, associated chordal abnormalities and non-severe MR. Electrophysiological changes include frequent PVCs on Holter monitoring and VF as the predominant cardiac arrest rhythm.

Current predictors for SCD events in iMVP lack robust evidence. To better understand the complex relationship between MVP and SCD, standardised reporting of clinical, electrophysiological, echocardiographic and other cardiac imaging variables, with documentation of long-term outcomes is required.

2.7 Tables

2.7.1 *Baseline characteristics in cases of MVP and SCD or cardiac arrest*

Baseline Characteristics			
	All cases (n=161)	iMVP (n=123)	Non-iMVP (n=38)
Age (years)			
Range	6-79	6-79	8-76
Mean (SD)	37 ± 16	36±16	40±17
Median (IQR)	32 (25-51)	30 (25-47)	36 (26-56)
Female sex	109 (68%)	85 (69%)	24 (63%)
Sudden cardiac death	100 (62%)	75 (61%)	25 (66%)
Circumstances of death or cardiac arrest	n=98 (%)	n=74 (%)	n=24 (%)
Sleeping	6 (6)	5 (7)	1 (4)
Normal daily activity*	45 (46)	34 (46)	11 (46)
Exertion or soon after†	22 (22)	17 (23)	5 (21)
Emotional stress	6 (6)	4 (5)	2 (8)
Driving	4 (4)	4 (5)	0
Anesthesia related‡	6 (6)	5 (7)	1 (4)
Pregnancy related§	4 (4)	3 (4)	1 (4)
Witnessed in hospital	5 (5)	2 (3)	3 (13)
Prior symptoms‖	n=71 (%)	n=48 (%)	n=23 (%)
Dizziness	14 (20)	11 (23)	3 (13)
Syncope	25 (35)	14 (29)	11 (48)
Dyspnea	9 (13)	5 (10)	4 (17)
Chest pain	20 (28)	15 (31)	5 (22)
Palpitations	39 (55)	28 (58)	11 (48)
Fatigue	6 (8)	4 (8)	2 (9)
None	12 (17)	10 (21)	2 (9)
Previous cardiac arrest	n=20 (%)	n=14 (%)	n=6 (%)
Yes#	8 (40)	3 (21)	5 (83)
No	12 (60)	11 (79)	1 (21)
Medication use	n=57 (%)	n=32 (%)	n=25 (%)
Digoxin	7 (13)	1 (3)	6 (24)
Beta-blocker**	16 (28)	7 (22)	9 (36)
Class 1††	10 (18)	0	10 (40)
Amiodarone	1 (2)	0	1 (4)
Other medications‡‡	15 (26)	9 (28)	6 (24)
Nil	17 (30)	16 (50)	1 (4)
Family history of SCD	n=28 (%)	n=22 (%)	n=6 (%)
Yes	4 (14)	3 (14)	1 (17)
No	24 (86)	19 (86)	5 (83)

iMVP, isolated mitral valve prolapse; IQR, inter-quartile range; SCD, sudden cardiac death; SD, standard deviation.

*Includes death at home, work (non-physical), or during commute

†1 case was post sexual intercourse

‡4 cases during induction, 1 case during anesthesia reversal, 1 case during peripheral arterial puncture

§2 cases were pregnant, 1 case during epidural injection, 1 case (classified as non-iMVP) was 2 days post-partum with likely tachycardia mediated cardiomyopathy due to permanent junctional reciprocating tachycardia

‖Multiple symptoms in some cases

#3 cases with documented ventricular fibrillation

**2 patients taking sotalol (classified as non-iMVP)

††Includes propafenone, procainamide, mexilitine, quinidine, disopyramide and flecainide

‡‡Includes amoxicillin, diuretics, anti-epileptics, primidone, methyldopa, perindopril, trastuzumab, inhaled glucocorticosteroids, danazol, domperidone and various psychotropic agents in 3 cases

2.7.2 *Electrical findings in cases of MVP and SCD or cardiac arrest*

Electrical Findings			
	All cases	iMVP	Non-iMVP
Baseline ECG changes*	n=81 (%)	n=59 (%)	n=22 (%)
Inferior TWI†	15 (19)	14 (24)	1 (5)
Other ST-T changes‡	16 (20)	11 (19)	5 (23)
PVCs§	40 (49)	30 (51)	10 (45)
Normal	23 (28)	19 (32)	4 (18)
Atrial fibrillation	9 (11)	5 (8)	4 (18)
Left ventricular hypertrophy	5 (6)	2 (3)	3 (14)
Other‖	9 (11)	5 (8)	4 (18)
Holter findings	n=36 (%)	n=24 (%)	n=12 (%)
No PVCs	4 (11)	2 (8)	2 (17)
PVCs & couplets only	20 (56)	15 (63)	5 (42)
Non-sustained VT	10 (28)	7 (29)	3 (25)
TDP/VF	2 (6)	0	2 (17)
Cardiac arrest rhythm	n=72 (%)	n=53 (%)	n=19 (%)
VF	58 (81)	43 (81)	15 (79)
VT	9 (13)	6 (11)	3 (16)
TDP	3 (4)	2 (4)	1 (5)
Asystole	2 (3)	2 (4)	0
PVS findings	n=26 (%)	n=22 (%)	n=4 (%)
Normal	13 (50)	12 (55)	1 (25)
Non-sustained VT	6 (23)	5 (23)	1 (25)
Sustained VT	2 (8)	1 (5)	1 (25)
VF	5 (19)	4 (18)	1 (25)
Site of origin of PVCs or VT	n=10 (%)	n=6 (%)	n=4 (%)
Left ventricle	3 (30)	2 (33)	1 (25)
Right ventricle	5 (50)	4 (67)	1 (25)
Both	2 (20)	0	2 (50)

PVCs, premature ventricular complexes; TDP, torsades de-pointes; TWI, T-wave inversion; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Multiple changes in some cases

†All leads (11 cases), lead III (1 case), leads II and III (2 cases), leads III and aVF (1 case)

‡TWI in lateral leads (7 cases), TWI in V1-3 (1 case), diffuse changes (1 case), not specified (7 cases)

§Includes multiple PVCs (1), multifocal PVCs (6), bigeminy (3) and couplets (1)

‖Includes premature atrial complexes, bundle branch blocks and accessory pathway (iMVP cases); Brugada pattern, prolonged QT, left axis deviation and poor R-wave progression (non-iMVP cases)

2.7.3 *Imaging findings in cases of MVP and SCD or cardiac arrest*

Imaging Findings			
	All cases	iMVP	Non-iMVP
Leaflet involvement*	n=83 (%)	n=57 (%)	n=26 (%)
Bileaflet	57 (69)	40 (70)	17 (65)
Posterior leaflet	23 (28)	15 (26)	8 (30)
Anterior leaflet	3 (4)	2 (4)	1 (4)
MR severity	n=38 (%)	n=23 (%)	n=15 (%)
Nil/trivial	9 (24)	6 (26)	3 (20)
Mild	12 (32)	9 (39)	3 (20)
Moderate	8 (21)	4 (17)	4 (27)
Severe	9 (24)	4 (17)	5 (33)

*Determination based on either non-invasive imaging reports and/or autopsy reports

2.7.4 *Cardiac structural findings*

Cardiac Structural Findings			
	All cases	iMVP	Non-iMVP
Mitral valve changes	n=88 (%)	n=73 (%)	n=15 (%)
Redundant leaflet(s)*	87 (99)	72 (99)	15 (100)
Annulus circumference (mm)†	n=19	n=15	n=4
Range	96-160	100-160	96-135
Median (IQR)	125 (100-136)	126 (113-138)	106 (97-120)
Anterior leaflet length (mm)	n=15	n=13	n=2
Range	20-35	20-35	20-28
Median (IQR)	30 (25-30)	30 (25-30)	
Posterior leaflet length (mm)	n=16	n=13	n=3
Range	15-30	15-30	15-30
Median (IQR)	25 (20-30)	25 (20-30)	28
Chordal changes	n=56 (%)	n=45 (%)	n=11 (%)
Normal	3 (5)	2 (4)	1 (9)
Abnormal‡	37 (66)	28 (62)	9 (82)
Ruptured	16 (29)	15 (33)	1 (9)
Left ventricle histology	n=40 (%)	n=30 (%)	n=10 (%)
Normal§	20 (50)	18 (60)	2 (20)
Abnormal‖	20 (50)	12 (40)	8 (80)
Other cardiac abnormalities	n=50 (%)	n=27 (%)	n=23 (%)
Left ventricular hypertrophy or cardiomegaly	14 (28)	0	14 (61)
Right ventricular fibrosis#	6 (12)	5 (19)	1 (4)
Coronary artery disease**	6 (12)	0	6 (26)
Other††	6 (12)	5 (19)	1 (4)
Nil	18 (36)	17 (63)	1 (4)

IQR, inter-quartile range.
*Includes descriptive terms myxomatous, ballooned, thickened, nodose, hooding, floppy, voluminous, opaque, edematous
†3 additional cases reported a dilated annulus without measurement
‡Descriptions included elongated, thickened and/or fused
§15 normal samples were from 1 series (all samples in that series were normal)[45]
‖Heterogeneous group of descriptors including: fibrosis affecting the interventricular septum (3), interstitial fibrosis (5), extensive papillary muscle fibrosis (1), slight papillary muscle fibrosis (2), subendocardial fibrosis affecting the papillary muscles (2), presence of myxomatous material within the papillary muscles (1), multifocal necrosis (3), high grade LVH changes (1), degenerated elastic fibres (1)
#1 case with arrhythmogenic right ventricular cardiomyopathy (non-iMVP)
**Includes left main coronary disease (1), anomalous right coronary artery (2), coronary vasospasm (1), prior inferior infarct (1), significant diffuse coronary disease in the setting of pseudoxanthoma elasticum (1)
††Includes tricuspid valve prolapse (3) and previous endocarditis (2) (iMVP cases); significant conduction system fibrosis (1) (non-iMVP case)

2.7.5 *Predictors of ventricular arrhythmias or SCD*

Author	Year	Study population	Predictor/association	Outcome/Endpoint
Clinical				
Gaffney[246]	1979	MVP	Higher heart rate Lower cardiac index	Clinical severity (combination of symptoms and VAs)
Puddu[215]	1983	MVP	Plasma catecholamine level	QTc
Sniezek[224]	1992	MVP	Adrenaline excretion	Complex VAs (Lown grade ≥3)
Zuppiroli[111]	1994	MVP	Female	Complex VAs (Lown grade ≥3)*
Babuty[123]	1994	MVP	Age (older)	Complex VAs (Lown grade ≥3)
Naksuk[247]	2016	MV surgery	Age (younger)	PVC reduction post-surgery in BiMVP
Fulton[114]	2017	MVP	Female	PVCs from PM
Electrical				
Campbell[248]	1976	MVP	Inferolateral T-wave changes	VT (>100bpm for ≥3 beats) or VF
Babuty[123]	1994	MVP	Late potentials	VT (≥3 beats)
Bobkowski[226]	2002	MVP	Late potentials	VAs (Lown grade ≥1) and VT (>120bpm for ≥4 beats)
Akcay[112]	2010	MVP	QTc dispersion	VT (>120bpm for ≥3 beats)*
Imaging				
Shah[121]	1982	MVP	MR	Complex VAs (Lown grade ≥3)
Nishimura[5]	1985	MVP	Redundant leaflets	Sudden death*
Kligfield[122]	1985	MVP	MR	VAs (>1% PVC frequency or exercise induced PVCs/VT or Lown grade ≥4 complex VAs)
Sanfilippo[110]	1989	MVP	Anterior leaflet thickness MR	VAs (≥10 PVCs/hr or VT at ≥100bpm for ≥3 beats)
Zuppiroli[111]	1994	MVP	Anterior leaflet thickness	Complex VAs (Lown grade ≥3)*
Babuty[123]	1994	MVP	MR	Complex VAs (Lown grade ≥3)
Zouridakis[113]	2001	MVP	MVP degree Anterior leaflet thickness	QT dispersion*
Turker[124]	2010	MVP	Moderate-severe MR	VAs (Lown grade ≥1)*
Carmo[88]	2010	MVP	Mitral annular disjunction	Non-sustained VT (NS)
Han[89]	2010	MVP	LGE in PM	Complex VAs (Lown grade ≥4)
Akcay[112]	2010	MVP	Anterior leaflet length	VT (>120 bpm for ≥3 beats)*
Sriram[52]	2013	OHCA	BiMVP	Appropriate ICD therapies at follow-up
Basso[9]	2015	MVP	LGE	Complex VAs (Lown grade ≥4b or VF)
Nordhues[115]	2016	MVP	BiMVP	All-cause mortality
Bui[127]	2017	MVP	Myocardial T1 time	Complex VAs (Lown grade ≥3)
Fulton[114]	2017	MVP	BiMVP LGE in PM	PVCs from PM

BiMVP, bileaflet MVP; ICD, implantable cardiac defibrillator; LGE, late gadolinium enhancement; MR, mitral regurgitation; MV, mitral valve; OHCA, out of hospital cardiac arrest; NS, not specified; PM, papillary muscle; PVCs, premature ventricular complexes; VAs, ventricular arrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Significant result on multivariate analysis; significant univariable predictors not presented

2.7.6 *Prospective follow-up studies in MVP with SCD rates*

Study	Patients	Mean age*	Females	Mean follow-up*	SCD events / 100,000 patient years
Nishimura[5]	237†	44	142	6.2	408
Duren[58]	300	42	164	6.2	219
Zuppiroli[59]	316	42	220	8.5	112

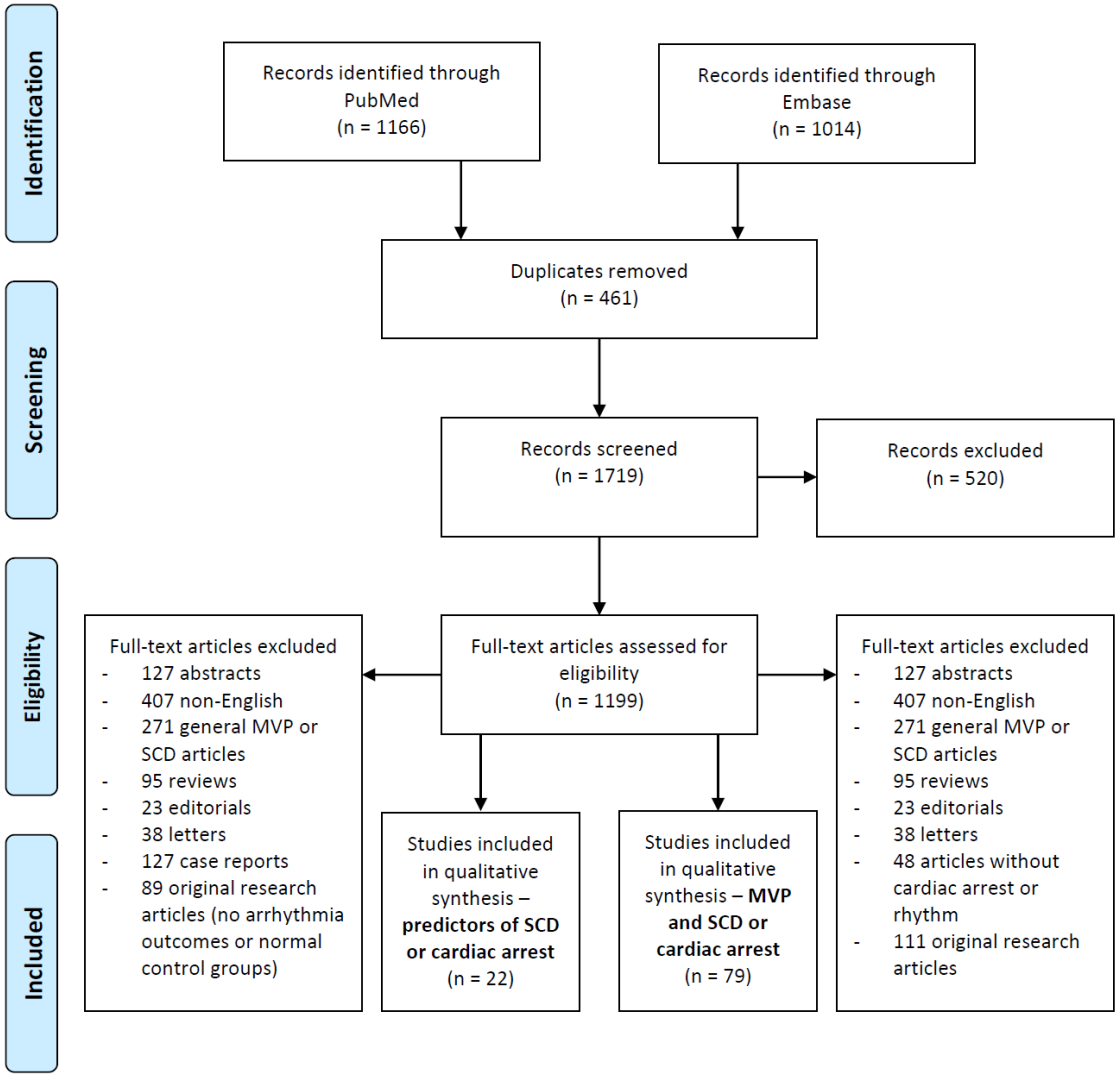
SCD, sudden cardiac death.

*In years

†97 patients had redundant leaflets – all cases of SCD occurred in those with redundant leaflets

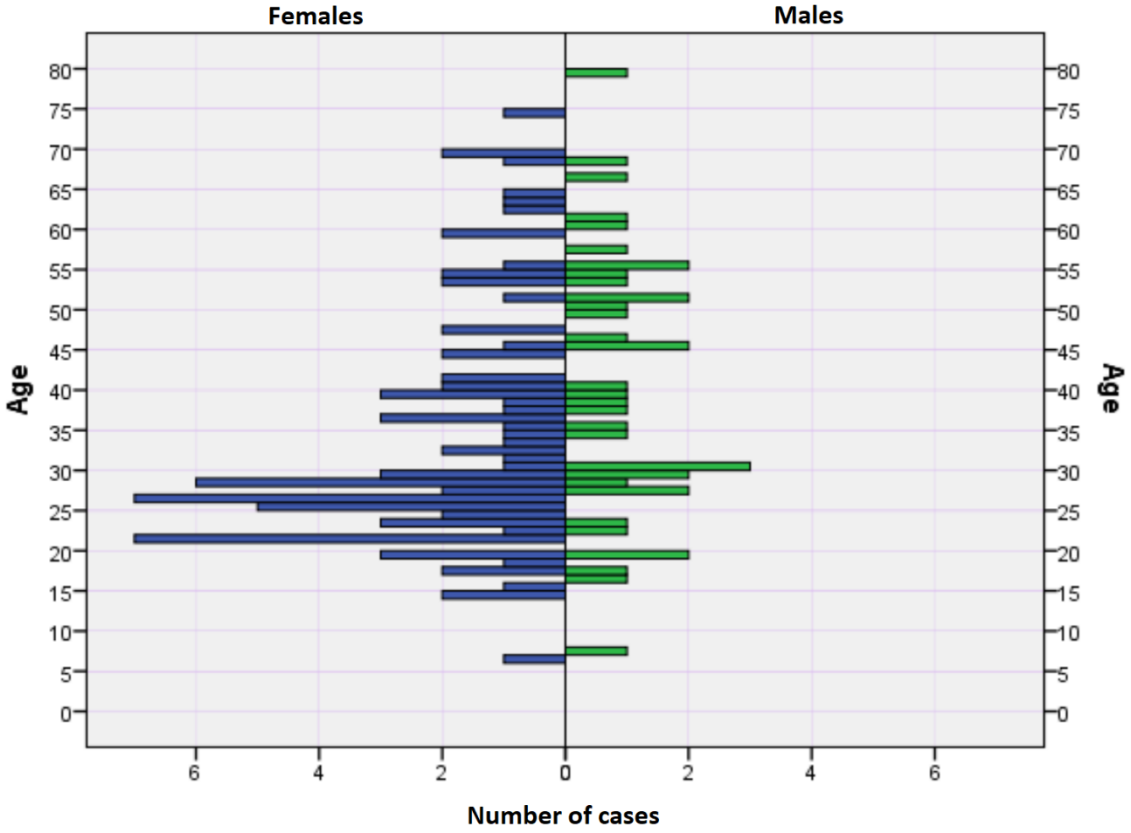
2.8 Figures

2.8.1 *Search algorithm*

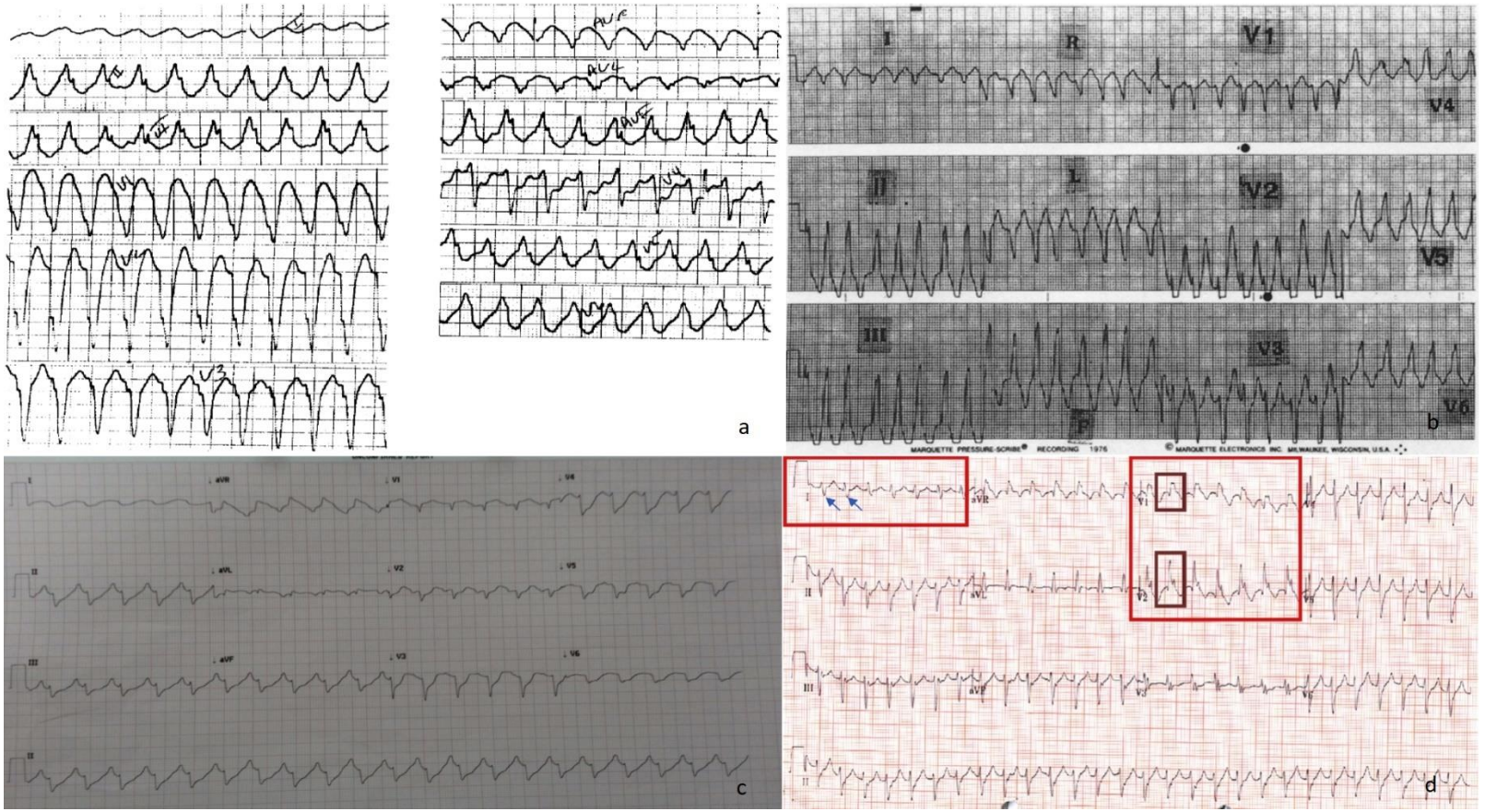


MVP, mitral valve prolapse; SCD, sudden cardiac death.

2.8.2 *Age at time of death or cardiac arrest in MVP according to sex*

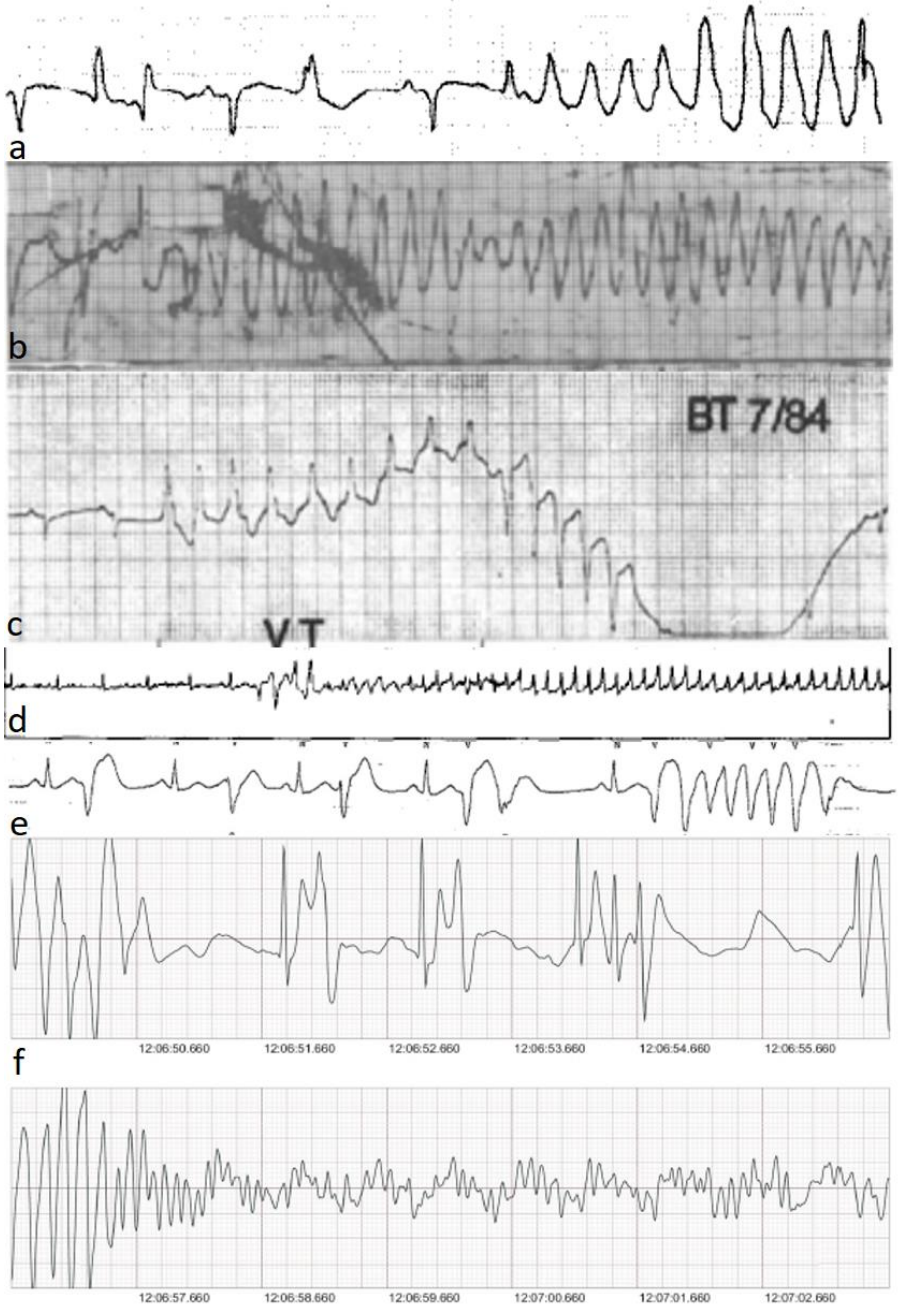


2.8.3 *12-lead electrocardiograms of ventricular tachycardia*



iMVP, isolated mitral valve prolapse.
a. Left bundle morphology, inferior axis (iMVP).[168]
b. Left bundle morphology, inferior axis (non-iMVP, patient taking procainamide).[178]
c. Left bundle morphology, superior axis (iMVP).[190]
d. Right bundle morphology, superior axis (iMVP).[243]

2.8.4 *Documented onset of ventricular arrhythmias*



iMVP, isolated mitral valve prolapse; PVC, premature ventricular complex; VF, ventricular fibrillation; VT, ventricular tachycardia.

a. Late diastolic PVC triggered polymorphic VT (non-iMVP, patient had arrhythmogenic right ventricular cardiomyopathy)[167]

b. Possible PVC triggered polymorphic VT (iMVP)[171]

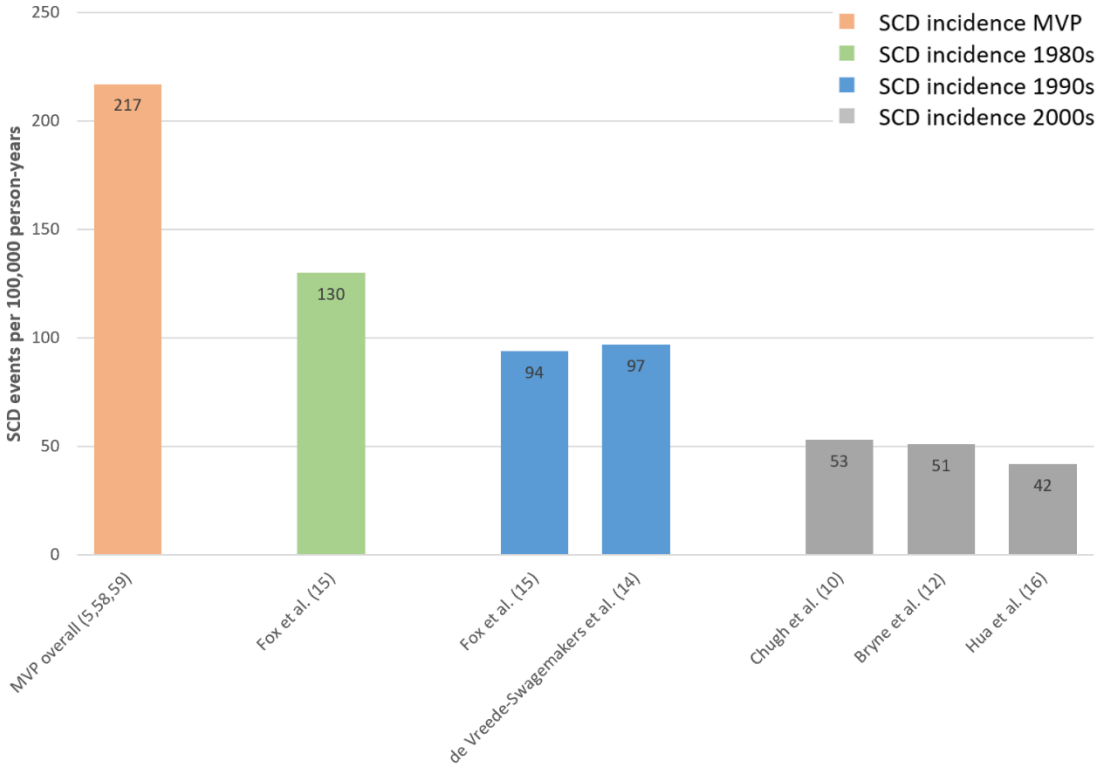
c. Monomorphic VT with pace termination (non-iMVP, patient taking procainamide)[178]

d. Late diastolic couplets triggering VT then VF (iMVP)[183]

e. Late diastolic PVC triggered polymorphic VT with multiple PVC morphologies in rhythm strip (iMVP)[189]

f. Long pause followed by supraventricular beat then early diastolic PVC triggered VF with multiple PVC morphologies in rhythm strip (iMVP)[244]

2.8.5 *SCD incidence in MVP versus population studies*



MVP, mitral valve prolapse; SCD, sudden cardiac death.

2.9 Supplemental Materials

2.9.1 *All cases included in study*

Year	Author	Cases	Description
1968	Barlow[30]	1	Review of 90 patients with non-ejection systolic click and late systolic murmurs. 1 case of 39M with SCD. (iMVP)
1970	Trent[31]	1	Report of 63F with MVP and SCD. (non-iMVP)
1971	Jeresaty[249]	1	Review of 24 patients with mitral ballooning on angiography. 1 case of 62F with SCD. (iMVP)
1973	Jeresaty[33]	1	Review of 100 patients with non-ejection click or MVP on left ventriculography. 1 case of 44F with SCD. (iMVP) 1 case of 62F with SCD (repeat case).
1973	Shappell[32]	1	Report of 27F with MVP and SCD. (non-iMVP)
1974	Marshall[250]	1	Report of 2 cases (27F and 36F) with MVP and SCD. (1 case iMVP and 1 case non-iMVP) Case of 27F (repeat case).
1975	Shappell[166]	1	Series of 4 patients with MVP. 1 case of 23F with VF. (iMVP) 2 cases (27F and 36F) of SCD (repeat cases). 1 case of NSVT (not included).
1976	Jeresaty[35]	2	Summary of 12 cases of MVP and SCD. 2 cases (39F and 40M) included. (both iMVP) 7 cases previously reported. 3 cases of personal communication without individual age or gender (not included).
1976	Kleid[34]	1	Report of 38F with MVP and SCD. (iMVP)
1976	Ritchie[167]	1	Report of 56M with MVP and VF. (non-iMVP)
1976	Winkle[168]	5	Series of 7 patients with MVP and VAs. 3 cases with VF and 2 cases with VT. (4 cases iMVP and 1 case non-iMVP) 2 cases excluded (1 with unmonitored cardiac arrest and 1 NSVT).
1977	Cobbs[251]	1	Report of 39F with MVP and VF. (iMVP)
1977	Mills[36]	2	Follow-up of 53 patients with MVP. 1 case of 58M with SCD. (non-iMVP) 1 case of 26F with VF. (iMVP)
1978	Davies[37]	13	Review of 90 cases of MVP at autopsy. 13 cases with MVP and SCD (12 cases iMVP and 1 case non-iMVP).
1979	Forbes[170]	1	Report of 25F with MVP and VF on anaesthesia induction. (non-iMVP)
1979	Watts[252]	1	Report of 26F with MVP and VF. (iMVP)
1980	Anderson[253]	2	Report of 2 cases (both 21F) with MVP and SCD. (both iMVP)
1980	Bennett[171]	1	Report of 15F with MVP and TDP. (iMVP)
1980	Mair[38]	3	Series of 3 cases (25F, 29F and 35F) with MVP and SCD. (all iMVP)
1980	Mautner[172]	2	Review of 22 patients with MVP and PVCs. 1 case of 51F with VF. (iMVP) 1 case of 50M with VT during anesthesia induction. (iMVP)
1981	Bharati[40]	1	Report of 45M with MVP and SCD. (iMVP)
1981	Salmela[39]	1	Report of 27M with MVP and SCD. (non-iMVP)
1982	Noneman[254]	1	Report of 29M with MVP and VF. (iMVP)
1982	Vesterby[255]	3	Series of 3 cases (23F, 68M, 55M) with MVP and SCD. (1 case iMVP and 2 cases non-iMVP)
1982	Virmani[256]	1	Review of 30 autopsies in joggers. 1 case of 27M with MVP and SCD. (iMVP)
1983	Bharati[41]	2	Series of 3 cases of SCD in teenagers.

			2 cases (17M and 19F) with MVP. (both iMVP)
1983	Chesler[42]	14	Series of 14 cases of MVP and SCD. (all iMVP)
1983	Conklin[257]	1	Report of 22F with MVP and VT during labor. (iMVP)
1983	Morady[173]	2	Series of 31 patients with VAs undergoing EPS. 2 patients (28F and 39F) with MVP and VF. (both iMVP)
1984	Kempf[174]	1	Series of 27 cases with SCD on ambulatory ECG monitoring. 1 case of 31F with MVP. (non-iMVP)
1984	Pocock[43]	1	Report of 24F with MVP and SCD. (non-iMVP)
1985	Andre-Fouet[258]	1	Report of 19M with MVP and SCD. (iMVP)
1985	Rosenthal[175]	5	Series of 20 patients with MVP and VAs. 5 patients with VF. (all iMVP)
1985	Sakuma[176]	1	Report of 54M with MVP, coronary vasospasm and VF. (non-iMVP)
1986	Casthely[177]	1	Report of 7M with MVP and VF during anaesthesia induction. (iMVP)
1986	Higgins[178]	1	Report of 36F with MVP and VT. (non-iMVP)
1986	Hoffman[259]	1	Report of 32F with MVP and VF. (iMVP)
1987	Broustet[260]	1	Report of 28F with MVP and SCD. (non-iMVP)
1988	Goldhammer[202]	1	Report of 46M with MVP and asystole. (iMVP)
1988	Scala-Barnett[179]	4	Series of 4 cases of MVP and SCD. (2 cases iMVP and 2 cases non-iMVP)
1988	Strasberg[261]	1	Report of 27M with MVP and VF. (iMVP)
1988	Vlay[262]	1	Report of 24F with MVP and SCD. (iMVP)
1989	Abraham[245]	1	Report of 33F with MVP and asystole during anesthesia. (iMVP)
1989	Topaz[180]	2	Series of 22 patients with cardiac arrest. 2 patients [19M (also anomalous RCA) and 28M] with MVP. (1 case iMVP and 1 case non-iMVP)
1989	Martini[263]	2	Series of 6 cases with VF. 2 cases (14F and 35M) with MVP. (both iMVP)
1990	Boudoulas[181]	9	Series of 9 patients with MVP and cardiac arrest. (8 cases iMVP and 1 case non-iMVP)
1990	Corrado[44]	2	Series of 22 athletes with SCD. 2 cases (17F and 23M) with MVP. (both iMVP)
1990	Nelson-Piercy[264]	1	Report of 67M with MVP, anomalous RCA and VF. (non-iMVP)
1990	Sadaniantz[265]	0	Report of 27M with MVP and SCD (repeat case).
1991	Dollar[45]	15	Review of 56 cases of MVP at autopsy. 15 cases of SCD related to MVP. (14 cases iMVP and 1 case non-iMVP)
1993	Vohra[182]	2	Series of 7 patients with MVP and VAs. 2 cases (28M and 45M) with SCD. (both non-iMVP)
1995	Martini[183]	1	Report of 42F with MVP, ARVC and SCD. (non-iMVP)
1997	Moritz[184]	1	Report of 6F with MVP and VF during anaesthesia induction. (iMVP)
1997	Wilde[266]	1	Report of 34M with MVP and VF. (iMVP)
1998	Ronneberger[46]	1	Report of 8M with MVP and SCD. (non-iMVP)
2000	Nolte[193]	1	Report of 26F with MVP, diffuse CAD due to PXE and SCD. (non-iMVP)
2001	Cannon[192]	1	Report of 25F with MVP and SCD. (iMVP)
2003	Abello[267]	1	Report of 28F with MVP and VF during pregnancy. (iMVP)
2003	Ciancarmerla[268]	1	Report of 49M with MVP and SCD. (iMVP)
2003	Nishida[269]	1	Series of 3 cases of SCD and alcohol abuse. 1 case of 37F with MVP. (non-iMVP)
2004	Chirachariyavej[270]	1	Report of 38M with MVP and SCD. (iMVP)
2004	Frassati[242]	3	Series of 14 cases of SCD in psychiatric patients. 3 cases (22M, 51M and 57M) with MVP. (1 case iMVP and 2 cases non-iMVP)
2005	Zeidan[185]	1	Report of 21F with MVP and VF during anaesthesia reversal. (iMVP)

2007	Anders[47]	6	Series of 6 cases of MVP and SCD. (iMVP)
2007	Kesavan[271]	1	Report of 75F with MVP, CAD and VT. (non-iMVP)
2007	Knackstedt[186]	1	Report of a 54M with MVP and VF. (iMVP)
2010	Franchitto[188]	1	Report of 25F with MVP and SCD. (iMVP)
2010	Oliviera[272]	1	Report of 57F with MVP and SCD (also heart failure on trastuzumab). (non-iMVP)
2011	Rordorf[273]	1	Report of 32F with MVP and VF (also DCM post-partum with PJRT). (non-iMVP)
2014	Abbadi[189]	1	Report of 26F with MVP and VF. (iMVP)
2014	Rajani[190]	1	Report of 27F with MVP and TDP. (iMVP)
2015	Lin[243]	1	Report of 30F with MVP and VT during pregnancy. (iMVP)
2015	Desai[274]	1	Report of 55M with MVP and SCD. (iMVP)
2015	Fais[275]	1	Report of 47F with MVP and SCD. (iMVP)
2016	Ahmed[191]	1	Report of 45M with MVP and VT. (iMVP)
2016	Vaidya[240]	5	Series of 5 patients with MVP, ICD and history of MV surgery (1 case also had HCM). (2 cases iMVP and 3 cases non-iMVP)
2017	Cacko[276]	1	Report of 28F with MVP and VF. (iMVP)
2017	Martini[277]	1	Report of 58M with MVP and VF (also Brugada ECG). (non-iMVP)
2017	Saha[244]	1	Report of 26F with MVP and VF during pregnancy. (iMVP)

SCD, sudden cardiac death; MVP, mitral valve prolapse; VF, ventricular fibrillation; NSVT, non-sustained ventricular tachycardia; VAs, ventricular arrhythmias; EPS, electrophysiology study; VT, ventricular tachycardia; TDP, torsade de pointes; PVCs, premature ventricular complexes; RCA, right coronary artery; ARVC, arrhythmogenic right ventricular cardiomyopathy; PXE, pseudoxanthoma elasticum; CAD, coronary artery disease; DCM, dilated cardiomyopathy; PJRT, persistent junctional reciprocating tachycardia, ICD, implantable cardiac defibrillator; MV, mitral valve; HCM, hypertrophic cardiomyopathy

2.9.2 *Predictors of ventricular arrhythmias or SCD*

	Author	Year	Study	N (% Female)	Age range	Study population	Diagnostic criteria	Predictor/association	Outcome/Endpoint
Clinical									
	Gaffney[246]	1979	Prospective Cohort	19 (100)*	19-46	MVP	M-mode or auscultation	Higher heart rate Lower cardiac index	Clinical severity (combination of symptoms and VAs)
	Puddu[215]	1983	Prospective Cohort	15 (67)	NR	MVP	Echo (NS)	Plasma catecholamine level	QTc (supine)
	Sniezek[224]	1992	Prospective Cohort	53 (58)	19-52	MVP	Echo (LAX)	Adrenaline excretion	Complex VAs (Lown grade ≥3)
	Zuppiroli[111]	1994	Prospective Cohort	119 (47)	12-78	MVP	Echo (LAX)	Female	Complex VAs (Lown grade ≥3)†
	Babuty[123]	1994	Prospective Cohort	58 (50)	NR	MVP	Echo (LAX or A4C)	Age (older)	Complex VAs (Lown grade ≥3
	Naksuk[247]	2016	Retrospective Cohort	32 (53)	NR	BiMVP with MV surgery	N/A	Age (younger)	Reduction in PVCs post MVR in BiMVP
	Fulton[114]	2017	Retrospective Cohort	18 (61)	NR	MVP	Echo (LAX)	Female	PVCs from PM
Electrical									
	Campbell[248]	1976	Prospective Cohort	20 (65)	12-61	MVP	Auscultation	Inferolateral T-wave changes	VT (>100bpm for 3 beats) or VF
	Babuty[123]	1994	Prospective Cohort	58 (50)	NR	MVP	Echo (LAX or A4C)	Late potentials	Non-sustained VT (≥3 beats and <30 seconds)
	Bobkowski[226]	2002	Prospective Cohort	151 (77)*	5-18	MVP	Echo (NS)	Late potentials	VAs (Lown grade ≥1) Non-sustained VT (>120bpm for ≥4 beats and <30 seconds)
	Akcay[112]	2010	Retrospective Case control	60 (72)	NR	MVP (with vs without VT)	Echo (NS)	QTc dispersion	VT (>120bpm for ≥3 beats)†
Imaging									
	Shah[121]	1982	Retrospective Cohort	88 (60)	12-84	MVP	M-mode	MR	Complex VAs (Lown grade ≥3)
	Nishimura[5]	1985	Prospective Cohort	237 (60)	10-69	MVP	Echo (NS)	Redundant leaflets	Sudden death†
	Kligfield[122]	1985	Prospective Cohort	80 (65)*	19-72	MVP	Echo (NS)	MR	>1% PVC frequency Exercise induced PVCs and VT

									Complex VAs (Lown grade 4)
	Sanfilippo[110]	1989	Retrospective Cohort	22 (55)*	NR	MVP	Echo (LAX or A4C)	Anterior leaflet thickness MR Leaflet displacement	VAs (≥10 PVCs/hr or NSVT at ≥100bpm for ≥3 beats)
	Zuppiroli[111]	1994	Prospective Cohort	119 (47)	12-78	MVP	Echo (LAX)	Anterior leaflet thickness	Complex VAs (Lown grade ≥3)†
	Babuty[123]	1994	Prospective Cohort	58 (50)	NR	MVP	Echo (LAX or A4C)	MR	Complex VAs (Lown grade ≥3) on Holter and exercise test
	Zouridakis[113]	2001	Prospective Cohort	89 (71)	NR	MVP	Echo (LAX or A4C)	MVP degree Anterior leaflet thickness	QT dispersion†
	Turker[124]	2010	Prospective Cohort	58 (55)	16-68	MVP	Echo (LAX)	Moderate-severe MR	VAs (Lown grade ≥1)†
	Carmo[88]	2010	Retrospective Cohort	38 (47)	NR	MVP	Echo (LAX)	Mitral annular disjunction	Non-sustained VT
	Han[89]	2010	Retrospective Cohort	16 (44)*	NR	MVP	Echo (NS)	LGE in PM	Complex VAs (Lown grade ≥4)
	Akcay[112]	2010	Retrospective Case control	60 (72)	NR	MVP (with vs without VT)	Echo (NS)	Anterior leaflet length	VT (>120bpm for ≥3 beats)†
	Sriram[52]	2013	Retrospective Cohort	24 (67)	5-60	Idiopathic OHCA	Echo (NS)	BiMVP	Appropriate ICD therapies at follow-up
	Basso[9]	2015	Prospective Cohort	44 (66)	24-64	MVP	Echo (LAX)	LGE (PM, inferobasal wall and total %)	Complex VA (Lown grade ≥4b or VF)
	Nordhues[115]	2016	Retrospective Case control	11338 (43)*	NR	BiMVP vs SiMVP	Echo (NS)	BiMVP	All-cause mortality (lower in BiMVP)
	Bui[127]	2017	Retrospective Cohort	32 (34)*	NR	MVP	CMR	Myocardial T1 time	Complex VAs (Lown grade ≥3)
	Fulton[114]	2017	Retrospective Cohort	18 (61)	NR	MVP	Echo or CMR	BiMVP LGE in PM	PVCs from PM

A4C, apical 4 chamber; bpm, beats per minute; BiMVP, bileaflet MVP; ICD, implantable cardiac defibrillator; LAX, long axis; LGE, late gadolinium enhancement; NR, not reported; NS, not specified; OHCA, out of hospital cardiac arrest; PM, papillary muscle; SiMVP, single leaflet MVP.

*Studies also included normal control groups which are not presented

†Significant result on multivariate analysis; significant univariable predictors not presented

CHAPTER 3

Characteristic Histopathological Findings and Cardiac Arrest Rhythm in Isolated Mitral Valve Prolapse and Sudden Cardiac Death

3.1 Overview

Background: The association between MVP and sudden death remains controversial. We aimed to describe histopathological changes in individuals with autopsy determined isolated MVP (iMVP) and sudden death and document cardiac arrest rhythm.

Methods and Results: The Australian National Coronial Information System (NCIS) database was used to identify cases of iMVP between 2000 and 2018. Histopathological changes in iMVP and sudden death were compared to 2 control cohorts matched for age, sex, height and weight (1 group with non-cardiac death and 1 group with cardiac death). Data linkage with ambulance services provided cardiac arrest rhythm for iMVP cases. From 77,221 cardiovascular deaths in the NCIS database, there were 376 cases with MVP. Individual case review yielded 71 cases of iMVP. Mean age was 49±18 years and 51% were female. Individuals with iMVP had higher cardiac mass (447g vs 355g, $p<0.001$) compared with non-cardiac death, but similar cardiac mass (447g vs 438g, $p=0.64$) compared with cardiac death. Individuals with iMVP had larger mitral valve annulus compared with non-cardiac death (121mm vs 108mm, $p<0.001$) and cardiac death (121mm vs 110mm, $p=0.002$), and more left ventricular fibrosis (79% vs

38%, p<0.001) compared with non-cardiac death controls. In those with iMVP and witnessed cardiac arrest, 94% had ventricular fibrillation.

Conclusions: Individuals with iMVP and sudden death have increased cardiac mass, mitral annulus size and left ventricular fibrosis compared to a matched cohort, with cardiac arrest due to ventricular fibrillation. The histopathological changes in iMVP may provide the substrate necessary for development of malignant ventricular arrhythmias.

3.2 Introduction

Mitral valve prolapse (MVP) is characterised by the atrial displacement of the mitral valve (MV) leaflet(s) during ventricular systole, with an estimated prevalence of 2.4%.[4] Reported complications of MVP include severe mitral regurgitation (MR) requiring MV surgery, infective endocarditis, stroke and sudden death.[1, 5]

The postulated mechanism of sudden death in individuals with MVP has been ventricular arrhythmias,[6, 9, 52, 278] although this association remains controversial.[1, 4, 122] While studies have reported the presence of significant ventricular arrhythmias in patients with MVP,[128, 169, 182] only 6 isolated case reports in the scientific literature have documented cardiac rhythm at time of death in patients with autopsy determined isolated MVP (iMVP, whereby other potential causes of death are excluded).[278]

Pathological characterization may provide clues regarding the link between iMVP, sudden death and possible underlying mechanisms. Since Barlow's original description

of MVP at autopsy,[30] studies have identified various cardiac anatomical changes in MVP such as increased annulus size or cardiac mass,[9, 45, 85] which may contribute to development of sudden death. However, these studies may not have controlled for influencing factors such as age, sex, height and weight.[93]

In this study we examined our Australian coronial database over a consecutive period of 17 years, with the aim to:

1. Describe clinical characteristics of individuals with iMVP and sudden death;
2. Describe underlying histopathological changes in individuals with iMVP and sudden death compared to matched control cohorts;
3. Describe underlying histopathological changes in individuals with iMVP and sudden death compared to individuals with non-iMVP and sudden death
4. Document cardiac arrest rhythm in individuals with autopsy determined iMVP and sudden death.

3.3 Methods

Source data used for this study was obtained from the National Coronial Information System (NCIS) database administered by the Department of Justice and Community Safety, Victoria, Australia. Due to the sensitive nature of the data collected, anonymised data collected for this study can be made available subject to approval from the database provider.

3.3.1 *Data source*

Beginning July 2000 (and January 2001 for the state of Queensland), all reportable deaths determined by an Australian Coroner are prospectively recorded in the NCIS database. The database classifies antecedent causes of death using the International Classification of Diseases-10 (ICD-10) system; and where available, contains individual autopsy reports and police reports regarding circumstances of death.

The NCIS database was used to identify cases of iMVP and sudden death. Once identified, data-linkage with Australian state-wide ambulance services was performed to retrieve initial cardiac rhythm during attempted resuscitation.

3.3.2 *Inclusion criteria*

An NCIS database search was performed in May 2018 and 329,106 cases were available for analysis. All individuals in whom MVP was coded (ICD-10 code I34.1) as a cause of death (either underlying or contributing) between July 2000 to May 2018 were screened and autopsy records examined. Inclusion criteria was the presence of MVP on autopsy examination (evidence of myxomatous leaflets on gross examination and/or histology). Following individual case review (including circumstances of death, demographics, clinical information and detailed pathological evaluation), the MVP cohort was then separated into two groups: an iMVP group with presumed sudden cardiac death due to MVP; and a non-iMVP group with death due to a possible

combination of MVP and other cardiac or systemic illnesses (Figure 3.8.1). Patients were adjudicated to have iMVP based on the presence of MVP at autopsy without another possible cause of death. Definition of sudden cardiac death included witnessed cases in a previously stable individual, and unwitnessed cases where an individual was found dead who at time of last witnessed contact was in a usual state of health.[17]

For those with iMVP, two control cohorts were randomly extracted from the NCIS database. The first cohort (presumed non-cardiac death) were individuals who died due to a motor vehicle accident (MVA, as categorised in the NCIS database) from 2013-2014. The second cohort (presumed cardiac death) were all individuals who died due to acute myocardial infarction (AMI, using ICD-10 code I21) from 2013-2014 with an additional search for individuals dying due to AMI aged between 18 and 35 from 2000-2018.

3.3.3 *Exclusion criteria*

Exclusion criteria in both the iMVP and MVA groups were the presence of another significant cardiac finding (clinical or autopsy) including ischaemic heart disease (≥70% stenosis in any coronary artery, presence of coronary stent or documented previous history), known cardiomyopathy, severe MR (who may have experienced non-arrhythmic sudden death), previous cardiac surgery (and those with cardiac implantable electronic devices), myocarditis (on histology), hypertrophic cardiomyopathy (on histology) or left ventricular wall thickness ≥25mm. Additionally for the MVA control

group, cases were excluded where MVP was found on autopsy or if individuals suffered burns because of the MVA.

Cases with incomplete autopsy records which did not document age, sex, height, weight or cardiac mass were excluded from all groups.

3.3.4 *Data collection*

Data collected for all groups included age, sex, height, weight and cardiac mass. Using these parameters, a cardiac mass predictor tool was used to determine whether the cardiac mass was >95% predicted.[93] Internal organ mass, left and right ventricular wall thickness, and mitral and tricuspid annulus circumference was also recorded. For subjects with iMVP and non-iMVP, information regarding leaflet involvement was also collected.

For Victorian cases of iMVP with sudden death (n=17), stored left ventricular histology slides were reviewed by an expert cardiac pathologist (S.P.) for qualitative assessment of fibrosis following haematoxylin and eosin staining. Standardised sampling of the left ventricle includes obtaining transmural biopsies from the mid portion of the anterior, lateral, posterior and septal walls. Diffuse fibrosis was noted if fibrosis was present in ≥2 sections.

State and territory ambulance services from Australian Capital Territory, New South Wales, Northern Territory, Queensland, Tasmania and Victoria were contacted to

provide initial cardiac rhythm and witness status of cardiac arrest. Two remaining states, South Australia and Western Australia (accounting for approximately 18% of the Australian population), did not have autopsy reports available on NCIS at the time of the study.

3.3.5 *Ethical approval*

Access to the NCIS database and subsequent data linkage was granted by the Justice Human Research and Ethics Committee (CF/16/4998), South Eastern Sydney Local Health District Human Research Ethics Committee (HREC/17/POWH/632) and the Victorian Institute of Forensic Medicine Research Advisory Committee and Ethics Committee (RAC 009-18). Due to the nature of this study, individual informed consent was waived as per the Ethics Committees listed above.

3.3.6 *Statistical analysis*

Continuous data are reported as means with standard deviation or medians with inter-quartile range and the Shapiro-Wilk test was used to evaluate normality. To determine differences between the iMVP cohort and matched controls, the paired t-test or the Wilcoxon signed ranks test was used to compare continuous variables where appropriate. To determine differences between the iMVP cohort and unmatched non-iMVP group, the Student's t-test or the Mann-Whitney U test was used to compare continuous variables where appropriate. Categorical data are presented as absolute figures with percentages and compared using the McNemar's test and Fisher's exact test

for matched and unmatched groups respectively. A 2-sided p-value <0.05 was considered significant. Cases were matched with control cohorts in a 1:1 ratio for parameters of age, sex, height and weight using SPSS Version 24 'Case Control Matching' command. All data analyses were performed using SPSS Version 24 (IBM Corp., Armonk, NY).

3.4 Results

3.4.1 *Patient population*

Between July 2000 and May 2018, there were 77,221 deaths attributable to a cardiovascular cause (ICD-10 codes I00-I25 and I30-I52) with 64,734 cases due to ischaemic heart disease (ICD-10 codes I20-I25). In total, there were 376 cases of MVP identified (see Figure 3.8.1) with complete autopsy records available for 152 cases. There were 71 cases with sudden cardiac death due to iMVP and 81 cases with non-iMVP. For the 81 cases with non-iMVP, there were 56 cases with suspected cardiac cause of death and 25 with suspected non-cardiac cause of death. Suspected cause of death (COD) for those with non-iMVP are presented in Figure 3.8.1 (footnote).

For cases of iMVP, a pool of 582 MVA cases and 478 AMI cases were obtained for the control samples. After 1:1 matching, 70 cases in each group were used for case-control analysis. A suitable match was unable to be obtained for one morbidly obese iMVP case (weight 220kg).

3.4.2 *Clinical characteristics*

Baseline clinical characteristics for all 71 cases of iMVP and sudden death are shown in Table 3.7.1.

Of the 71 cases of iMVP and sudden death, 36 (51%) were female. Age ranged from 16 to 87 years with mean age 49±18 years.

Additional cardiovascular history (including the presence of hypertension, dyslipidaemia or obesity) was present in 43% of individuals. In 23%, no other medical history was noted. At least one cardiac medication was being taken by 29% of individuals whilst 42% of individuals were not taking any prescribed medications.

Of the 71 cases with autopsy confirmed iMVP, whether there was a premortem diagnosis of MVP was able to be ascertained in 64 cases and of these, 34 cases (53%) were previously undiagnosed. Importantly, in those with a premortem diagnosis of MVP, there were no cases with documented severe MR or significant cardiomyopathy.

In total, 41% of deaths occurred in individuals who were either resting (22%) or sleeping (17%), while 32% of deaths occurred during daily (non-exertional) activity. Death during (or very soon after) physical exertion occurred in 14% and death while using the toilet occurred in 9%. Approximate time of death was evenly distributed over a 24-hour period.

3.4.3 *Internal organ masses*

Data regarding cardiac and other internal organ masses are shown in Table 3.7.2 and Table 3.7.3.

Compared to those dying from MVA, individuals with iMVP had significantly greater cardiac mass (447g vs 355g, $p<0.001$), but also significantly greater lung ($p<0.001$), liver ($p=0.002$), kidneys ($p=0.002$) and spleen ($p<0.001$) masses. Brain mass was not significantly different.

Compared to those dying as a result of an AMI, individuals with iMVP had similar cardiac (447g vs 438g, $p=0.64$) and other internal organ masses, although there was a trend towards higher combined kidney mass in the AMI group ($p=0.07$).

Compared to those with non-iMVP, individuals with iMVP had similar cardiac (447g vs 440g, $p=0.72$), lung and brain masses. Individuals with iMVP had significantly greater liver ($p=0.001$), kidney ($p=0.003$) and spleen ($p=0.006$) masses.

3.4.4 *Histopathological findings*

Histopathological data are shown in Table 3.7.2 and Table 3.7.3. Using a cardiac mass predictor tool,[93] cardiac mass was >95% predicted in 36% of iMVP cases and this was significantly greater than the MVA cohort (6%, $p<0.001$) but not significantly different

to the AMI cohort (23%, p=0.09) and non-iMVP cohort (23%, p=0.10). Left and right ventricular thickness was not significantly different between the iMVP group, both control groups and the non-iMVP group.

Median mitral valve circumference was 121mm (115-139) which was significantly greater than both the MVA (p<0.001) and AMI (p=0.002) control groups but similar to the non-iMVP group (p=0.60). There was no significant difference between the groups with respect to tricuspid valve circumference. Leaflet involvement in iMVP was predominantly bileaflet (87%) followed by posterior leaflet (9%) then anterior leaflet (4%), while 3 cases described concomitant tricuspid valve prolapse. The proportion of cases with bileaflet prolapse was similar between those with iMVP and those with non-iMVP (79%, p=0.41) including those with suspected cardiac and non-cardiac COD.

Abnormal left ventricular histology was present in 79% of iMVP cases which was significantly higher than the MVA group (p<0.001) but similar to the AMI group (p=0.14) and non-iMVP group (p=0.08) including those with suspected cardiac and non-cardiac COD. Reported patterns of fibrosis in those with iMVP were predominantly interstitial and/or perivascular. In 4 cases histological abnormalities involving the papillary muscles were specifically documented.

Based on individual histology review for 17 cases, fibrosis distribution patterns were either multi-segment (n=4, e.g. fibrosis affecting 2 or more segments in the subendocardial-midmural layer of the left ventricle), focal (n=5, e.g. interstitial fibrosis in 1 sampled section) or a combination of both (n=4, e.g. multi-segment fibrosis in the

subendocardial-midmural layer with one section showing focal midmural fibrosis). No fibrosis was detected in 4 cases. Additionally, fibrosis involved the subendocardial-midmural layer in 85% (11/13) of cases with isolated midmural myocardial fibrosis in the other 2 cases. Transmural fibrosis was present in 2 cases (15%).

3.4.5 *Cardiac arrest rhythm*

Resuscitation by emergency medical services was documented in 40 iMVP cases (Figure 3.8.2). Initial cardiac arrest rhythm was VF in 94% (17/18) of witnessed cases and 32% (7/22) of unwitnessed cases. The remaining cases had documented asystole and no cases had ventricular tachycardia or pulseless electrical activity as the initial cardiac arrest rhythm.

Clinical data with cardiac arrest rhythm strip and histological findings for 5 representative cases are shown in Figure 3.8.3.

3.5 Discussion

MVP is a common cardiac condition in clinical practice, yet its association with (and potential mechanism of) sudden death has been difficult to elucidate. To our knowledge, this 17-year nationwide study is the largest case-control study to investigate histopathological findings in iMVP and sudden death, and the first study to systematically document cardiac arrest rhythm in cases of autopsy determined iMVP. The key findings are as follows:

1. In cases of iMVP and sudden death, the mean age was 49 years, half (51%) were female and 87% of cases had bileaflet prolapse;
2. Mitral valve annulus circumference was significantly larger in cases of iMVP with sudden death compared with matched control cohorts;
3. Individuals with iMVP and sudden death had increased cardiac mass compared to matched individuals with non-cardiac death; but similar cardiac mass compared to matched individuals with cardiac death;
4. Left ventricular fibrosis in cases of iMVP and sudden death predominantly (85%) involved the subendocardial-midmural aspect of the ventricle;
5. VF was the predominant (94%) cardiac arrest rhythm in individuals with iMVP and witnessed cardiac arrest.

3.5.1 *Clinical characteristics*

Mean age in our cohort was 49 years which is similar to previous autopsy series,[45] but higher than previous case series of MVP and sudden death,[43] possibly reflecting reporting bias in non-autopsy studies.

Our study found an even distribution between males and females. Previous autopsy studies have found somewhat conflicting results with either equal distribution,[85] or female predominance,[9, 45] although prevalence of redundant MVP appears equally distributed in population screening studies.[4] Non-autopsy studies have suggested that female sex may carry greater risk of malignant MVP,[52, 111, 114, 278] although the reasons for this are unexplained. Sex differences in seeking medical attention for symptoms[279]

may account for differences in premortem detection. Results from this study indicate that male patients with iMVP are as susceptible to sudden death events as female patients.

Our study found that 73% of sudden death episodes in iMVP occurred during sleep, rest or regular daily activity with an equal distribution of events over a 24-hour period. Despite historical studies implicating increased adrenergic drive in patient with MVP and ventricular arrhythmias,[224] our study indicates that sudden death in patients with iMVP does not necessarily require an acute precipitating event such as physical or emotional stress.

After application of pre-specified exclusion criteria, one case had possible long QT syndrome which may have caused sudden death, although the reported association between MVP and repolarisation abnormalities may confound matters.[112]

3.5.2 *Cardiac and other organ masses*

Previous studies have noted increased cardiac mass in individuals with MVP and sudden death.[9, 85] In our study, 36% of cases had cardiac mass >95% predicted. Importantly, in the groups where influencing factors (age, gender, height and weight) were controlled for (iMVP, MVA and AMI), those with iMVP had similar cardiac mass compared to those with AMI and significantly higher cardiac mass compared to those with MVA. Interestingly, those with iMVP and AMI related sudden death also had

significantly increased intrathoracic and intraabdominal organ mass when compared to those with non-cardiac death.

Although increased kidney and spleen mass has been reported in patients with sudden cardiac death compared to non-cardiac death,[280] the reasons for this are unexplored. One possibility is that increased intrathoracic and intraabdominal organ mass may reflect edema from acute biventricular failure in sudden cardiac death, hence implicating a common terminal process (i.e. cardiovascular cause of sudden death) in those with iMVP and AMI related sudden death.

3.5.3 *Histopathological findings*

In addition to increased cardiac mass, median left ventricular thickness in cases of iMVP and sudden death was 15mm which is considered the upper limit of normal in autopsy cases.[281] In combination, these gross pathological changes suggest that underlying structural abnormalities involving the left ventricle may be an important factor in cases of iMVP and the development of sudden cardiac death.

The majority of our cohort with iMVP had bileaflet prolapse which is consistent with previous reports indicating a predominantly bileaflet subset of malignant MVP.[52] Furthermore, median mitral valve annulus circumferences in those with iMVP were greater than expected based on both our current control cohorts and previous population control data.[92] Previous studies have reported interlinking associations between the presence of bileaflet prolapse, abnormal mitral annular physiology and ventricular

arrhythmias.[88, 118, 282] These findings suggest that disorganised mitral annular function may represent an anatomical cause of electrical instability, and hence be as important as the presence of myxomatous prolapse in the development of sudden death in MVP.[120]

Additionally, 79% of iMVP cases had abnormal histology of the left ventricle. The subendocardial-midmural distribution of fibrosis is consistent with other conditions which result in left ventricular remodelling such as hypertrophic cardiomyopathy, dilated cardiomyopathy and severe aortic stenosis,[230, 231, 283] as well as a previous autopsy study of MVP.[9] Based on standardised sampling, fibrosis affecting the level of the mid-ventricle – as opposed to previously reported focal changes[9] – along with increased overall cardiac mass indicates that a diffuse remodelling process may occur in those with iMVP and sudden death. Recent studies involving cardiac magnetic resonance imaging have linked the presence of fibrosis with ventricular arrhythmias.[9, 89, 125] Taken together, the presence of cardiac fibrosis in conjunction with left ventricular remodelling may provide further necessary substrate for malignant ventricular arrhythmias in the pathogenesis of iMVP and sudden death.

Histopathological findings of increased cardiac mass, mitral annular dilatation and left ventricular fibrosis from our study suggest that patients with iMVP have antemortem changes in their cardiac and mitral valve structure that predispose them to sudden death. Future cardiac imaging studies focusing on these findings may allow the application of risk stratification parameters for living patients with iMVP.

3.5.4 *Findings in non-iMVP*

Individuals with non-iMVP (including those with suspected cardiac and non-cardiac COD) differed significantly from those with iMVP with regards to age, height and weight. In conjunction with the documented effects of these parameters on various internal organ masses,[93, 284] the interpretation of internal organ mass data between those with iMVP and non-iMVP is confounded.

Direct comparisons between the iMVP group with the non-iMVP group did not yield any significant differences in terms of proportion with bileaflet prolapse, mitral annulus size or proportion with left ventricular histological changes. Importantly, we implemented strict selection criteria for the iMVP cohort in order to select MVP cases in which there was a high likelihood that sudden death was as a result of MVP. Within the 81 non-iMVP cases, patients may still have had MVP as a precipitating mechanism for their death but it was unclear whether this was the likely COD due to existence of potential confounders. These patients did not qualify as having iMVP based on our exclusion criteria.

Consequently, the attributable role of MVP with regard to SCD in the setting of other co-existent conditions requires refining.

3.5.5 *Cardiac arrest rhythm*

This study provides the largest collection of cases of autopsy determined iMVP and their corresponding cardiac arrest rhythm. In those with witnessed cardiac arrest, 94% had initial VF (as documented by emergency medical services) indicating that a malignant ventricular arrhythmia is the likely initiating event in patients with iMVP and sudden death.

3.5.6 *Limitations*

In this autopsy study, we are unable to report on certain premortem characteristics in iMVP such as the degree of MR (although cases with known severe MR were excluded). Importantly most of the cases with iMVP were previously undiagnosed. This study may be subject to referral bias regarding coronial deaths, however unexpected deaths in Australia are mandated to be reported to a state coroner. Pathological examination confirmed redundant MVP in all cases. Hence, these results are only applicable to cases of redundant leaflet MVP, although this appears to be the population most at risk of sudden death events.[5] Findings from histopathology do not routinely include papillary muscles or inferobasal wall precluding our ability to comment on fibrosis in those specific regions. However, the presence of fibrosis in the mid left ventricle suggests a diffuse remodelling process in addition to previously described focal changes. We are unable to comment on the importance of MVP in the pathogenesis of death for patients with non-iMVP. Further work investigating the attributable risk of MVP for SCD in the setting of co-existent conditions is warranted.

3.6 Conclusion

This nationwide autopsy study indicates that the majority of cases of iMVP and sudden death had bileaflet prolapse, significantly enlarged mitral valve annulus, increased cardiac mass and histopathological findings of cardiac fibrosis, with ventricular fibrillation being the commonest presenting rhythm in cases of witnessed cardiac arrest. The histopathological changes in iMVP may provide the substrate necessary for development of ventricular arrhythmias leading to sudden cardiac death.

3.7 Tables

3.7.1 *Baseline clinical characteristics in iMVP*

Clinical characteristics (n=71)			
Age range	16-87	***Medications***	n=38 (%)
Female Sex	36 (51%)	Cardiac	11 (29)
Medical History	n=58 (%)	Aspirin	2
Cardiac	25 (43)	Warfarin	1
Obesity	12	Beta-blocker‡‡	3
Hypertension	9	Digoxin	2
Dyslipidaemia	9	Anti-hypertensive§§	7
Endocarditis (healed)	1	Lipid lowering	5
Atrial fibrillation	2	Other‖‖	14 (37)
Possible long QT syndrome*	1	No medications	16 (42)
PVC ablation†	1	***Activity at time of death***	n=66 (%)
Pericarditis	1	Normal daily activity##	21 (32)
Marfanoid‡	1	Sitting / resting	15 (23)
Symptoms§	6	Sleeping	12 (18)
Other	21 (36)	Exertion (or soon after)	9 (14)
Chronic respiratory disease‖	4	Using toilet	6 (9)
Cancer#	4	Physical pain	2 (3)
Psychiatric**	8	Emotional stress	1 (2)
Alcoholism	1	***Approximate time of death***	n=53 (%)
Endocrine††	2	0600-1400	20 (38)
GORD	1	1400-2200	17 (32)
No other medical history	14 (24)	2200-0600	16 (30)

GORD gastro-oesophageal reflux disease, PVC premature ventricular complex
*ECG unavailable
†For left ventricular origin PVC possibly related to MVP
‡Normal aorta at autopsy
§Includes syncope (2), palpitations (3) and dizziness (1)
‖Includes asthma (2), chronic obstructive pulmonary disease (1) and obstructive sleep apnea (1)
#Includes non-metastatic prostate cancer (3) and previously undiagnosed non-Hodgkin's lymphoma (1)
**Includes depression alone (2), anxiety alone (1), depression and anxiety (3) and schizophrenia (2)
††Includes hypothyroidism (1) and hypopituitarism (1)
‡‡Includes 1 patient taking sotalol
§§Includes 2 patients taking loop diuretics
‖‖Includes inhaled bronchodilators (5), non-steroidal anti-inflammatory drugs (1), thyroxine (1), prednisolone (1), benzodiazepines (3), anti-depressants (5), olanzapine (1), antacid (3) and sulfasalazine (1)
##Includes cases where individuals were found at home, at work performing routine (non-exertional) tasks or walking

3.7.2 *Histopathological findings in 70 iMVP cases versus controls*

	iMVP cases	**MVA cases**	**p-value***	**AMI cases**	**p-value***
Baseline characteristics					
Age	49±18	49±18	0·28	50±17	0·55
Female	35 (50%)	35 (50%)	1	35 (50%)	1
Weight (kg)	77±18	78±16	0·52	78±17	0·16
Height (cm)	172±11	172±10	0·49	172±9	0·36
Internal organ masses					
Cardiac (g)	447±107	355±78	<0·001	438±117	0·48
Left lung (g)	617±175	454±167	<0·001	667±250	0·12
Right lung (g)	728±214	522±170	<0·001	772±271	0·21
Brain (g), *n=64*	1414±147	1390±149	0·27	1383± 164	0·16
Liver (g), *n=67*	1846±512	1599±386	<0·001	1894±428	0·31
Kidneys (g), *n=67*	326±110	274±60	<0·001	345±86	0·20
Spleen (g), *n=67*	223±111	140±58	<0·001	211±107	0·46
Gross pathological changes					
Cardiac mass					
>95% predicted[93]	25 (36%)	4 (6%)	<0·001	16 (23%)	0·09
LV thickness (mm)	*n=49*	*n=42*		*n=49*	
Median (IQR)	15 (13-19)	14 (12-15)	0·10	15 (12-20)	0·69
RV thickness (mm)	*n=40*	*n=36*		*n=43*	
Median (IQR)	4 (3-5)	4 (3-5)	0·67	4 (3-5)	0·23
MV circumference (mm)	*n=26*	*n=16*		*n=13*	
Median (IQR)	121 (115-139)	108 (91-115)	<0·001	110 (98-115)	0·002
TV circumference (mm)	*n=21*	*n=15*		*n=12*	
Median (IQR)	130 (120-140)	120 (120-130)	0·18	125 (116-148)	0·91
Leaflet involvement					
Reported†	54				
Bileaflet	47 (87%)				
Posterior leaflet	5 (9%)				
Anterior leaflet	2 (4%)				
Left ventricular histological changes					
Abnormal	55 (79%)‡	25 (36%)§	<0·001	61 (87%)‖	0·14
Fibrosis or scarring	52	20		37	
Myocyte hypertrophy	5	3		5	
Contraction band	3			6	
PM fibrosis#	2				
PM calcification	1				
No abnormalities found	15 (21%)	45 (64%)		9 (13%)	

IQR, inter-quartile range; LV, left ventricle; MV, mitral valve; PM, papillary muscle; RV, right ventricle; TV, tricuspid valve.

*Compared to iMVP cases

†All 70 cases reported abnormal valve morphology with descriptors such as redundant, thickened, ballooned, hooded, prolapsed, floppy, pendulous, voluminous, myxomatous or billowing

‡>1 abnormality in some cases

§Other descriptors (>1 in some cases) include interfiber edema (1), inflammatory cells (2), hemmorhage (1)

‖Other descriptors (>1 in some cases) include acute/subacute infarct (16), mural infarct (6), healed infarct (4), myocyte necrosis (7), coagulative necrosis (4), myocardial rupture (2), inflammatory cells (4), interstitial haemorrhage (1), amyloid (1)

#1 case had previous PVC ablation

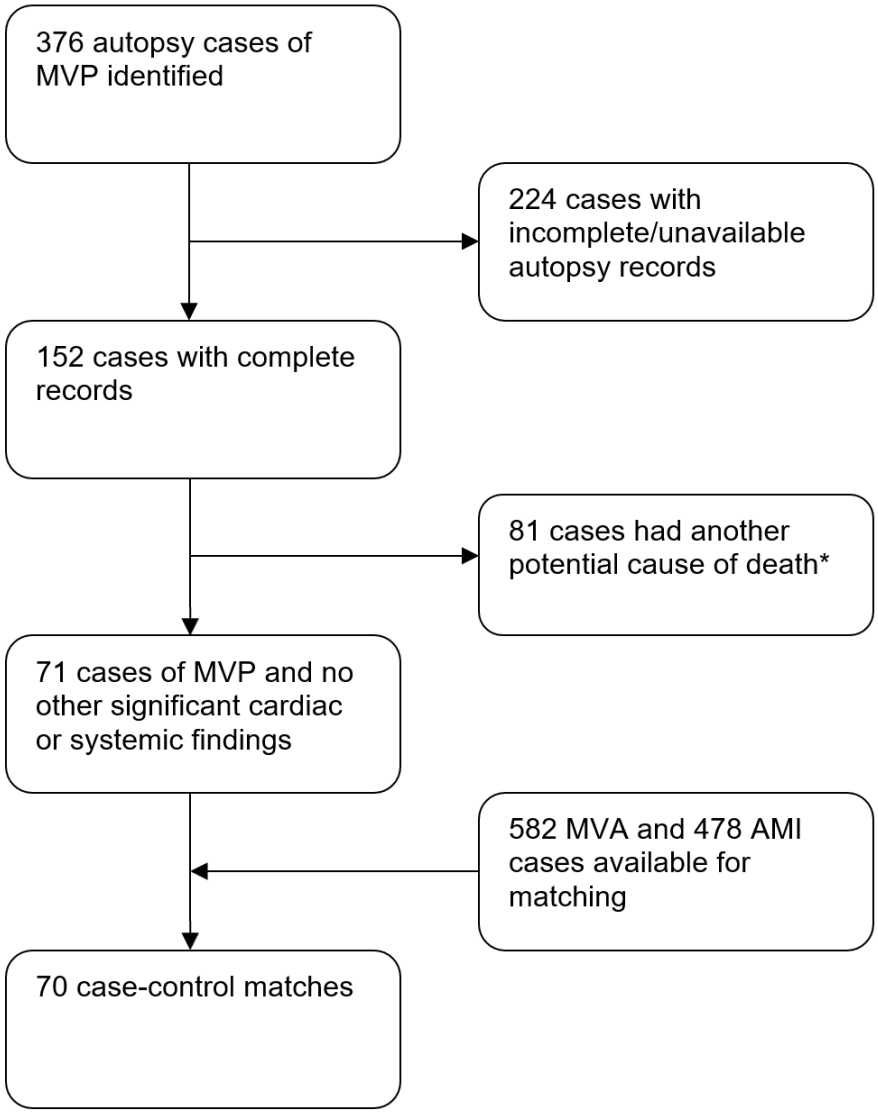
3.7.3 *Histopathological findings in iMVP versus non-iMVP cases*

	iMVP cases	**non-iMVP cases**					
		Total	**p-value***	**Cardiac COD**	**p-value***	**Other COD**	**p-value***
	n=70	*n=81*		*n=56*		*n=25*	
Baseline characteristics							
Age	49±18	62±17	<0.001	61±17	<0.001	62±19	0.002
Female	35 (50%)	38 (47%)	0.77	25 (45%)	0.60	13 (52%)	0.82
Weight (kg)	77±18	70±21	0.03	76±21	0.78	56±15	<0.001
Height (cm)	172±11	168±12	0.048	169±12	0.17	166±12	0.03
Internal organ masses							
Cardiac (g)	447±107	440±127	0.72	472±129	0.23	368±92	0.001
Left lung (g)	617±175	589±194	0.37	598±200	0.58	570±183	0.26
Right lung (g)	728±214	682±198	0.18	696±207	0.40	652±174	0.11
Brain (g)	1414±147	1363±189	0.09	1359±186	0.09	1370±201	0.30
Liver (g)	1846±512	1567±504	0.001	1676±545	0.09	1349±320	<0.001
Kidneys (g)	326±110	279±75	0.003	291±72	0.053	255±78	0.004
Spleen (g)	223±111	175±90	0.006	179±71	0.02	167±122	0.04
Gross pathological changes							
Cardiac mass >95% predicted	25 (36%)	19 (23%)	0.10	14 (25%)	0.20	5 (20%)	0.15
LV thickness (mm)	15 (13-19)	15 (12-20)	0.45	15 (12-20)	0.29	14 (13-17)	0.80
RV thickness (mm)	4 (3-5)	4 (3-5)	0.47	4 (3-5)	0.54	4 (3-5)	0.56
MV circumference (mm)	121 (115-139)	120 (105-139)	0.60	125 (110-140)	1.0	103 (100-130)	0.13
TV circumference (mm)	130 (120-140)	130 (114-144)	0.73	133 (116-149)	0.41	120 (113-131)	0.30
Leaflet involvement							
Reported	54	53		35		18	
Bileaflet	47 (87%)	42 (79%)	0.41	29 (83%)	0.37	13 (72%)	0.28
Posterior leaflet	5 (9%)	10 (19%)		6 (17%)		4 (22%)	
Anterior leaflet	2 (4%)	1 (2%)		0		1 (6%)	
Left ventricular histological changes							
Abnormal	55 (79%)	67 (89%)	0.08	46 (87%)	0.24	21 (95%)	0.07
Fibrosis or scarring	52	63		43		20	
Myocyte hypertrophy	5	10		7		3	
Contraction band	3	2		2		0	
PM fibrosis / calcification	3	2		2		0	

COD, cause of death; IQR, inter-quartile range; LV, left ventricle; MV, mitral valve; PM, papillary muscle; RV, right ventricle; TV, tricuspid valve.
*Compared to iMVP cases

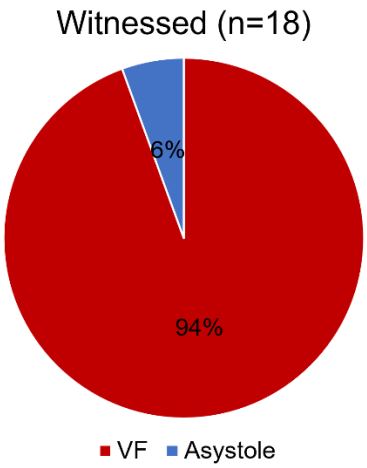
3.8 Figures

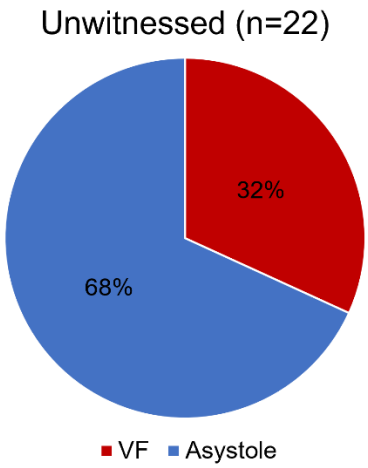
3.8.1 *Case identification*



*Other significant findings include: ischaemic heart disease (36), previous cardiac surgery (8), histological myocarditis (4), significant left ventricular hypertrophy (3), dilated cardiomyopathy (2), severe mitral regurgitation (1), arrhythmogenic right ventricular cardiomyopathy (1), bicuspid aortic valve with aortic coarctation (1), infection (7), respiratory (6), drug overdose (3), cirrhosis (3), head injury (3), metastatic carcinoma (1), hyponatraemia (1), suicide (1)

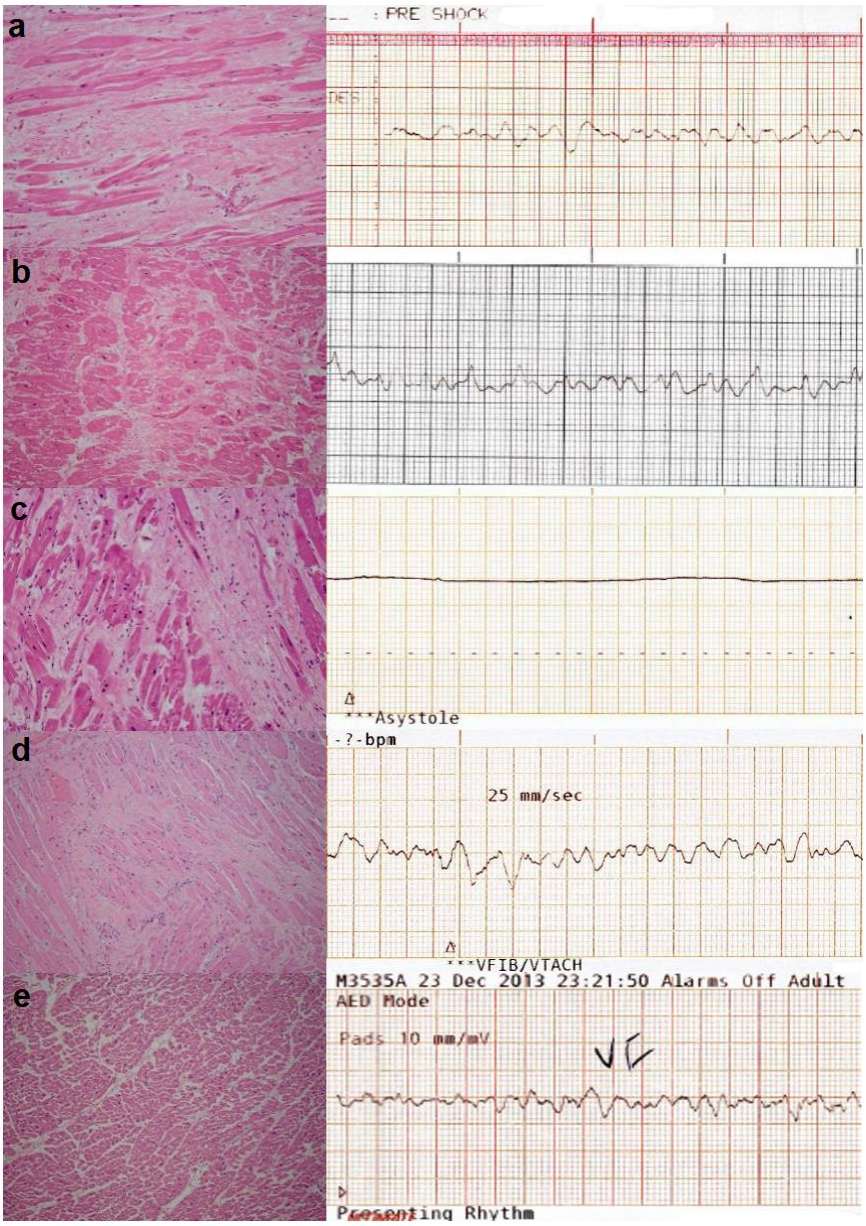
3.8.2 *Initial cardiac rhythm in cases of autopsy determined iMVP*





VF, ventricular fibrillation.

3.8.3 *Histological analysis with initial cardiac rhythm for iMVP and SCD*



a. 31-year-old female with witnessed cardiac arrest whilst resting in bed and VF. Histopathological examination showed myxomatous change in both mitral valve leaflets with focal left ventricular fibrosis in a subendocardial-midmural distribution and papillary muscle fibrosis.
b. 45-year-old female found on the toilet with VF after an unwitnessed cardiac arrest. Histopathological examination showed thickening and billowing of both mitral valve leaflets with multi-segment left ventricular fibrosis in a subendocardial-midmural distribution.
c. 34-year-old female found collapsed in the bathroom with asystole after an unwitnessed cardiac arrest. Histopathological examination showed myxomatous change in both mitral valve leaflets with multi-segment left ventricular fibrosis in a midmural distribution.
d. 25-year-old female with witnessed cardiac arrest whilst washing dishes and VF. Histopathological examination showed myxomatous change in both mitral valve leaflets with multi-segment left ventricular fibrosis in a subendocardial-midmural distribution.
e. 47-year-old female found collapsed in the bathroom with VF after an unwitnessed cardiac arrest. Histopathological examination showed thickened and floppy mitral valve leaflets with no evidence of left ventricular fibrosis.

CHAPTER 4

Systematic Quantification of Histological Ventricular Fibrosis in Isolated Mitral Valve Prolapse and Sudden Cardiac Death: Evidence of Non-Uniform Left Ventricular Remodelling

4.1 Overview

Background: Cardiac fibrosis in mitral valve prolapse (MVP) has been implicated in the development of sudden cardiac death (SCD). However, the pattern and degree of ventricular fibrosis in this population remains poorly characterised.

Methods: Individuals with isolated MVP and SCD (iMVP-SCD) were identified from the Victorian Institute of Forensic Medicine (VIFM), Australia. A case-control study design was used and iMVP-SCD patients were matched for age, sex and body-mass index to control cases with non-cardiac death. Cardiac tissue sections were stained with Masson's Trichrome and analysed to determine collagen deposition in the left ventricular free wall (anterior, lateral and posterior portions), interventricular septum and right ventricle. Within the iMVP-SCD cases, the distribution of fibrosis within the LV was specifically characterised.

Results: In total there were 34 cases (17 with iMVP-SCD matched 1:1 with 17 controls) yielding 149 samples and 1,788 histological sections. The iMVP-SCD group had increased left ventricular (anterior, lateral and posterior; all $p<0.001$) and interventricular septum fibrosis ($p<0.001$), but similar amounts of right ventricular

fibrosis (p=0.62) compared to the control group. In those with iMVP-SCD, left ventricular fibrosis was significantly higher in the lateral and posterior wall when compared to the anterior wall and interventricular septum (all p<0.001). Within the lateral and posterior wall, iMVP-SCD cases had a significant endocardial-to-epicardial gradient of cardiac fibrosis (p<0.01) similar to other known conditions which cause cardiac remodelling.

Conclusions: Our study indicates that non-uniform left ventricular remodelling occurs in patients with iMVP and SCD. These findings suggest that both generalised and localised LV fibrosis are important components in the pathogenesis of SCD in MVP. Whether pre-mortem detection of this fibrosis pattern can identify high-risk patients with MVP merits further study.

4.2 Introduction

Mitral valve prolapse (MVP) is characterised by atrial displacement of the mitral valve leaflet(s) during ventricular systole and has a population prevalence of 2.4%.[4] Increasingly, the presence of MVP has been associated with malignant ventricular arrhythmias (VAs) and sudden cardiac death (SCD).[6-9, 52, 278, 285]

The presence of localised left ventricular and papillary muscle fibrosis in MVP are thought to be important factors in the development of both malignant ventricular arrhythmias and SCD in patients with MVP.[9, 89] Other studies have suggested that increased right ventricular fibrosis – indicating a generalised biventricular cardiomyopathic process – plays a contributing role in the development of malignant

ventricular arrhythmias in patients with MVP.[94, 95] However, these studies obtained biopsies from the right side of the interventricular septum which may have confounded such findings. Additionally, data is lacking regarding the significance of generalised left ventricular fibrosis in addition to the documented localised changes.

Consequently, detailed left ventricular assessment for transmural and circumferential fibrosis along with characterization of right ventricular fibrosis may provide additional insights into the potential pathogenic role attributable to cardiac fibrosis in individuals with isolated MVP and SCD (iMVP-SCD, whereby other potential causes of death are excluded).

The aim of this case-control study was to comprehensively and systematically quantify left and right ventricular fibrosis in individuals with iMVP-SCD compared to a matched control cohort. Additionally, we aimed to further characterise the distribution and pattern of left ventricular fibrosis in iMVP-SCD.

4.3 Methods

4.3.1 *Patient selection*

The Victorian Institute of Forensic Medicine (VIFM) is a large state-wide multi-disciplinary forensic medical center based in Melbourne, Australia. Between July 2000 and May 2018, all individuals in whom MVP was coded – International Classification of Diseases-10 (ICD-10) code 34.1 – as a cause of death (either underlying or

contributing) were screened and complete autopsy records examined. Each Victorian case with MVP was manually reviewed (including autopsy report, police report and toxicology report) by a board-certified cardiologist and pathologist to determine circumstances of death, demographics, clinical information and salient pathological findings. Following individual case adjudication, cases with of SCD related to iMVP were identified and left ventricle samples taken at autopsy were used for detailed fibrosis evaluation. We have previously shown that malignant VAs as the predominant rhythm in cases of iMVP-SCD with witnessed cardiac arrest.[285]

Inclusion criteria was the presence of MVP on autopsy examination (evidence of myxomatous leaflets on gross examination and/or histology). Patients were adjudicated to have iMVP based on the presence of MVP at autopsy without another possible cause of death. Definition of sudden cardiac death included witnessed cases in a previously stable individual, and unwitnessed cases where an individual was found dead who at time of last witnessed contact was in a usual state of health.[17]

Excluded cases were those with another significant cardiac finding (clinical or autopsy) including ischaemic heart disease (≥70% stenosis in any coronary artery, presence of coronary stent or documented previous history), known cardiomyopathy, severe mitral regurgitation, previous cardiac surgery, myocarditis (on histology), hypertrophic cardiomyopathy (on histology) or left ventricular wall thickness ≥25mm.

Cases from VIFM with noncardiac death and normal gross cardiac findings at postmortem examination were selected as controls matched in a 1:1 ratio based on age,

gender and body mass index (BMI) to mitigate any potential cardiac influences related to BMI.[286]

4.3.2 *Ethical approval*

Ethical approval for this study was granted by Victorian Institute of Forensic Medicine Research Advisory and Ethics Committee (RAC 002-18 and EC 4-2018).

4.3.3 *Specimen procurement*

At the time of coronial autopsy, standardised transmural samples were obtained from the mid portion of the left ventricular free wall (anterior, lateral and posterior), interventricular septum and right ventricular free wall and outflow tracts as previously published.[287] Samples for both iMVP-SCD cases and controls were obtained using this method.

4.3.4 *Specimen preparation for histological analysis*

Specimens were fixed in 10% neutral buffered formalin (Point of Care Diagnostics Scientific, Australia) at the time of sampling and embedded in paraffin. The extent of fibrosis was determined by staining 4μm thick ventricular sections (microtome) with Masson's Trichrome. Individual sections were then digitally scanned using Pannoramic SCAN II (3D Histech, Hungary) and images with a 20x magnification were taken using CaseViewer Version 2.2 (3D Histech, Hungary).

4.3.5 *Specimen analysis for cardiac fibrosis*

Cardiac fibrosis was calculated as fibrosis percentage, using a standardised methodology previously published by our group.[288, 289] Fibrosis was defined as the area of connective tissue divided by sum of areas of connective tissue and cardiac muscle cells.[290] For each section, both cases and controls were de-identified. The following regions from the sections were then selected for fibrosis quantification at 20X magnification for both the iMVP-SCD cases and controls (Figure 4.8.1):

- 12 regions (4 x inner third regions, 4 x middle third regions and 4 x outer third regions from the myocardial wall) from each left ventricular free wall section (anterior, lateral and posterior walls)
- 12 regions (4 x left ventricular third regions, 4 x middle third regions and 4 x right ventricular third regions) from the interventricular septum section
- 12 regions from the right ventricle section (including free wall and/or outflow tract)

For each region, a fibrosis percentage was calculated using an unbiased thresholding image analysis tool, Image J (Figure 4.8.1).[291] Large areas of perivascular fibrosis were excluded from analysis to mitigate potential changes of cardiac remodelling related to blood pressure.[292-294]

4.3.6 *Statistical analysis*

Continuous data are reported as means with standard deviation or medians with inter-quartile range as appropriate. The paired t-test compared parametric continuous variables, while the Wilcoxon sign rank test and Kruskal Wallis test compared non-parametric continuous variables. Categorical data are presented as absolute figures and compared using McNemar's test. A 2-sided p-value <0.05 was considered significant. All data analyses were performed using SPSS Version 25 (IBM Corp., Armonk, NY).

4.4 Results

4.4.1 *Baseline findings*

Between July 2000 and May 2018, there were 30 Victorian cases of death involving MVP with complete autopsy records. 17 cases were deemed to have iMVP-SCD (mean age 47±16 years, 71% female) which were matched to 17 cases of non-cardiac death for parameters of age, sex, height and weight (Table 4.7.1). In total, 149 cardiac tissue sections from iMVP-SCD cases and controls were available for analysis yielding 1788 histological regions. 21 cardiac tissue specimens (out of 170 in total) were unavailable for analysis.

There were no significant differences between the iMVP-SCD cases and control group with regard to presence of cardiovascular risk factors. However, those with iMVP-SCD had significantly higher cardiac mass compared with controls (445g vs 378g, p=0.009).

4.4.2 *Overall cardiac fibrosis quantification*

Those with iMVP-SCD had increased amounts of fibrosis within the left ventricular free wall (3.1% vs 1.9%, p<0.001) compared to controls (Table 4.7.2 and Figure 4.9.1). In those with iMVP-SCD, the overall distribution of left ventricular free wall fibrosis demonstrated a significant endocardial-epicardial gradient with highest amounts in the inner third (4.1%) followed by the middle third (3.3%, p<0.001 compared to inner third) and then outer third (2.5%, p<0.001 compared to middle third).

Additionally, individuals with iMVP-SCD also had more interventricular septum (2.6% vs 1.7%, p<0.001) fibrosis compared to controls (Table 4.7.2 and Figure 4.9.1 & 4.9.5). Overall, the degree of right ventricular free wall fibrosis (2.8% vs 2.6%, p=0.62) was similar to controls (Table 4.7.2 and Figures 4.9.1 & 4.9.6).

4.4.3 *Distribution of cardiac fibrosis*

Within the 4 sections of the left ventricle, individuals with iMVP-SCD had significantly higher amounts of fibrosis in all regions – inner, middle and outer thirds of the anterior, lateral and posterior wall as well as the left ventricular third, middle third and right ventricular third of the interventricular septum – compared to the control cohort (Table 4.7.2, Figure 4.8.2 and Figures 4.9.1-4.9.5).

In those with iMVP-SCD, significantly higher levels of cardiac fibrosis were found in the lateral and posterior regions when compared to both the anterior and septal regions

(all $p<0.001$). There were no significant differences in fibrosis deposition when comparing the anterior wall with interventricular septum ($p=0.80$) and lateral wall with posterior wall ($p=0.68$) respectively.

Additionally, in cases of iMVP-SCD, both the lateral and posterior sections of the left ventricle demonstrated a significant epicardial to endocardial gradient of fibrosis – more fibrosis in the endocardial regions ($p=0.003$ for trend in the lateral wall and $p<0.001$ for trend in the posterior wall) – which was not present in the anterior or interventricular septal regions ($p=0.08$ for trend in the anterior wall and $p=0.23$ for trend in the interventricular septum).

4.5 Discussion

In this comprehensive study of histological fibrosis in patients with iMVP-SCD, we systematically quantified the extent and distribution of cardiac fibrosis in a cohort of individuals with iMVP-SCD compared to a matched control cohort. The following key findings were demonstrated:

1. There was increased left ventricular free wall and interventricular septum fibrosis in individuals with iMVP-SCD compared with the control cohort ($p<0.001$);
2. Right ventricular fibrosis was similar between individuals with iMVP-SCD and the control cohort ($p=0.62$) therefore specifically implicating left ventricular fibrosis in the pathogenesis of SCD;

3. In those with iMVP-SCD, left ventricular fibrosis was greatest in the lateral and posterior wall indicating non-uniform fibrotic distribution;
4. A significant endocardial-epicardial gradient of left ventricular fibrosis within the lateral and posterior walls was apparent in those with iMVP-SCD suggestive of ventricular remodelling.

Findings from out study suggests a generalised left ventricular remodelling process occurs in individuals with iMVP-SCD as evidenced by the significantly higher cardiac mass and more left ventricular (free wall and interventricular septum) fibrosis compared to a matched control cohort. While previous studies reported increased cardiac mass in cases of MVP and SCD, influencing factors were not necessarily controlled for.[285] Furthermore, other studies have predominantly shown localised increases in left ventricular fibrosis involving the papillary muscles and adjacent ventricular wall in those with MVP and SCD.[9, 50] This study involved comprehensive assessment of overall left ventricular fibrosis and we found higher levels of fibrosis circumferentially around the left ventricle (anterior, lateral posterior and septal) and within all regions (inner third, middle third, outer third of the myocardial wall) compared to controls. Findings of increased cardiac mass in conjunction with an overall increase in left ventricular fibrosis provide strong evidence that generalised left ventricular remodelling and fibrotic changes occur in those with iMVP-SCD in addition to previously reported localised changes.

This study also provides a systematic assessment of right ventricular fibrosis in individuals with iMVP-SCD compared with a matched control cohort. Two previous *in*

vivo studies found higher levels of right ventricular septal fibrosis in patients with MVP suggesting a generalised biventricular cardiomyopathic process,[94, 95] although isolated (i.e. non-septal) right ventricular fibrosis was not assessed. We demonstrated that while those with iMVP-SCD had more fibrosis in the right ventricular aspect of the interventricular septum, the amount of isolated right ventricular fibrosis (free wall and/or outflow tract) was similar compared to the control group. Similar degrees of isolated right ventricular fibrosis between those with iMVP-SCD cases and controls specifically implicates left ventricular fibrosis and remodelling in the pathogenesis of iMVP related SCD.

Within the iMVP-SCD group, we quantitatively demonstrated an endocardial to epicardial fibrosis gradient which is consistent with other conditions known to cause left ventricular remodelling and SCD, such as hypertrophic and dilated cardiomyopathy.[230, 231] However, in our cases of iMVP-SCD, this gradient of fibrosis was limited to the lateral and posterior portions of the left ventricle. Additionally, while the anterior and interventricular septum sections in those with iMVP-SCD contained more fibrosis compared to controls, this was significantly less than the lateral and posterior sections in those with iMVP-SCD. Of importance, the papillary muscle attachment within the left ventricle results in closer coupling within the lateral and posterior wall.[76] These findings suggest that complex interactions between the papillary muscle attachment and the left ventricle in individuals with iMVP-SCD may result in non-uniform left ventricular remodelling. Specifically, it is postulated that higher mechanical stress and subsequent fibrosis occurs in this region due to the closer coupling of the papillary muscles.[7, 9, 130] Furthermore, our results are in keeping with recent non-invasive studies showing both

non-uniform increases in left ventricular fibrosis utilizing cardiac magnetic resonance imaging and left ventricular mechanical dispersion utilizing speckle-tracking echocardiography in patients with MVP.[125, 131] These findings also affirm previous observations that patients with 'malignant' MVP are more likely to exhibit electrocardiogram repolarization abnormalities in the inferior and lateral regions.[9, 35, 52, 169] Collectively, findings from these clinical studies along with our histopathological results suggests that non-uniform left ventricular cardiac remodelling is an important pathophysiological component in the development of SCD in patients with iMVP.

4.5.1 *Implications*

While the association between MVP and SCD is increasingly recognised, the underlying pathophysiology remains elusive.[7] To our knowledge, this is the first study to systematically quantify histological ventricular fibrosis in cases of iMVP-SCD. Based on our findings, we postulate that individuals with iMVP experience fibrotic changes concentrated around the base of the papillary muscles due to mechanical stresses imparted by a myxomatous mitral valve with additional LV remodelling. Therefore, a sequence involving papillary muscle tension with the subsequent development of both localised and generalised left ventricular fibrosis may be important in the pathogenesis of SCD in MVP. Isolated right ventricular fibrosis however does not appear to be consequential in this process. The use of non-invasive cardiac imaging techniques to characterise the distribution and extent of left ventricular fibrosis in living patients with MVP for SCD risk stratification merits further study.

4.5.2 *Limitations*

We acknowledge certain limitations of this study. Given the nature of this autopsy-based study, we are unable to comment on clinical characteristics such as history of syncope or findings from electrocardiography or Holter monitoring. Due to varying procedures with specimen handling over the 18-year period covered in the study, a proportion of cardiac tissue specimens were unavailable for analysis. We were unable to characterise left ventricular fibrosis in the basal and apical regions and papillary muscles due to the left ventricular sampling methodology during coronial autopsy. While increased papillary muscle fibrosis has been reported elsewhere,[9] histological characterization of the left ventricular basal and apical regions would provide further insights into the complex process of non-uniform left ventricular remodelling in individuals with iMVP-SCD. Sampling of the right ventricle during coronial autopsy involved the free wall and/or outflow tract, hence we are unable to differentiate between fibrosis in these two areas. However, this would have been applicable to both the iMVP-SCD group and control group mitigating potential bias.

4.6 Conclusion

Our study demonstrates that non-uniform left ventricular remodelling occurs in patients with iMVP and SCD. These findings suggest that both generalised and localised left ventricular fibrotic changes are important in the pathogenesis of SCD in patients with MVP.

4.7 Tables

4.7.1 *Baseline demographics for 17 iMVP-SCD cases and controls*

	iMVP-SCD	**Controls**	**p-value**
Age	47±16	47±16	0.84
Female	12 (71%)	12 (71%)	1.0
Height (cm)	169±10	167±10	0.16
Weight (kg)	74 (69-100)	75 (67-95)	0.74
BMI	26 (22-32)	27 (24-32)	0.58
Cardiovascular history			
Hypertension	0	1	1.0
Atrial fibrillation	1	1	0.48
Diabetes	0	1	1.0
Dyslipidaemia	0	1	1.0
Cardiac mass (gm)	445 (356-600)	378 (293-506)	0.009

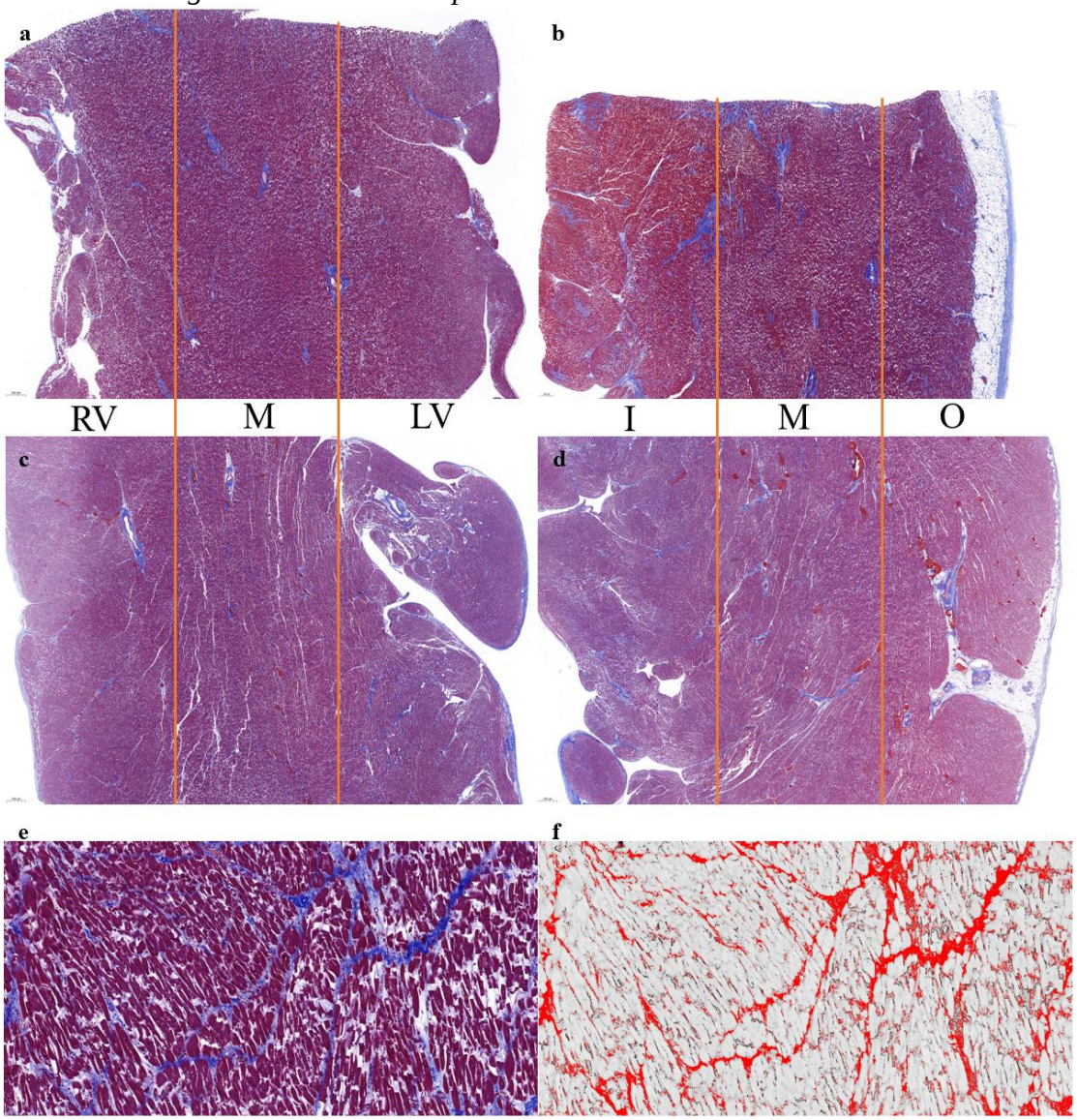
4.7.2 *Ventricular fibrosis percentage for iMVP-SCD and controls*

	iMVP-SCD	Controls	p-value
Left ventricle free wall – overall	3.1 (2.3-4.5)	1.9 (1.4-2.4)	<0.001
Inner third	4.1 (2.7-4.4)	1.9 (1.4-2.5)	<0.001
Middle third	3.3 (2.4-4.4)	1.8 (1.4-2.3)	<0.001
Outer third	2.5 (2.0-3.5)	1.9 (1.4-2.3)	<0.001
Anterior wall – overall	2.7 (2.0-3.4)*	1.9 (1.4-2.4)	<0.001
Inner third	3.4 (2.0-6.9)	2.0 (1.5-2.7)	<0.001
Middle third	2.8 (1.9-3.1)	1.8 (1.3-2.3)	<0.001
Outer third	2.4 (1.9-2.8)	1.7 (1.3-2.2)	0.002
Lateral wall – overall	4.4 (2.5-9.2)*	1.9 (1.5-2.4)	<0.001
Inner third	10.4 (4.3-16.2)	1.7 (1.4-2.6)	<0.001
Middle third	5.4 (2.4-8.2)	1.9 (1.5-2.4)	<0.001
Outer third	3.5 (2.3-4.0)	1.9 (1.6-2.6)	<0.001
Posterior wall – overall	4.0 (2.8-5.9)*	2.0 (1.5-2.4)	<0.001
Inner third	7.2 (4.2-13.4)	1.9 (1.5-2.4)	<0.001
Middle third	4.1 (3.2-5.3)	1.9 (1.5-2.4)	<0.001
Outer third	2.8 (2.4-3.9)	2.0 (1.5-2.5)	<0.001
Interventricular septum – overall	2.6 (1.9-4.1)*	1.7 (1.3-2.2)	<0.001
Left ventricular third	2.8 (1.7-4.3)	1.7 (1.2-2.2)	<0.001
Middle third	2.7 (1.9-5.1)	1.7 (1.2-2.1)	<0.001
Right ventricular third	2.4 (1.8-3.0)	1.7 (1.4-2.3)	<0.001
Right ventricle – overall	2.8 (2.0-3.7)	2.6 (1.8-3.9)	0.624
Inner third	2.2 (1.6-3.3)	2.4 (1.5-3.2)	0.728
Middle third	3.0 (2.2-4.0)	2.6 (1.9-4.2)	0.621
Outer third	3.0 (2.2-3.8)	2.7 (2.0-4.5)	0.575

*Comparison of overall fibrosis in patients with iMVP-SCD: anterior wall vs lateral wall p<0.001, anterior wall vs posterior wall p<0.001, anterior wall vs interventricular septum p=0.80, lateral wall vs posterior wall p=0.68, lateral wall vs interventricular septum p<0.001, posterior wall vs interventricular septum p<0.001

4.8 Figures

4.8.1 *Histological ventricular samples*



Panels **a** and **b** shows low magnification (2x) images of sections from the interventricular septum and lateral left ventricle respectively in a patient with iMVP-SCD after trichrome staining. Panels **c** and **d** shows low magnification (2x) images of sections from the interventricular septum and lateral left ventricle respectively in a control patient after Masson's trichrome staining. RV denotes right ventricular third, M denotes middle third, LV left ventricular third, I inner third and O outer third. Small scale bar at the bottom left of panels **a**, **b**, **c** and **d** represent 0.5mm. Panels **e** and **f** show 20x magnification image of left ventricle with trichrome stained collagen in blue (**e**) and corresponding fibrosis quantification using ImageJ (**f**).[291]

4.8.2 *Left ventricular fibrosis percentage for iMVP-SCD and controls*

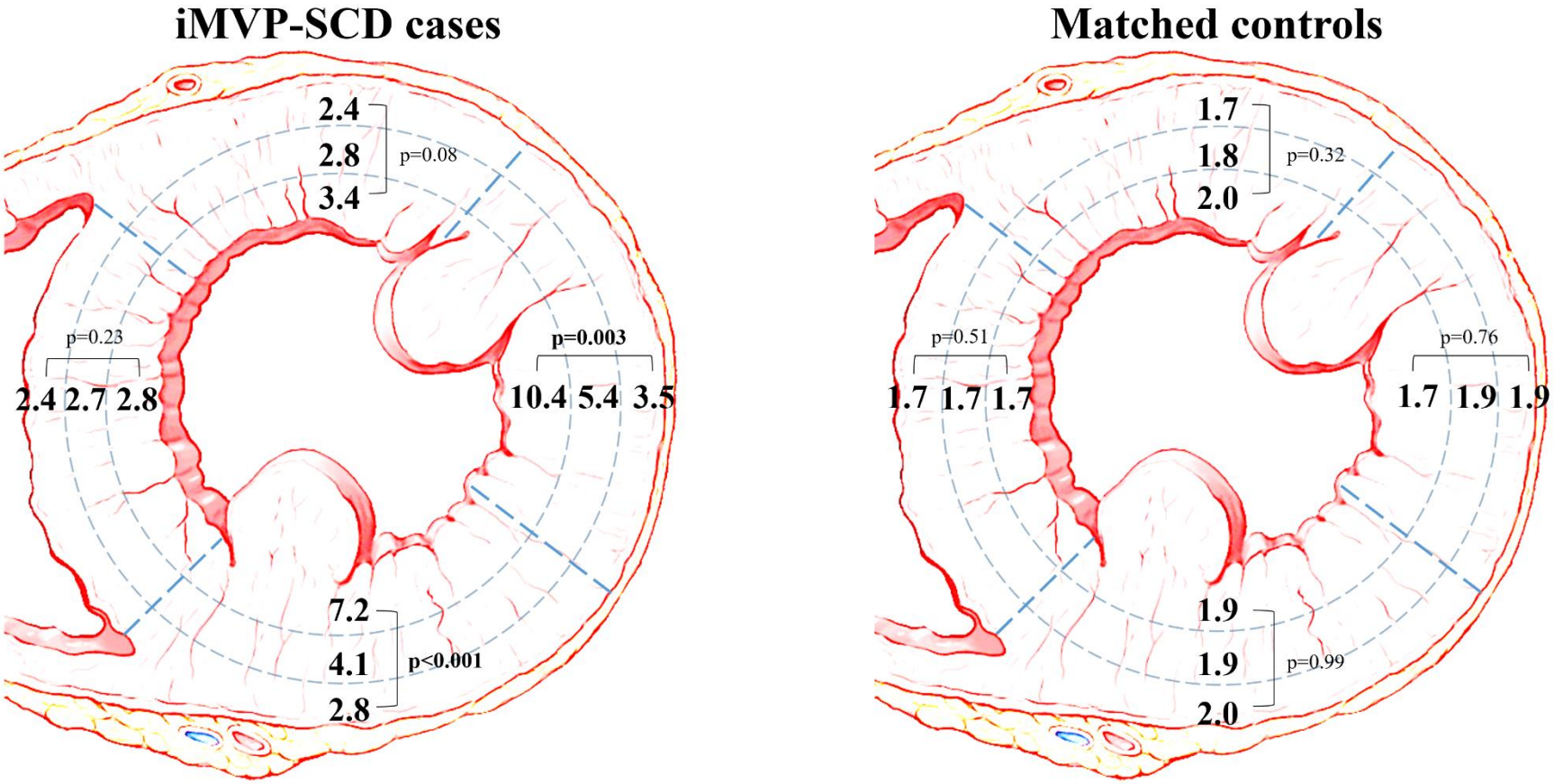
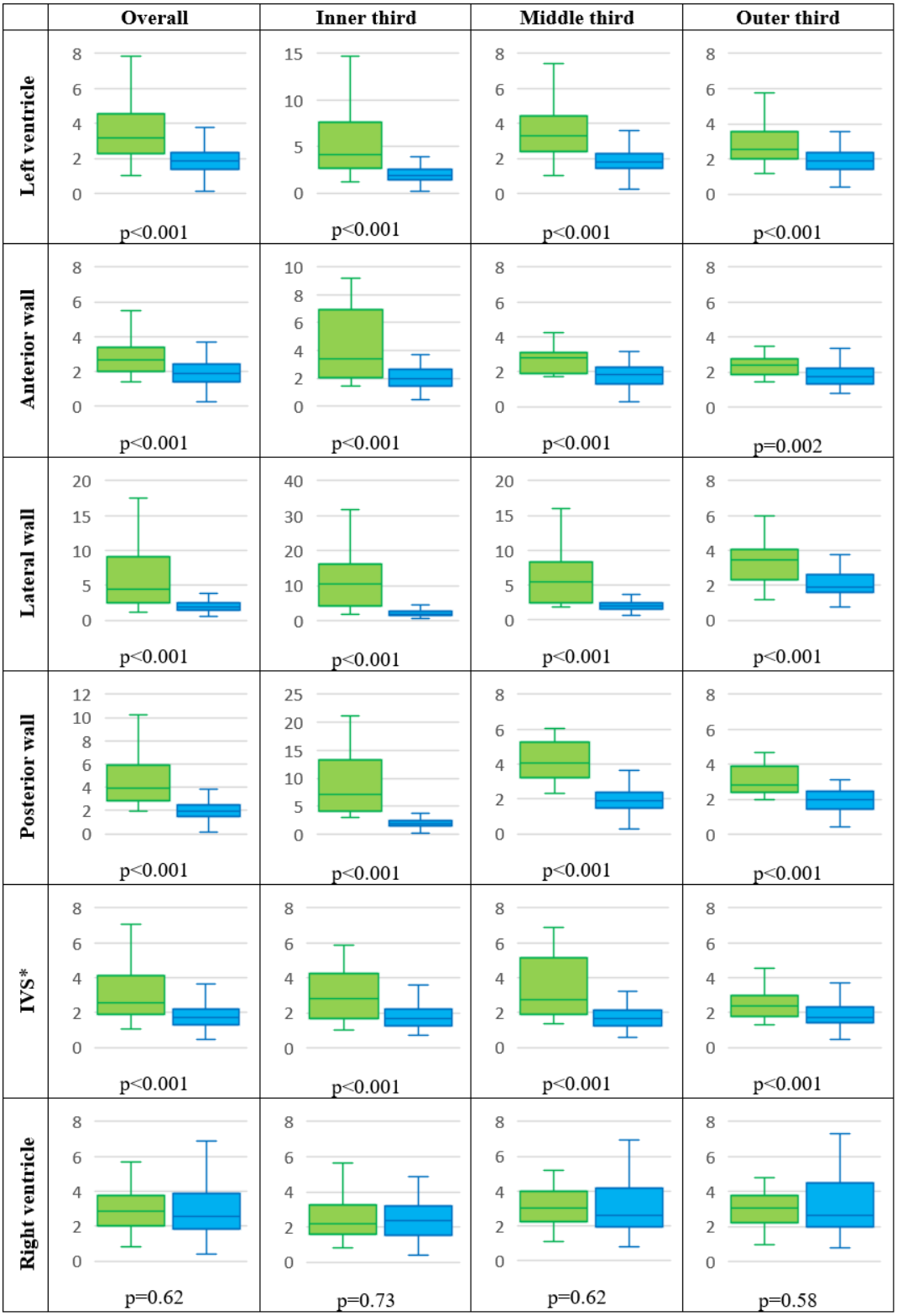


Image shows short axis view of the left ventricle with septal, anterior, lateral and posterior walls (clockwise from left) and anterolateral and posteromedial papillary muscles. Circular dashed lines delineate inner, middle and outer thirds (left ventricular third, middle third and right ventricular third for the septal region) of the left ventricle. Numbers indicate median fibrosis for the iMVP-SCD and control cohorts respectively within the delineated region. Presented p-values obtained using the Kruskal-Wallis test.

Image adapted from original illustration by Patrick J. Lynch, medical illustrator, CC BY 2.5, https://commons.wikimedia.org/w/index.php?curid=1490819

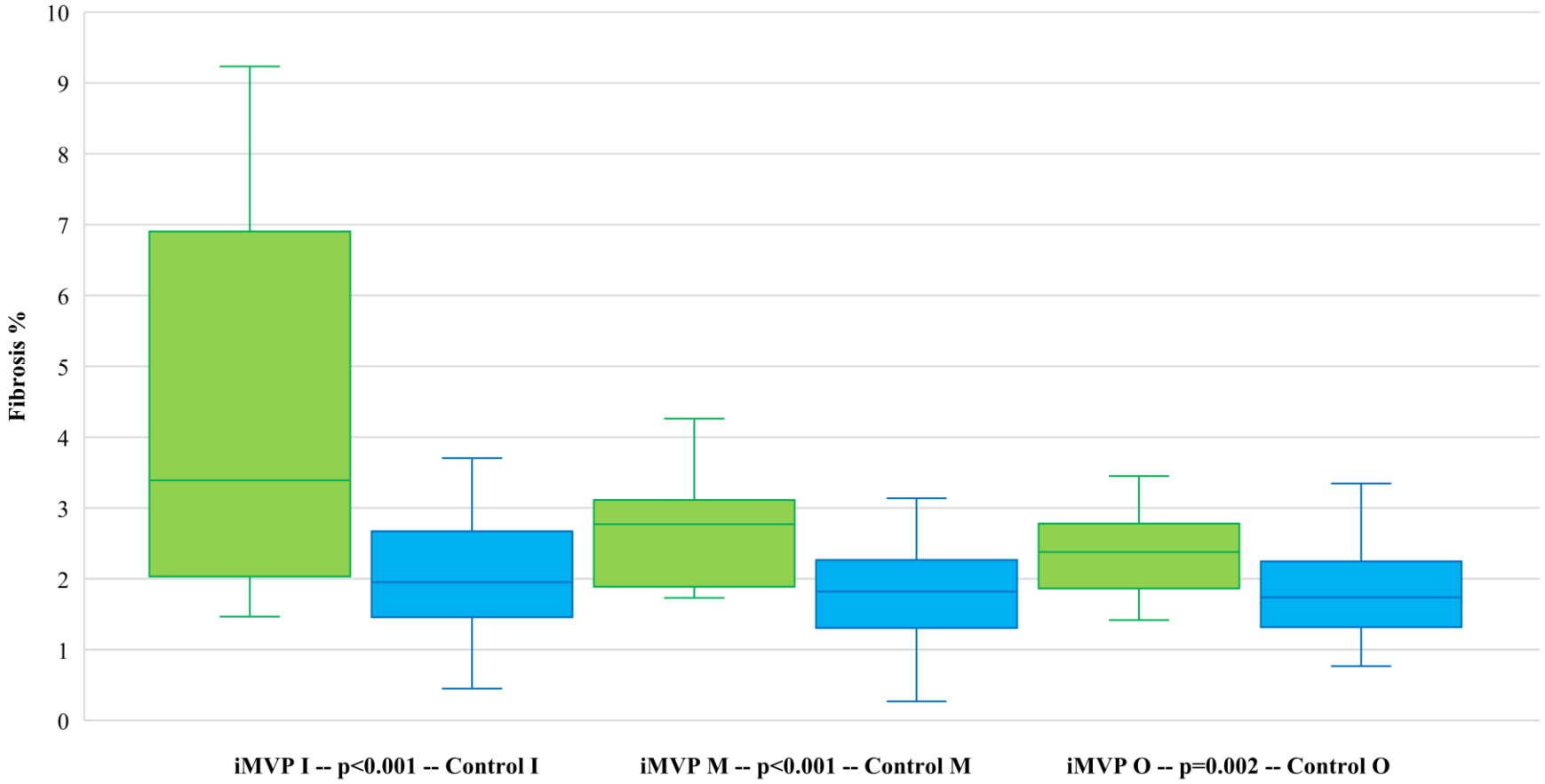
4.9 Supplemental Materials

4.9.1 *Fibrosis percentage for iMVP-SCD (■) and controls (■)*



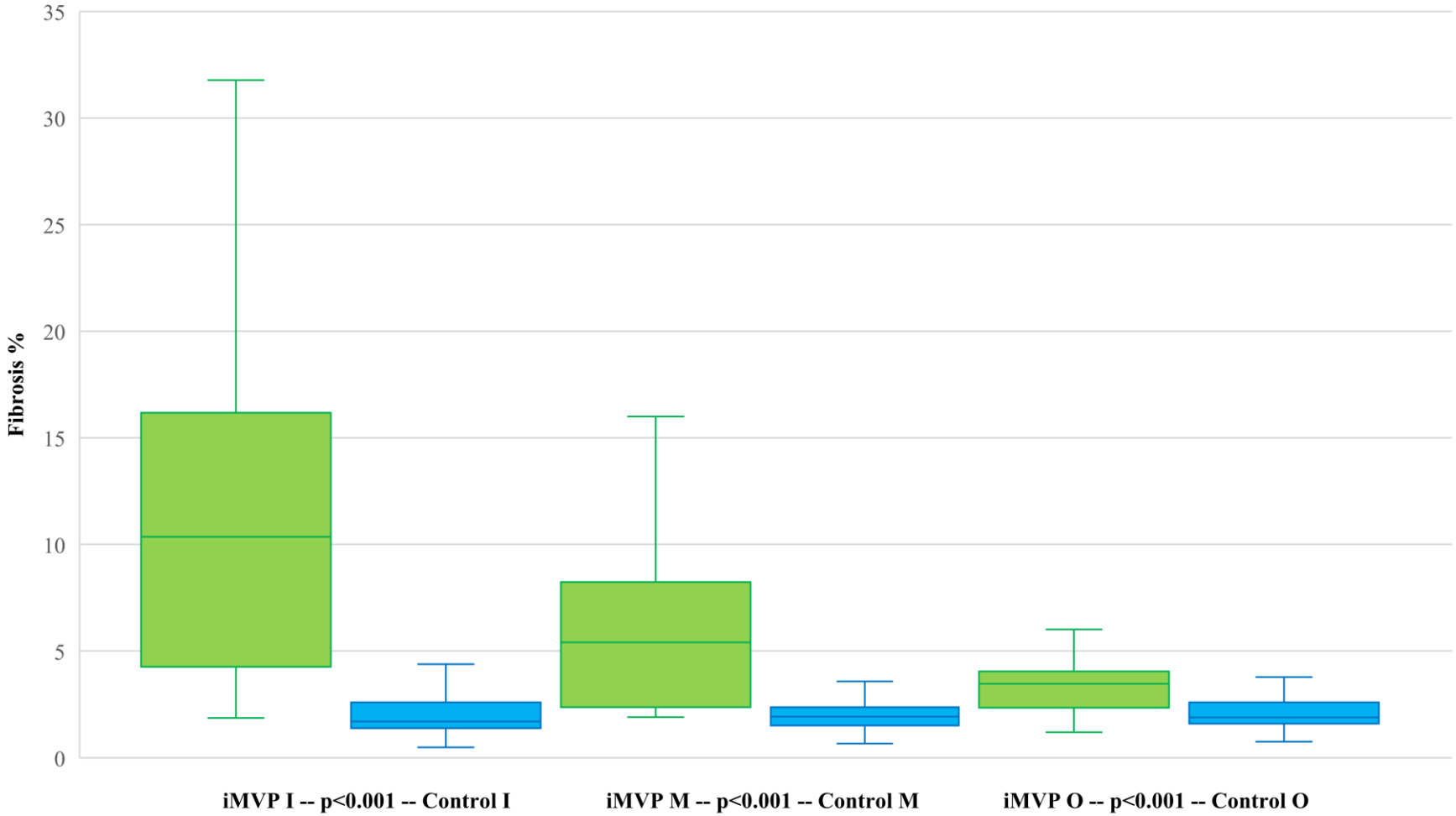
IVS indicates interventricular septum; Y-axis represents fibrosis percentage
Inner, middle and outer third for IVS equivalent to the left ventricular, middle and right ventricular third

4.9.2 *Anterior wall fibrosis for iMVP-SCD (▪) and controls (▪)*



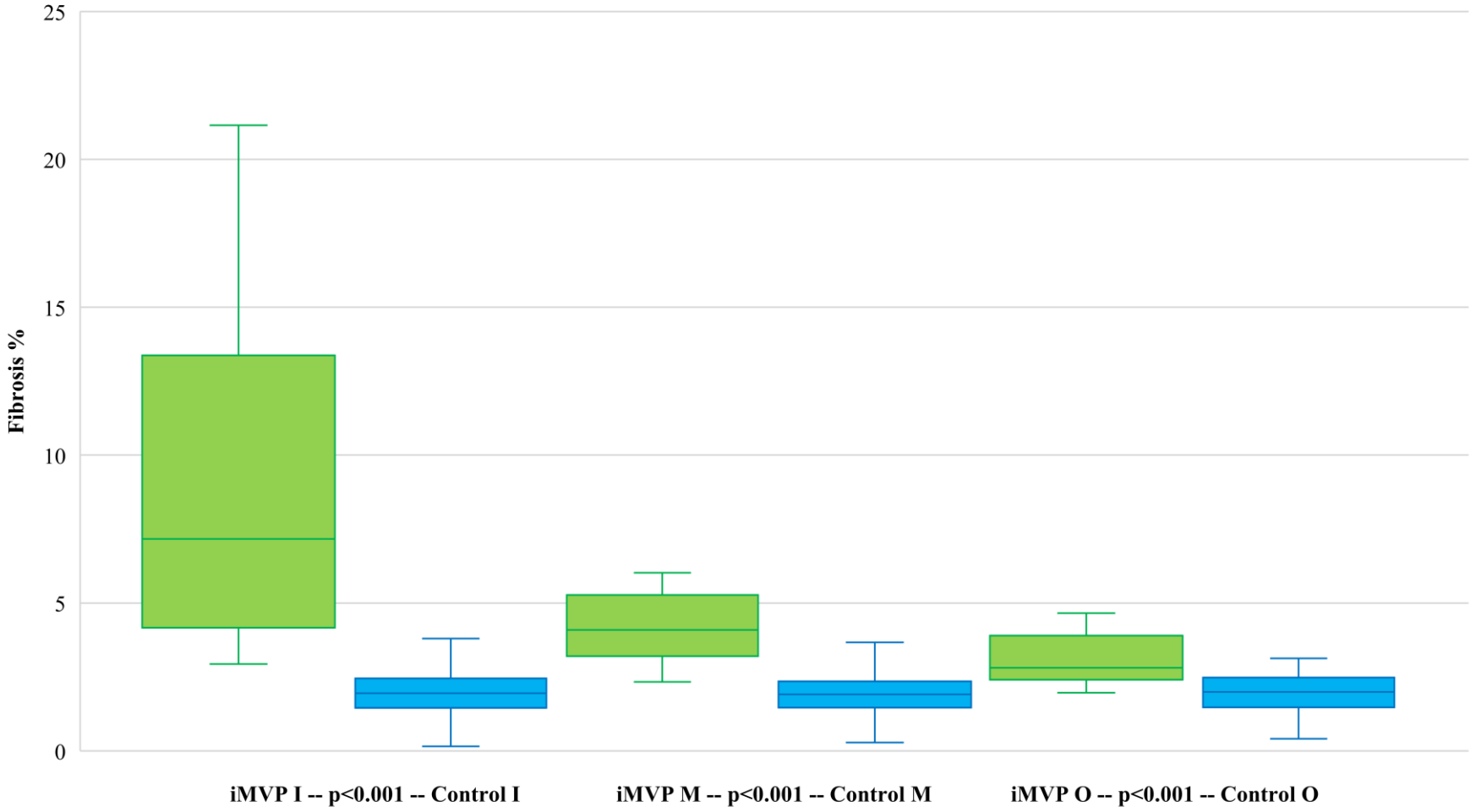
I, M, O indicates inner third, middle third and outer third of the ventricular wall respectively for both iMVP cases and controls.

4.9.3 *Lateral wall fibrosis for iMVP-SCD (▪) and controls (▪)*



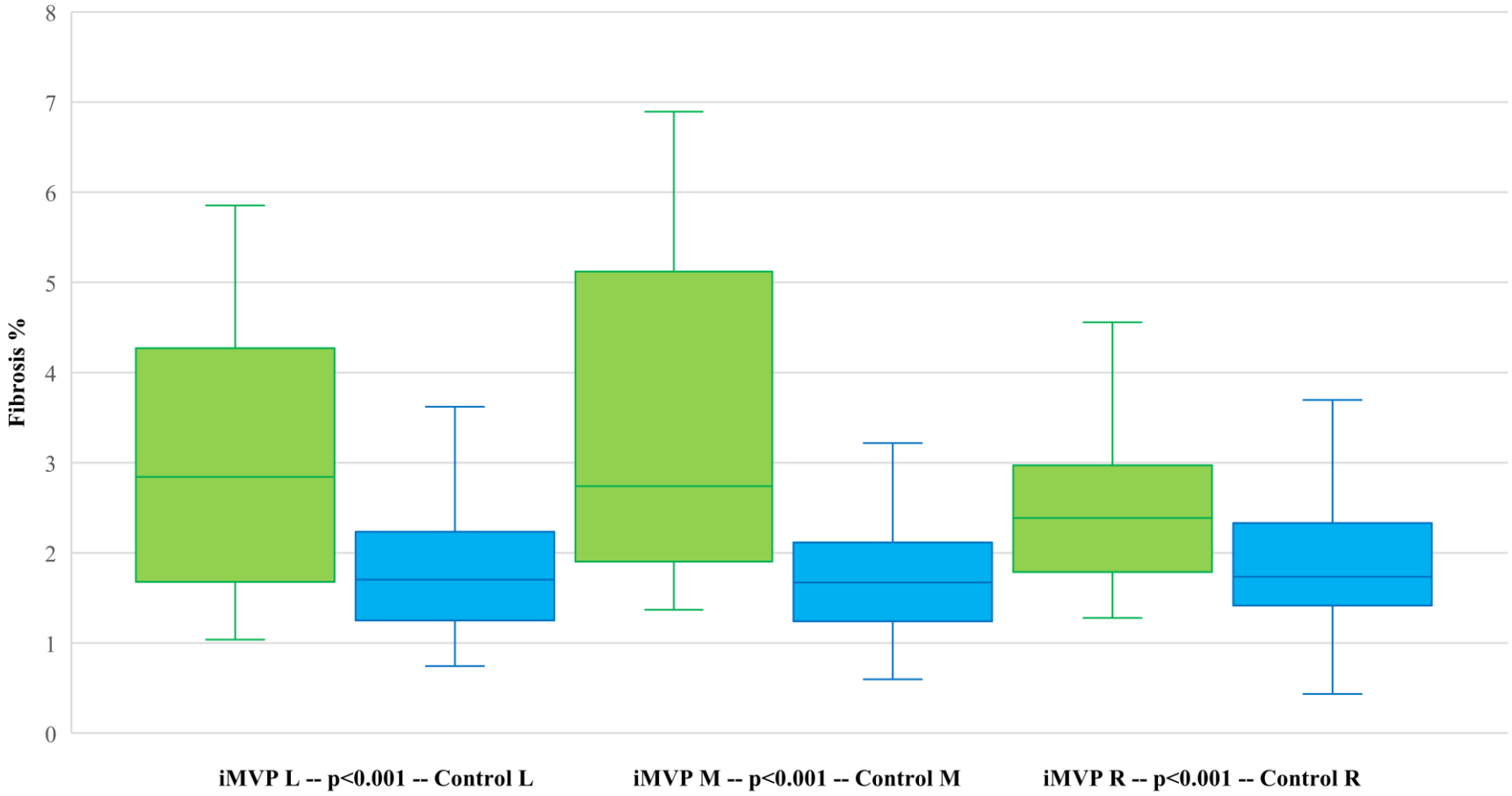
I, M, O indicates inner third, middle third and outer third of the ventricular wall respectively for both iMVP cases and controls.

4.9.4 *Posterior wall fibrosis for iMVP-SCD (▪) and controls (▪)*



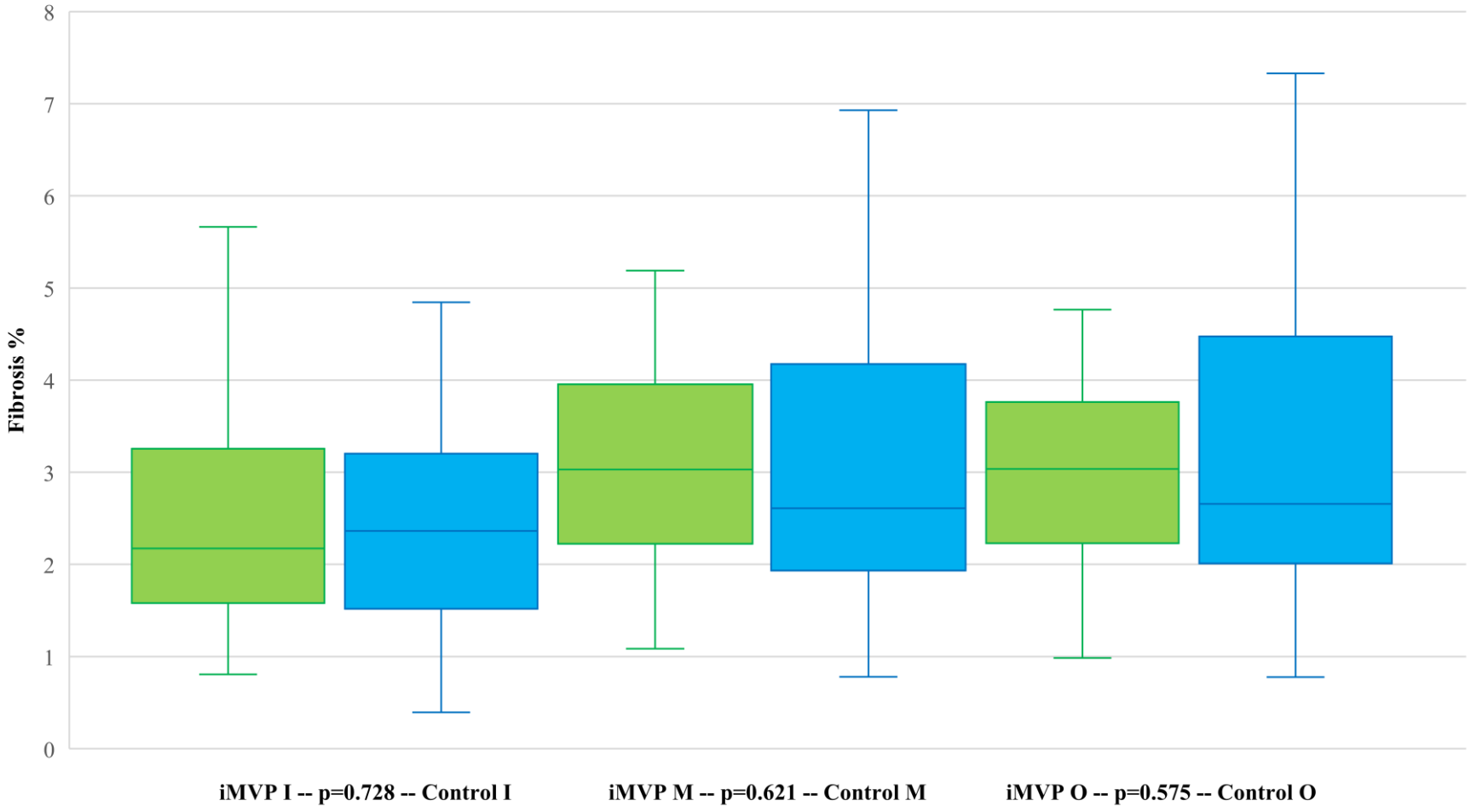
I, M, O indicates inner third, middle third and outer third respectively for both iMVP cases and controls.

4.9.5 *Interventricular septum fibrosis for iMVP-SCD (▪) and controls (▪)*



L, M, R indicates left ventricular third, middle third and right ventricular third of the interventricular septum respectively for both iMVP cases and controls.

4.9.6 *Right ventricular fibrosis for iMVP-SCD (▪) and controls (▪)*



I, M, O indicates inner third, middle third and outer third respectively for both iMVP cases and controls.

CHAPTER 5

Continuous Cardiac Rhythm Monitoring for Ventricular Arrhythmias in Mitral Valve Prolapse

5.1 Overview

Background: Recent evidence implicates the role of malignant ventricular arrhythmias (VAs) in the pathogenesis of sudden cardiac death in patients with mitral valve prolapse (MVP). This study aimed to compare the cumulative incidence and characteristics of VAs in patients with MVP and control cohorts using an implantable cardiac monitor (ICM). Subgroup analysis within the MVP group aimed to determine whether certain factors were associated with the development of VAs.

Methods: Patients undergoing diagnostic echocardiography at a tertiary institution diagnosed with MVP were prospectively recruited. Incidence and characteristics of VAs (defined as ventricular tachycardia ≥ 8 beats or ventricular fibrillation) detected on ICM were compared with 2 control cohorts – control low risk (Control-L) with absence of significant cardiovascular history; and control high risk (Control-H) with significant cardiovascular history (including coronary artery disease or cardiac surgery), abnormal echocardiogram (including left ventricular hypertrophy or reduced ejection fraction) or abnormal electrocardiogram (including Brugada pattern, long QT or early repolarization). Within the MVP group, comprehensive assessment with echocardiography, cardiac magnetic resonance imaging (MRI) for late gadolinium

enhancement (LGE), 24-hour Holter monitoring and signal average ECG was performed to determine potential predictors of VAs.

Results: Overall, 21 patients with MVP underwent ICM insertion compared with 75 Control-L and 49 Control-H patients. There were no significant differences between the MVP group and control groups with regards to age, gender and anti-arrhythmic use. Patients with MVP had a significantly higher cumulative incidence of VAs compared to both the Control-L (HR 7.1, 95%CI 2.6-19.2, p<0.001), and Control-H (HR 1.7, 95%CI 1.1-2.7, p=0.01) cohorts, compared using a Cox proportional-hazards model. Compared with the Control-L cohort, patients with MVP were more likely to experience overnight episodes of VAs. Within the MVP group, a higher proportion of those with VAs had LGE on CMR than those without VAs (78% vs 20%, p=0.02).

Conclusions: Patients with MVP have a significantly higher incidence of VAs compared with control cohorts. Presence of LGE on cardiac MRI is associated with the development of VAs in patients with MVP.

5.2 Introduction

Mitral valve prolapse (MVP) is characterised by the atrial displacement of the mitral valve leaflets during systole.[4] Reported complications of MVP include mitral regurgitation (MR) requiring mitral valve surgery, cerebrovascular events, infective endocarditis and sudden cardiac death (SCD).[1]

Recent evidence implicates the role of malignant ventricular arrhythmias (VAs) in patients with MVP who experience SCD.[7, 8, 278, 285] Evidence indicates that patients with

MVP have more premature ventricular complexes, complex VAs compared to control cohorts based on 24-hour Holter monitoring.[217] Furthermore, patients with MVP and a previous cardiac arrest are more likely to have recurrent VAs compared to other cardiac arrest survivors.[52] However, there is limited data regarding long term continuous cardiac rhythm monitoring for VAs in unselected patients with MVP.

In this study, we aimed to compare the incidence and characteristics of VA episodes detected on long term continuous cardiac rhythm monitoring through an insertable cardiac monitor (ICM) in patients with MVP and control groups. Additionally, within the MVP cohort, we investigate whether certain factors were associated with the development of VAs.

5.3 Methods

5.3.1 *Patient selection*

All patients undergoing diagnostic echocardiography at the Austin Hospital – a tertiary hospital in Melbourne, Australia – between May 2016 and May 2018 were prospectively screened for the presence of MVP. All patients who consented to ICM insertion for long-term cardiac rhythm monitoring were recruited.

Two control cohorts were obtained from the Austin Hospital ICM database. All patients with an ICM which was inserted and followed-up at Austin Hospital between January 2012 and December 2017 were included as controls. Due to a higher incidence of

cardiac arrhythmias in patients with structural heart disease,[295] the control cohorts were further stratified as low-risk controls (Control-L) or high-risk controls (Control-H). Patients with a history of coronary artery disease (acute coronary syndrome and/or coronary revascularization), previous cardiac surgery, significant left ventricular hypertrophy (≥15mm), reduced left ventricular ejection fraction (<50%) or abnormal baseline ECG (including Brugada pattern, long QT, early repolarization or QRS duration >120ms) were considered as Control-H. Patients without significant cardiovascular history and normal baseline ECG (including isolated atrial fibrillation and first degree heart block) were considered as Control-L.

Exclusion criteria were age <18 or >85 years and existing cardiovascular implantable electronic device for all groups.

Ethical approval for this study was granted by Austin Health Human Research Ethics Committee.

5.3.2 *Implantable cardiac monitor*

Continuous ambulatory ECG monitoring was performed using one of three ICM systems (either SJM Confirm, Abbott, Illinois, USA; or Reveal XT, Medtronic, Minnesota, USA; or Reveal Linq, Medtronic, Minnesota, USA) at the discretion of the implanting physician.

ICM insertion for patients at our institution involves a small incision (1-2cm depending on ICM system) in the 4th intercostal space in the left parasternal region. Adequate signal detection is confirmed prior to wound closure.

In addition to storing patient triggered events, ICM devices for patients were routinely set to automatically trigger for the following arrhythmic events:

- Tachycardia events (heart rate ≥ (210-age) for ≥ 8 beats)
- Atrial fibrillation (AF) based on R-R irregularity for ≥ 10 minutes
- Bradycardia events (heart rate ≤ 40 beats per minute for ≥ 4 beats)
- Ventricular standstill ≥ 4 seconds

Throughout the study period, ICM data was downloaded routinely 2 weeks after initial insertion and then at 3 monthly intervals by trained cardiac physiologists under the supervision of a cardiac electrophysiologist. Individual ICM episodes are all verified with significant arrhythmic events stored on an electronic database. Two cardiac electrophysiologists (H-C.H. and H.S.L) reviewed electrograms (EGMs) for all stored arrhythmic events for the MVP patients and both control groups.

The primary outcome was the incidence of VAs which was a composite of ventricular tachycardia (VT) defined as ≥ 8 beats of VT at ≥ 120 beats per minute or ventricular fibrillation (VF) over a 24-month period, compared between the MVP patients and the 2 control groups. For each individual episode of VA, the time of event (overnight episode defined as between 2300 and 0700 hours), morphology, duration, presence of preceding

premature ventricular complexes (within the previous 5 beats) and presence of short-long-short sequence (SLS) activation were documented.[296]

5.3.3 *Echocardiography and assessment of cardiac function*

For those with MVP, all patients underwent transthoracic echocardiogram (TTE) performed in the left decubitus position using commercially available ultrasound systems (either Vivid 9, General Electric Healthcare, Milwaukee, WI, USA; or iE33, Philips, Bothell, WA, USA). Echocardiography assessment of patients with MVP was provided by two echocardiography cardiologists (P.C. and H.S.) who were blinded to arrhythmia outcomes and consistent with published literature.[68, 88, 112, 297-299] The high reproducibility of echocardiographic parameters in our laboratory has been previously reported.[300]

5.3.4 *Electrocardiogram and signal averaged electrocardiogram*

For those with MVP, all patients underwent ECG and signal averaged ECG (SAECG) performed in the supine positions using a commercially available ECG system (MAC 5500, General Electric Healthcare, Milwaukee, WI, USA). SAECG was performed at a high pass filter setting of 40-250Hz with 400 beat target. Late potentials were present if 2 out of the 3 following criteria were met – total filtered QRS duration >114ms, low amplitude signal (< 40μV) duration > 38ms and root mean square voltage in terminal 40ms of QRS < 20 μV – consistent with published guidelines.[158]

For the control groups, all ECGs were individually reviewed by 2 cardiac electrophysiologists (H-C.H. and H.S.L.) to determine presence of Brugada pattern, prolonged QT, early repolarization or QRS duration >120ms prior to control group assignment.

5.3.5 *Holter analysis*

For those with MVP-ICM, 24-hour Holter monitoring was performed using the Digitrak XT (Koninklijke Philips N.V., Netherlands). All recordings were independently analysed by 2 cardiac electrophysiologists (H-C.H. and H.S.L.).

After obtaining a normal QRS complex, computational analysis was used to determine premature ventricular complex (PVC) burden (expressed as total PVCs per hour) while the longest run of NSVT was also recorded.

5.3.6 *Cardiac MRI*

In the MVP-ICM group, cardiac magnetic resonance (CMR) imaging was used to identify myocardial fibrosis. CMR was performed on a whole body 1.5-T scanner (Avanto; Siemens Healthcare, Erlangen, Germany) as previously described,[301] with a 6-channel body phased array coil anteriorly and spine coils posteriorly automatically selected by the system. Phase sensitive inversion recovery imaging was performed at 8 minutes after contrast administration administration (0.2mmol/kg gadoterate

meglumine, Dotarem, Guebert, Villepinte, France) to identify areas of late gadolinium enhancement indicating cardiac fibrosis. CMR analysis was performed by a cardiac radiologist (R.L.) who was blinded to the arrhythmia outcomes.

5.3.7 *Statistical analysis*

Continuous data are reported as means with standard deviations and medians with inter-quartile range as appropriate. The Shapiro-Wilk test was used to evaluate normality in continuous variables. The Student's t-test and Mann-Whitney U test were used to compare continuous variables where applicable. Categorical data are presented as absolute numerical figures with percentages. Fisher's exact test was used to compare categorical variables. Cumulative incidence curves were generated using the Kaplan Meier method and compared using the log-rank test. Patients were censored if they had early removal of their ICM, cardiac surgery or death (unrelated to arrhythmia) during the initial 24-month follow-up period. A 2-sided P value of <0.05 was considered significant. All data analyses were performed using SPSS Version 25 (IBM Corp., Armonk, NY).

5.4 Results

In total, 66 patients with MVP were identified and 21 underwent ICM insertion (40 patients declined ICM insertion [17 were female] and 5 had an existing cardiovascular implantable electronic device). Additionally, we identified 75 patients for the Control-L group and 49 patients for the Control-H group.

5.4.1 *Baseline characteristics*

Patients with MVP-ICM were similar to both control groups with respect to age and gender (Table 5.7.1). Approximately one-third of patients with MVP-ICM had a history of syncope which was significantly less compared to those in the Control HR group. All patients with MVP-ICM had a calculated left ventricular ejection fraction ≥ 50% and the majority (86%) of patients had bileaflet redundant MVP and non-severe mitral regurgitation. Those with MVP-ICM had a higher left ventricular end diastolic diameter compared to both control groups, likely reflecting the presence of associated mitral regurgitation. There were no significant differences between the MVP-ICM group and control groups with regards to use of anti-arrhythmic drugs.

Within the initial 24-month follow-up period, 1 patient with MVP-ICM had early ICM removal (patient preference), 2 patients with MVP-ICM underwent mitral valve surgery, and 1 patient in the control HR group died due to stroke.

5.4.2 *Ventricular arrhythmias*

Over 24-month follow-up, the MVP group had a significantly higher incidence of VAs (≥ 8 beats of VT) compared to both the Control-L (HR 7.1, 95%CI 2.6-19.2, p<0.001), and Control-H (HR 1.7, 95%CI 1.1-2.7, p=0.01) groups, Figure 5.8.1. No patients in the MVP or Control-L group experienced sustained VAs as defined by VT at ≥ 120 bpm lasting ≥ 30 seconds. There were 2 patients in the Control-H group with sustained VAs

– a 32-year-old man with Brugada syndrome and 5 minutes of VT followed by VF who self-reverted into sinus rhythm, and a 67-year-old man with left ventricular hypertrophy and 49 minutes of VT.

Characteristics of VAs for the groups are shown in Table 5.7.2. Notably, patients with MVP had more overnight episodes of VAs compared to the Control-L group (p=0.02). There were no significant differences between the groups with regards to proportion with polymorphic VT or VF, proportion with a preceding PVC or SLS sequence related VAs.

Within the MVP group, 11 patients had NSVT while 10 did not have any NSVT during the study period (Table 5.7.3). There were no significant differences between the groups with regards to age, gender, symptoms, echocardiogram parameters, infero-lateral T-wave changes, late potentials on SAECG or 24-hour Holter findings. Notably however, a higher proportion of those with NSVT had LGE on CMR than those without NSVT (78% vs 20%, p=0.02).

5.4.3 *Other arrhythmias*

Cumulative incidence of atrial fibrillation, supraventricular tachycardia and bradycardic events are shown in the data supplement (see Supplemental Results and Figure 5.9.2-5.9.4).

5.5 Discussion

While MVP has been strongly linked to sudden cardiac death due to malignant VAs,[7, 8, 278] there is limited information regarding continuous cardiac rhythm monitoring in this group of patients. Key findings from this study are:

1. Patients with MVP experienced significantly higher rates of VAs compared to control cohorts;
2. Patients with MVP and VT had higher rates of late gadolinium enhancement compared to patients with MVP and no VT.

This study demonstrates that patients with MVP have a significantly higher incidence of VAs on continuous cardiac rhythm monitoring compared to control cohorts. Previous work investigating VAs in patients with MVP has accepted VT ≥3 beats as the outcome measure or included a highly selected population with secondary prevention ICDs.[9, 52] In a cohort of unselected patients, we defined VA episodes as VT ≥8 beats which has been shown to be incrementally predictive of adverse outcomes.[148] Importantly, we found a significantly increased incidence of VAs in patients with MVP compared to 2 control cohorts including those deemed to be at high risk of arrhythmic outcomes. Of note, the majority of these patients had bileaflet redundant MVP, which is suggested to carry greater risk of malignant VAs.[52]

Other findings in this study give rise to possible mechanistic insights into VA development in patients with MVP. Patients with MVP experienced significantly more nocturnal episodes compared to the Control-L cohort. This suggests that episodes of VT

within the MVP population are not necessarily related to adrenergic drive supporting our previous finding that a significant proportion of sudden cardiac death events in MVP occurred during restful activity.[285]

Additionally, myocardial fibrosis may provide the necessary substrate for re-entry. Histopathological studies have demonstrated increased left ventricular fibrosis in patient with MVP.[9, 285] In living patients with MVP, LGE has been shown to correlate with PVCs and NSVT of ≥ 3 beats on 24-hour Holter monitoring.[9, 89] However, this is the first study to associate the presence of LGE with NSVT of ≥ 8 beats in patients with MVP. Coupled with previous findings documenting cardiac arrest due to VF in patients with MVP,[52, 285] PVC induced VT degenerating into VF may provide a plausible electrophysiological sequence in patients with MVP and sudden death.

Certain negative findings from our study should be noted. Despite previous reports,[278] female gender, leaflet length and thickness, mitral regurgitation, mitral annular disjunction, infero-lateral T-wave changes on ECG and late potentials on SAECG were not significantly associated with VT in our MVP cohort.

5.5.1 *Limitations*

We acknowledge certain limitations in our study. MVP patients were recruited and monitored prospectively, while information for control cohorts were retrieved from a database raising the possibility of episode under-recognition. However, overall

incidence of VT and other arrhythmic events in our control groups were similar to previous reports.[154, 155, 295] Some patients with MVP declined ICM insertion raising the possibility of self-selection bias within the recruited cohort, although the incidence of VT was still higher than a traditional high-risk control cohort. Given the relatively small study cohort, our ability to provide detailed comment on our negative findings is limited including the possibility for type II errors. No patients in the MVP cohort had sustained VAs or sudden death. Nevertheless, our findings provide important incremental knowledge about the nature of VAs in patients with MVP. Based on our findings, larger scale studies of continuous cardiac rhythm monitoring in patients with MVP would be important.

5.6 Conclusion

Patients with MVP have a significantly higher incidence of NSVT detected with long term continuous cardiac rhythm monitoring compared with control cohorts. Within the MVP cohort, presence of LGE on cardiac MRI was associated with the development of VT.

5.7 Tables

5.7.1 *Baseline demographics*

	MVP n=21	Control LR n=75	p-value*	Control HR n=49	p-value*
Age	67 (60-71)	61 (47-73)	0.29	67 (54-77)	0.71
Female gender	12 (57%)	32 (43%)	0.32	23 (47%)	0.60
Clinical Indication					
Syncope	8 (38%)	43 (57%)	0.14	35 (71%)	0.01
Pre-syncope		5 (7%)		5 (10%)	
Palpitations		17 (23%)		2 (4%)	
Cryptogenic stroke		8 (11%)		5 (10%)	
Monitor atrial fibrillation burden		2 (3%)			
Brugada pattern ECG				2 (4%)	
Echocardiogram					
Normal	0	75 (100%)		28 (57%)	
Abnormal	21 (100%)†	0		21 (43%)‡	
LVEF (%)	60 (55-67)	63 (60-69)	0.13	50 (46-63)	0.03
LVEDD (mm)	53 (50-60)	46 (43-53)	<0.001	47 (43-53)	0.0002
IVST (mm)	10 (9-12)	10 (9-12)	0.73	11 (9-13)	0.06
PWT (mm)	9 (9-10)	9 (8-10)	0.81	10 (9-11)	0.046
ECG					
Normal	21 (100%)§	75 (100%)‖		17 (35%)	
Abnormal	0	0		32 (65%)#	
Cardiovascular history					
Cardiac surgery	0	0	1.0	10 (20%)**	0.03
Coronary stent	1 (5%)	0	0.22	6 (12%)	0.67
Atrial fibrillation	2 (10%)	7 (9%)	1.0	6 (12%)	1.0
Stroke	2 (10%)	9 (12%)	1.0	6 (12%)	1.0
Hypertension	2 (10%)	36 (48%)	0.002	22 (45%)	0.005
Dyslipidaemia	10 (48%)	19 (25%)	0.06	18 (37%)	0.43
Diabetes	0	4 (5%)	0.57	12 (24%)	0.01
Anti-arrhythmic drugs					
Beta-blockers	7 (33%)	15 (20%)	0.24	16 (33%)	1.0
Verapamil/diltiazem	1 (5%)	1 (1%)	0.39	1 (2%)	0.51
Amiodarone	1 (5%)	1 (1%)	0.39	1 (2%)	0.51

IVST, inter-ventricular septum thickness; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness

*Compared to MVP cases

†All patients had MVP; other significant findings included severe mitral regurgitation (3)

‡Echocardiogram abnormalities include valve surgery (3), left ventricular non-compaction (2), dilated cardiomyopathy (6), left ventricular hypertrophy ≥ 15mm (8), hypertrophic cardiomyopathy (2), segmental left ventricular dysfunction (5) and severe pulmonary hypertension (1)

§Includes atrial fibrillation (1) and inferolateral T-wave changes (6)

‖Includes isolated first degree heart block (4) and atrial fibrillation (3)

#Includes left bundle branch block (9), right bundle branch block (6), intraventricular conduction defect (2), Brugada (7), long QT (3), early repolarisation (2) and left ventricular hypertrophy with strain (3)

**Includes coronary artery bypass graft (6), aortic valve replacement (3) and aortic arch repair (1)

5.7.2 *Ventricular arrhythmia characteristics*

	MVP 15 episodes	**Control LR 13 episodes**	**p-value***	**Control HR 14 episodes**	**p-value***
Patients	11/21 (52%)	8/75 (11%)	<0.001	9/49 (18%)	0.008
Age	64 (56-72)	65 (51-74)	1.0	66 (54-75)	0.71
Female	5 (45%)	6 (75%)	0.35	4 (44%)	1.0
Syncope history	5 (45%)	5 (63%)	0.65	7 (78%)	0.20
Preceding RR interval (ms)	850 (570-960)	700 (585-805)	0.37	750 (570-840)	0.61
Overnight episode	6 (40%)	0	0.02	2 (22%)	0.21
Arrhythmia type					
NSVT	15 (100%)	13 (100%)	1.0	12 (86%)	0.22
Monomorphic	13 (87%)	13 (100%)	0.48	10 (83%)	1.0
Polymorphic	2 (13%)	0	0.48	2 (17%)	1.0
Sustained VT	0	0	1.0	1 (7%)	1.0
VF	0	0	1.0	1 (7%)	1.0
Preceding PVC	5 (33%)	3 (23%)	0.69	4 (29%)	1.0
SLS sequence	4 (27%)	1 (8%)	0.33	0	0.10

NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex; SLS, short long short; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Compared to MVP cases

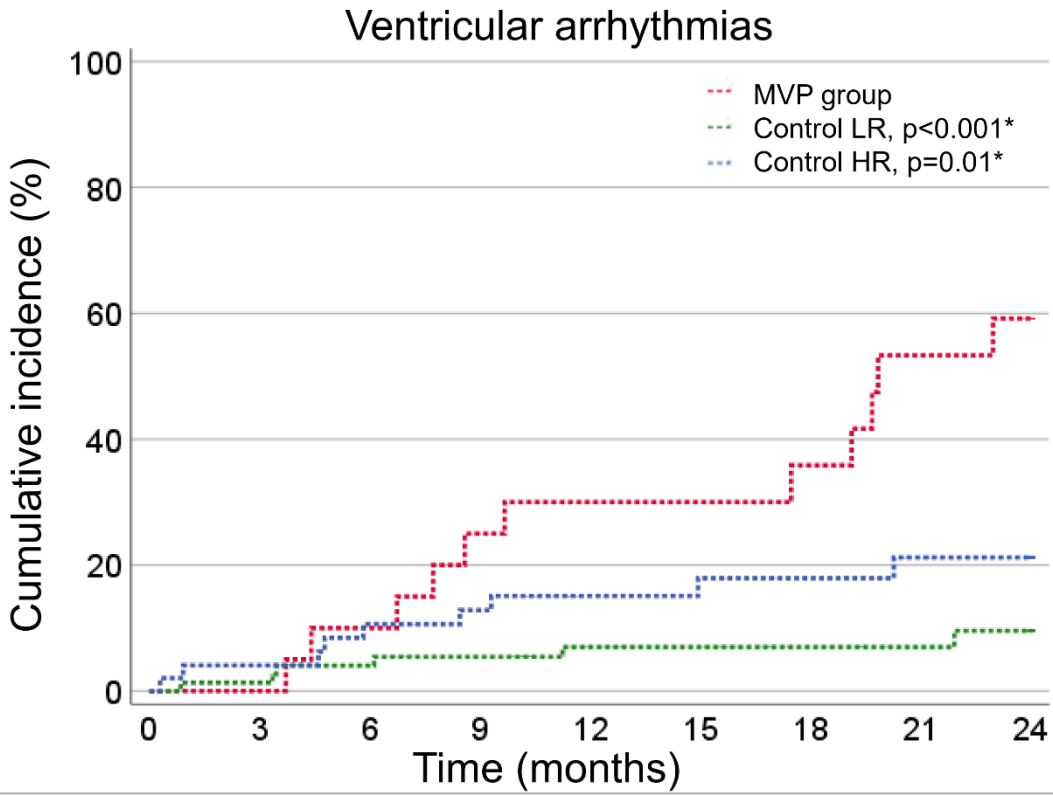
5.7.3 *Characteristics of MVP patients with and without VT*

	MVP with VT (n=11)	**MVP no VT (n=10)**	**p-value**
Age	64 (56-72)	69 (63-71)	0.31
Female gender	5 (45%)	7 (70%)	0.39
Syncope	5 (45%)	2 (20%)	0.36
Palpitations	9 (82%)	6 (60%)	0.36
Echocardiogram parameters			
Ejection fraction	60 (55-66)	60 (54-69)	0.92
End diastolic diameter	53 (51-55)	53 (48-57)	0.57
Bileaflet redundant	9 (82%)	9 (90%)	1.0
Anterior leaflet length	26 (25-32)	29 (27-35)	0.26
Anterior leaflet thickness	56 (52-69)	57 (53-72)	0.78
Posterior leaflet length	18 (17-21)	20 (14-22)	0.86
Posterior leaflet thickness	55 (54-68)	57 (45-75)	0.78
Mitral annular disjunction	3 (27%)	1 (10%)	0.60
Mitral regurgitation			
Mild	4 (36%)	5 (50%)	0.44
Moderate	7 (64%)	2 (20%)	
Severe	0	3 (30%)	
ECG			
Infero-lateral T-wave changes	3 (27%)	3 (30%)	1.0
SAECG			
QRSd > 114ms	8	3	0.09
Low amplitude signal duration > 38ms	5	4	1.0
Terminal 40ms RMS < 20μV	6	3	0.39
Overall late potentials	5	3	0.66
Late gadolinium enhancement	7/9 (78%)*	2/10 (20%)†	0.02
24-hour Holter monitor			
PVC/hr	95 (2-372)	17 (7-230)	0.83
≥ 3 beats NSVT	3 (27%)	4 (40%)	0.66

*Areas include basal antero-septal, septal, infero-septal, inferior and infero-lateral
†Areas include basal inferior and mid-wall infero-lateral

5.8 Figures

5.8.1 *Cumulative incidence of ventricular arrhythmias*



At risk									
MVP	21	20	18	15	14	14	11	8	7
Control LR	75	74	70	66	56	51	41	36	34
Control HR	49	47	41	39	31	28	26	22	19

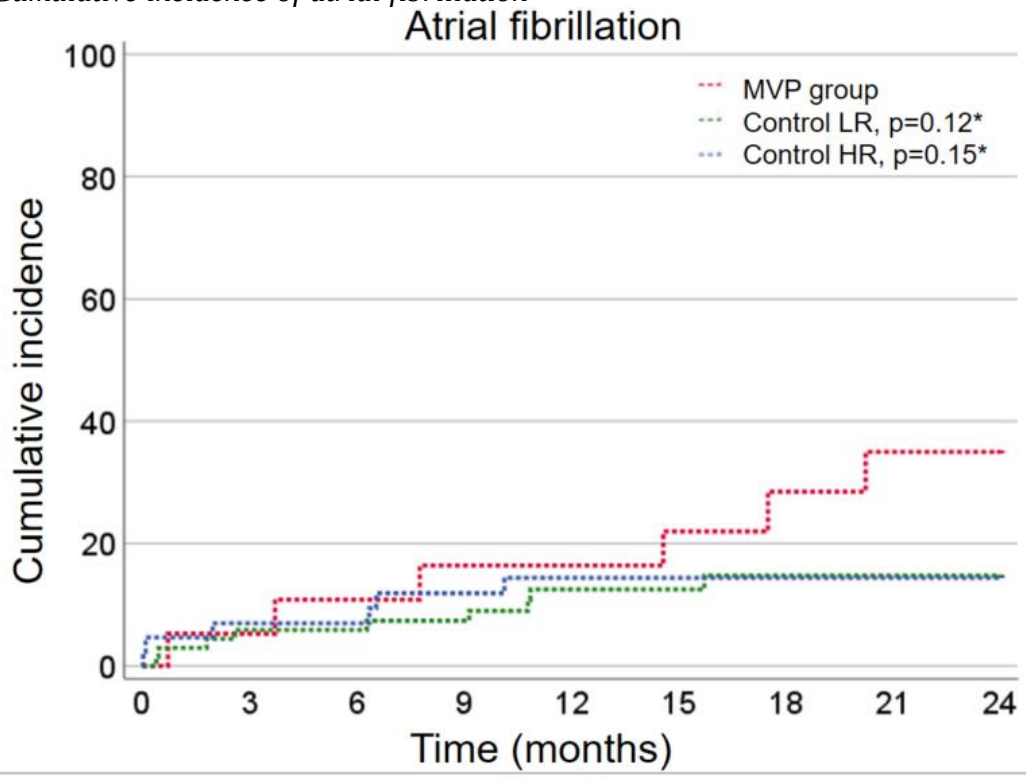
*Compared with MVP group using log-rank test

5.9 Supplemental Materials

5.9.1 *Other arrhythmias*

Compared with the control LR group, patients with MVP had non-significant differences in newly diagnosed AF, SVT and bradycardic events, Figure 5.9.2-5.9.4. Compared with the control HR group, patients with MVP had non-significant differences in newly diagnosed AF and SVT but significantly less bradycardic events (p=0.02). Within the MVP group, 4 patients commenced anticoagulation for newly diagnosed AF and no patients experienced a cerebral embolic event during follow-up. Overall, 1 (5%) patient in the MVP cohort, 5 (7%) patients in the control LR cohort and 8 (16%) patients in the control HR cohort received a permanent pacemaker during the study period.

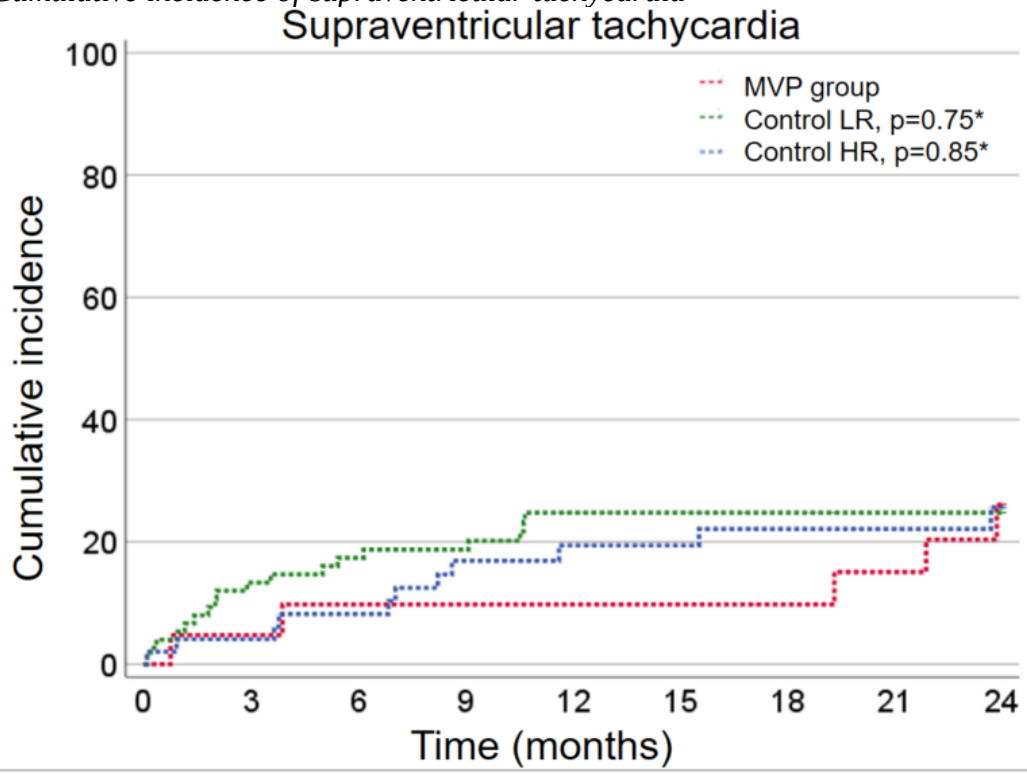
5.9.2 *Cumulative incidence of atrial fibrillation*



At risk									
MVP	19	17	16	15	15	14	11	10	10
Control LR	68	64	63	57	46	41	33	28	26
Control HR	43	40	38	35	30	30	28	26	22

*Compared with MVP group using log-rank test

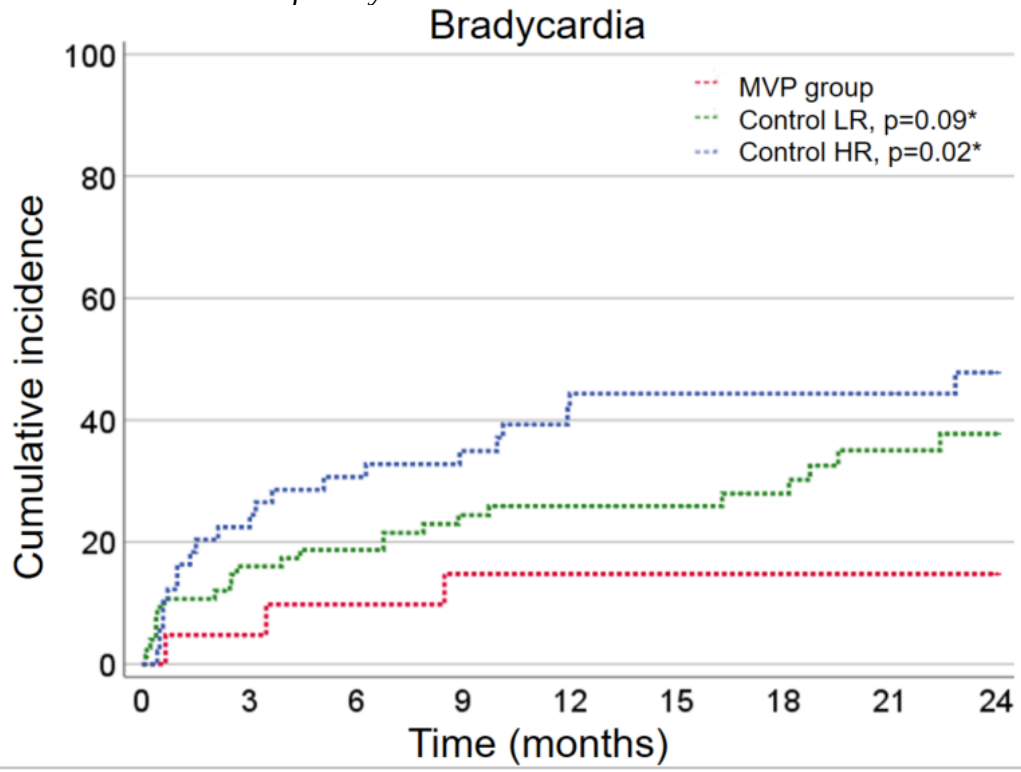
5.9.3 *Cumulative incidence of supraventricular tachycardia*



At risk									
MVP	21	19	18	18	18	18	17	16	14
Control LR	75	65	61	57	46	42	35	29	26
Control HR	49	47	43	37	32	30	27	24	20

*Compared with MVP group using log-rank test

5.9.4 *Cumulative incidence of bradycardia*



At risk									
MVP	21	19	18	17	17	17	15	15	14
Control LR	75	63	60	51	44	39	32	25	22
Control HR	49	38	33	30	23	21	19	18	13

*Compared with MVP group using log-rank test

CHAPTER 6

Bileaflet redundant mitral valve prolapse and ventricular arrhythmias – effects of mitral regurgitation and mitral valve surgery

6.1 Overview

Background: In a high-risk cohort of patients with bileaflet redundant mitral valve prolapse (BiRMVP), the potential relationship between mitral regurgitation (MR) severity and ventricular arrhythmia (VAs) development requires clarification. Furthermore, whether amelioration of MR through mitral valve (MV) surgery improves VA burden in an unselected group of patients requires prospective evaluation.

Methods: Patients undergoing echocardiography were screened for the presence of bileaflet (≥2mm atrial displacement of both MV leaflets) redundant (≥5mm thickness of either or both MV leaflets) MVP. Degree of MR was assessed according to American Society of Echocardiography guidelines. Presence of mitral annular disjunction (MAD) and late gadolinium enhancement (LGE) was assessed using echocardiography and cardiac magnetic resonance (CMR) respectively. Premature ventricular complex (PVC) burden and VA complexity was assessed using 24-hour Holter monitoring. Additionally, patients who were referred for MV surgery for MVP were also recruited and underwent Holter monitoring pre-operatively and post-operatively.

Results: In total, 44 patients with BiRMVP were recruited and stratified according to degree of MR (mild n=15, moderate n=15, severe n=14). There were no differences in

baseline characteristics of age, sex, ejection fraction, ventricular wall thickness and pulmonary artery pressure between the 3 groups of MR severity. Those with moderate or severe MR had a higher left ventricular end diastolic diameter compared to those with mild MR. Presence of MAD and LGE was also similar between groups. There were no significant differences between the 3 groups in terms of PVC burden (0.3% [IQR, 0.08-11.1%] vs. 0.5% [IQR, 0.1-9.4%] vs. 0.4% [IQR, 0.02-2.3%] for mild, moderate and severe MR respectively, p=0.84) or Lown grade ≥4 complex VAs (60% vs. 73% vs. 71% for mild, moderate and severe MR respectively, p=0.70). Surgical correction of MR did not improve PVC burden (0.4% [IQR, 0.02-2.2%] vs. 0.7% [0.03-2.0%] for pre-operative and post-operative respectively, p=0.33) in the overall cohort. **Conclusions:** Our findings indicate that severity of MR does not affect VA burden or complexity in patients with BiRMVP. Additionally, surgical correction of MR does not affect VA burden or complexity in an unselected cohort of patients with MVP.

6.2 Introduction

Mitral valve prolapse (MVP) is a condition characterised by ventricular displacement of the mitral valve (MV) leaflet(s) during systole. The estimated prevalence of MVP is 2.4%, while redundant leaflet MVP (defined by leaflet thickening ≥5mm on echocardiography) is 1.3%.[4] Reported complications include mitral regurgitation (MR) requiring surgery, stroke, endocarditis, ventricular arrhythmias (VAs) and sudden death.[5, 302]

Currently, the presence of redundant leaflet MVP is the only independent predictor of sudden death events,[5, 278] while bileaflet redundant MVP (BiRMVP) has been found as an independent risk factor for cardiac arrest in patients with MVP.[52] Within this group of higher risk patients, the importance of MR requires clarification. There are conflicting reports regarding the relationship of MR with regards to ventricular arrhythmias (VAs) in patients with MVP.[122, 124, 125, 278, 285] Furthermore, while case reports have indicated reduced VA burden in MVP patients post cardiac surgery,[189, 208, 238-240, 303] there is limited prospective data for this cohort.[278]

In this study, we sought to describe the effects of MR with regards to VAs in patients with BiRMVP. Additionally, we prospectively evaluated the effect of MV surgery with respect to VAs in patients with BiRMVP.

6.3 Methods

6.3.1 *Patient selection*

The Austin Hospital is a tertiary referral hospital in Melbourne, Australia. To assess the impact of MR severity on VAs, all patients undergoing diagnostic echocardiography at Austin Hospital between May 2016 and December 2017 were screened for inclusion.

To assess the impact of MV surgery on VAs, all patients undergoing MV surgery for MVP at Austin Hospital between May 2016 and May 2019 were screened for inclusion.

6.3.2 *Ethical approval*

Ethical approval for this study was granted by Austin Health Human Research Ethics Committee (HREC/Austin/15/322).

6.3.3 *Echocardiography*

All transthoracic echocardiogram (TTE) were performed in the left decubitus position using commercially available ultrasound systems (either Vivid 9, General Electric Healthcare, Milwaukee, WI, USA; or iE33, Philips, Bothell, WA, USA).

Presence of BiRMVP was assessed on 2-D echocardiography which involved the atrial displacement of both MV leaflets ≥2mm during systole in the parasternal long axis (PLAX) view.[68] Leaflet thickness was also obtained in end-diastole in the PLAX view. This was measured from the leading edge to the trailing edge of the thickest area in the mid-portion of the leaflet.[4] Included patients were required to have prolapse of both mitral leaflets with thickening ≥5mm in one or both leaflets. Two echocardiography cardiologists (H.S. and P.C.), who were blinded to the arrhythmia outcomes, assessed patients for inclusion and provided quantification of MR based on current American Society of Echocardiography guidelines.[298]

Additional echocardiographic measurements included Simpson's biplane left ventricular ejection fraction (LVEF), left-ventricular end-diastolic diameter (LVEDD), intraventricular septum thickness, posterior wall thickness, right ventricular systolic

pressure and mitral annular disjunction (MAD) defined as the separation of the left atrial wall-MV junction and the top of the left ventricle wall in the PLAX view.[88] The high reproducibility of echocardiographic parameters in our laboratory has been previously reported.[300]

6.3.4 *Holter analysis*

24-hour Holter monitoring was performed using the Digitrak XT (Koninklijke Philips N.V., Netherlands) system. All recordings were independently analysed by 2 electrophysiology cardiologists (H-C.H. and H.S.L.).

After obtaining a normal QRS complex, computational analysis was used to determine premature ventricular complex (PVC) burden (expressed as 100 x total PVCs/total heartbeats) and PVC complexity categorised using Lown grading classification.[145]

For the MV surgery cohort, Holter monitoring was performed approximately 6 weeks pre-operatively and 3 months post-operatively.

6.3.5 *Cardiac surgery*

During the study period, 4 cardiac surgeons (G.M., S.M., P.H., and N.R.) were responsible for the procedures in our cohort of patients. Where possible, the MV was repaired by excision of excess leaflet tissue, closure of clefts and annuloplasty ring insertion. In cases where MV repair was not possible, MV replacement was performed.

All patients who were referred for surgical correction of BiRMVP related MR were recruited. In addition, those undergoing surgery for redundant single leaflet MVP and non-redundant leaflet MVP were included as supplemental cases.

6.3.6 *Cardiac MRI*

Cardiac magnetic resonance (CMR) was performed on a whole body 1.5-T scanner (Avanto; Siemens Healthcare, Erlangen, Germany) as previously described,[301] with a 6-channel body phased array coil anteriorly and spine coils posteriorly automatically selected by the system. Modified Look-Locker inversion recovery (MOLLI) T1 mapping acquisition was performed in the short axis plane in the mid-ventricular level, with breath holding at end-expiration, prior to and 15 minutes after contrast administration (0.2mmol/kg gadoterate meglumine, Dotarem, Guebert, Villepinte, France), with subsequent calculation of extracellular volume.[304] Phase sensitive inversion recovery imaging was performed at approximately 8 minutes after contrast administration to identify areas of late gadolinium enhancement (LGE) indicating cardiac fibrosis. CMR analysis was performed by a cardiac radiologist (R.P.L.) who was blinded to the arrhythmia outcomes.

6.3.7 *Statistical analysis*

Continuous data are reported as means with standard deviations and medians with inter-quartile range. The Shapiro-Wilk test was used to evaluate normality in continuous

variables. The Student's t-test and one-way analysis of variance were used to compare parametric continuous variables, while the Mann-Whitney U and the Kruskal-Wallis tests were used to compare non-parametric continuous variables where applicable. Categorical data are presented as absolute numerical figures with percentages. Fisher's exact test was used to compare categorical variables. Matched samples were compared using the Wilcoxon sign-rank test and McNemar's test as indicated. A 2-sided P value of <0.05 was considered significant. All data analyses were performed using SPSS Version 24 (IBM Corp., Armonk, NY).

6.4 Results

6.4.1 *Mitral regurgitation and ventricular arrhythmias*

Baseline characteristics are shown in Table 6.7.1.

For the 3 groups of MR severity (mild, moderate and severe), there were no significant differences in age, sex, medical history and medications. Of note, there were no patients taking amiodarone. LVEDD was lower in patients with mild MR compared to those with moderate and severe MR (51mm vs. 55mm vs. 56mm, p=0.003). Other echocardiography parameters were not significantly different between the groups as were the of presence of MAD (60% vs. 47% vs 21% for mild, moderate and severe MR respectively, p=0.11) and focal LGE (33% vs. 64% vs. 54% for mild, moderate and severe MR respectively, p=0.28). Values from T1 mapping and extra-cellular volume calculations were also not significantly different between the groups.

Salient findings from 24-hour Holter monitoring are shown in Figure 6.8.1. There were no significant differences between the 3 groups in terms of PVC burden (0.3% vs. 0.5% vs. 0.4% for mild, moderate and severe MR respectively, p=0.84) or Lown grade ≥4 complex ventricular arrhythmias (60% vs. 73% vs. 71% for mild, moderate and severe MR respectively, p=0.70).

6.4.2 *Effect of cardiac surgery on ventricular arrhythmias*

During the study period, 14 patients with BiRMVP underwent MV surgery (Table 6.7.2). All patients undergoing MV repair (n=12) also had annuloplasty ring insertion. Overall, there was no significant difference in PVC burden (0.4% [IQR, 0.02-2.2%] vs. 0.7% [0.03-2.0%] for pre-operative and post-operative respectively, p=0.33) or complex VAs (p=1.0) between pre-operative and post-operative Holter monitoring (Figure 6.8.2). Within this cohort, subgroup analysis of change in PVC burden and complex VAs for those with and without LGE and MAD are shown in Table 6.7.3. Of note, in BiRMVP patients with evidence of LGE, there was an overall increase in PVC burden (0.2% [IQR, 0.02-1.4%] vs. 0.8% [IQR, 0.09-3.3%] for pre-operative and post-operative burden respectively, p=0.03) after MV surgery.

One patient with BiRMVP experienced a significantly improved PVC burden post-operatively while one patient had significantly increased PVC burden post-operatively (both detailed below).

An additional 9 patients with non-BiRMVP also underwent MV surgery during the study period (Table 6.9.1). Similarly, there was no difference in PVC burden or complex VAs between pre-operative and post-operative Holter monitoring.

6.4.3 *Significant change in PVC burden post cardiac surgery*

A 46-year-old female had significantly reduced PVC burden post MV repair (Table 6.7.2). Two pre-operative Holter recordings (12 months apart) showed PVC burdens of 15.2% and 10.6% respectively, with a 12-lead ECG showing ventricular bigeminy with alternating PVC morphologies (Figure 6.8.3) likely originating from the papillary muscles or mitral annulus. Echocardiogram showed LVEDD 53mm, LVEF 55%, BiRMVP, moderate MR and MAD (Figure 6.8.4). Two pre-operative CMR scans (12 months apart at 2 centers) specifically excluded LGE. At surgery, both MV leaflets were myxomatous with an unstable annulus; intervention involved triangular resection of P2, P2/P3 cleft closure and annuloplasty ring (36mm) insertion. Post-operative echocardiogram showed satisfactory MV repair without MAD (Figure 6.8.4). Holter monitoring showed PVC burden of 0.03%.

A 74-year-old male had significantly increased PVC burden post MV repair (Table 6.7.3). Pre-operative Holter recording showed a PVC burden of 2.18%. Echocardiogram showed LVEDD 6.1cm, LVEF 50%, severe MR and MAD. Pre-operative CMR demonstrated mid-inferolateral segment mid-myocardial/subepicardial LGE. At surgery, both MV leaflets were myxomatous with an unstable annulus; intervention involved bileaflet delamination and annuloplasty ring (40mm) insertion. Post-operative

echocardiogram showed satisfactory MV repair without MAD but LVEF 32%. Holter monitoring showed PVC burden of 12.3%.

6.5 Discussion

This study investigated the relationship between degree of MR and VAs in patients with BiRMVP and prospectively investigated the potential role of MV surgery in reducing VA burden. Our key findings include:

1. In patients with BiRMVP, severity of MR does not affect degree of VAs
2. MV surgery does not have an effect on VAs in unselected patients with MVP
3. The role of MV surgery in reducing VA burden in selected patients with MVP warrants further investigation

The role of MR with regards to VAs in patients with BiRMVP requires clarification. Previous studies have found that the significant MR was a predictor for VAs in patients with MVP,[122, 124] and that conservatively managed flail MR was predictive for sudden death although the mechanism of death may have been related to hemodynamic decompensation.[126] Conversely, other studies have suggested that MVP rather than MR severity was associated with the development of VAs and sudden cardiac death.[9, 118, 125, 278, 285] Importantly however, our current study focused specifically on patients with BiRMVP, who are a subset of patients deemed to be potentially at higher risk of malignant VAs.[52] We did not find any significant differences with MR severity and VAs in patients with BiRMVP in terms of PVC burden and complex VAs. This included both cases of de-novo MVP and MVP pre and post MV surgery. We determine

that within this higher risk cohort, the degree of MR does not affect the burden or degree of VAs.

This study also sought to resolve the potential role of MV surgery for the reduction of VAs in patients with MVP.[278] The current evidence is predominantly centered on case reports describing generally improved VA burden post MV surgery,[189, 208, 238-240, 303] attributable in part to improved mitral annular stability.[189, 208, 238, 239, 303] Nevertheless, malignant VAs may persist in some patients even after MV surgery.[240] To our knowledge, this is the first prospective study to systematically investigate the effect of MV surgery on VAs in patients with MVP. We found that MV surgery had no effect on VAs in this unselected group of patients with MVP. These findings are in keeping with a previous retrospective study indicating that MV surgery does not affect VA burden in an unselected group of patients with BiRMVP,[247] providing further evidence that the degree of MR has minimal impact on VAs in patients with BiRMVP.

Interestingly, in our patients with BiRMVP and LGE on CMR, there was an overall increase in PVC burden post-operatively. This suggests that identifiable left ventricular substrate abnormalities in patients with BiRMVP may trigger VAs and not necessarily be reversed with surgical intervention. This potential insight into the pathogenesis of VAs in BiRMVP is further supported by our two patients with significant changes in PVC burden post MV surgery – one significantly reduced whereas another significantly increased. Both patients had BiRMVP with MAD and previous reports have indicated that these abnormalities may contribute to VAs.[52, 88, 118, 120, 282] We hypothesise that the amelioration of MAD and improved mitral annulus stability in the 46-year-old female

patient was relevant in the improvement of her PVC burden, especially given that her PVCs were likely originating from the papillary muscles and/or mitral annulus.[305] However, our findings suggest that these factors may only partially account for the development of VAs. Patients with co-existent LGE on CMR and possibly reduced left ventricular function, as evident in the 74-year-old male, may have additional substrate for VAs which may not be reversed with MV surgery indicating the potential role for early intervention. The aforementioned retrospective study found that VA burden was improved in a younger surgical cohort, with the authors postulating that early amelioration against the development of arrhythmogenic substrate may be important.[247] Findings in our patients lend support to this theory, although larger prospective studies investigating the effects of MV surgery in patients with BiRMVP with a specific focus on LGE and MAD are required.

6.5.1 *Limitations*

We acknowledge certain limitations in this study. Findings from our study are applicable only to patients with BiRMVP, although this appears to be the population most at risk for adverse events.[5, 52] A lack of association between MV surgery with VAs may be due to the generally low overall VA burden in the surgical group or limited patient numbers. However, this cohort represents the largest collection of prospectively evaluated and unselected cases of MVP undergoing MV surgery. We are also unable to determine potential differences between mitral valve repair and replacement. Additionally, while MR severity does not appear to be related to VAs in patients with

BiRMVP, the complex interplay between LGE, MAD and left ventricular decompensation with regards to VAs requires clarification.

6.6 Conclusion

Our findings indicate that severity of MR does not affect VA burden or complexity in patients with BiRMVP. Additionally, surgical correction of MR does not affect VA burden or complexity in an unselected cohort of patients with BiRMVP. The role of MV surgery in patients with BiRMVP, MAD and a high burden of VAs warrants further investigation.

6.7 Tables

6.7.1 *Clinical and imaging characteristics according to MR severity*

	Mild MR (n=15)	Moderate MR (n=15)	Severe MR (n=14)	p-value
Age (years)	59±11	56±12	58±16	0.80
Female	9 (60%)	7 (47%)	6 (43%)	0.62
Medical history				
Cardiovascular				
IHD	1	0	0	1.0
AF	2	3	4	0.59
CCF	0	0	1	0.32
Cerebrovascular disease	1	0	1	0.76
Cardiovascular risk factors				
Hypertension	2	2	4	0.55
Hypercholesterolaemia	3	6	7	0.25
Smoking	7	5	3	0.45
Diabetes	0	2	0	0.32
Other	2*	3†	4‡	0.59
Nil	2	3	3	0.89
Medications				
Cardiovascular				
Aspirin	4	2	1	0.46
Clopidogrel	1	0	0	1.0
Anticoagulant	1	2	3	0.49
β-blocker	6	3	3	0.52
Sotalol	1	1	2	0.68
Digoxin	0	0	1	0.32
Verapamil	0	0	1	0.32
Renin-angiotensin blockade	3	3	5	0.62
Statin	4	4	7	0.33
Amlodipine	0	1	0	1.0
Spironolactone	0	0	1	0.32
Frusemide	0	0	2	0.10
Proton pump inhibitor	3	3	1	0.67
Antidepressant	2	0	2	0.44
Other	4§	4‖	5#	0.84
Nil	2	3	2	1.0
LVEF (%)	60 (57-67)	60 (55-66)	59 (54-64)	0.53
LVEDD (mm)	51±4	55±4	56±5	0.003
IVST (mm)	9 (9-10)	10 (8-12)	10 (9-11)	0.51
PWT (mm)	9 (9-10)	9 (8-10)	10 (8-10)	0.91
RVSP (mmHg)	23 (20-26)	25 (22-29)	26 (21-36)	0.26
MAD	9 (60%)	7 (47%)	3 (21%)	0.11
Late gadolinium enhancement	4/12 (33%)	9/14 (64%)	7/13 (54%)	0.28
T1 MOLLI native (ms)	987±30	1013±43	1009±49	0.29
T1 MOLLI post-contrast (ms)	391±41	398±44	414±55	0.48
ECV (%)	27±2	29±3	29±4	0.57

AF, atrial fibrillation; CCF, congestive cardiac failure; IHD, ischaemic heart disease; IVST, intra-ventricular septum thickness; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness; RVSP, right ventricular systolic pressure

*Includes breast cancer and migraine

†Includes chronic obstructive pulmonary disease, pituitary dysfunction, iron deficiency anaemia

‡Includes lymphoma, asthma, systemic lupus erythematosus, Hashimoto's disease, osteoporosis

§Includes doxycycline, meloxicam, betahistine, hormone replacement

‖Includes seretide, Spiriva, thyroxine, desmopressin, oral contraceptive pill, metformin

#Includes symbicort, thyroxine, amoxicillin, hydroxychloroquine, denosumab

6.7.2 *BiRMVP surgical cases*

Case	Age/ Sex	MAD	LGE	MV surgery	Additional surgery	Pre-operative parameters				Post-operative parameters					
						MR	AAD	PVC%	Lown grade	MR	AAD	PVC%	p-value*	Lown grade	p-value†
1	46F	Y	N	Repair	PFO	Mod	Nil	10.6	4b	Nil	Nil	0.027		3	
2	78F	N	Y	Replace	Patch repair of LV	Sev	Nil	2.84	5	Nil	Nil	3.38		5	
3	59M	N	Y	Repair	LAA	Mod	Nil	0.015	1	Mild	Nil	0.023		4a	
4	44M	N	Y	Repair	LAA	Sev	Nil	0.010	3	Mild	Nebivolol	1.65		4a	
5	67M	N	Y	Repair	PFO, LAA	Sev	Nil	0.41	4a	Mild	Nil	0.66		4a	
6	62F	Y	Y	Repair	LAA	Mod	Sotalol	0.53	4a	Mild	Atenolol	0.78		4a	
7	42M	N	Y	Repair	LAA, cryo, TV	Sev	Carvedilol	0.19	4a	Nil	Sotalol	0.15	0.33	5	1.0
8	42F	N	NA	Repair	PFO, LAA, cryo	Sev	Bisoprolol	2.14	5	Mild	Amiodarone	0.69		4a	
9	74M	N	N	Replace	Nil	Sev	Nil	0.37	5	Mild	Metoprolol	1.61		4a	
10	52M	N	Y	Repair	Nil	Sev	Sotalol, digoxin	0.22	3	Nil	Sotalol	3.18		5	
11	25M	Y	Y	Repair	Nil	Mod	Nil	0.019	5	Nil	Metoprolol	0.016		4a	
12	75M	Y	Y	Repair	LAA	Sev	Nil	2.18	5	Nil	Metoprolol	12.3		5	
13	44F	Y	N	Repair	PFO	Sev	Nil	0.66	5	Mild	Nil	0.32		3	
14	55M	N	N	Repair	LAA, cryo	Sev	Metoprolol	0.0063	1	Nil	Amiodarone	0.0075		1	

AAD, anti-arrhythmic drugs; CABG, LAA, left atrial appendage (closure); LGE, late gadolinium enhancement; MAD, mitral annular disjunction; PFO, patent foramen ovale (closure); TV, tricuspid valve (annuloplasty)

*Compared to pre-operative parameters using Wilcoxon sign-rank test

†Compared to pre-operative parameters using McNemar's test

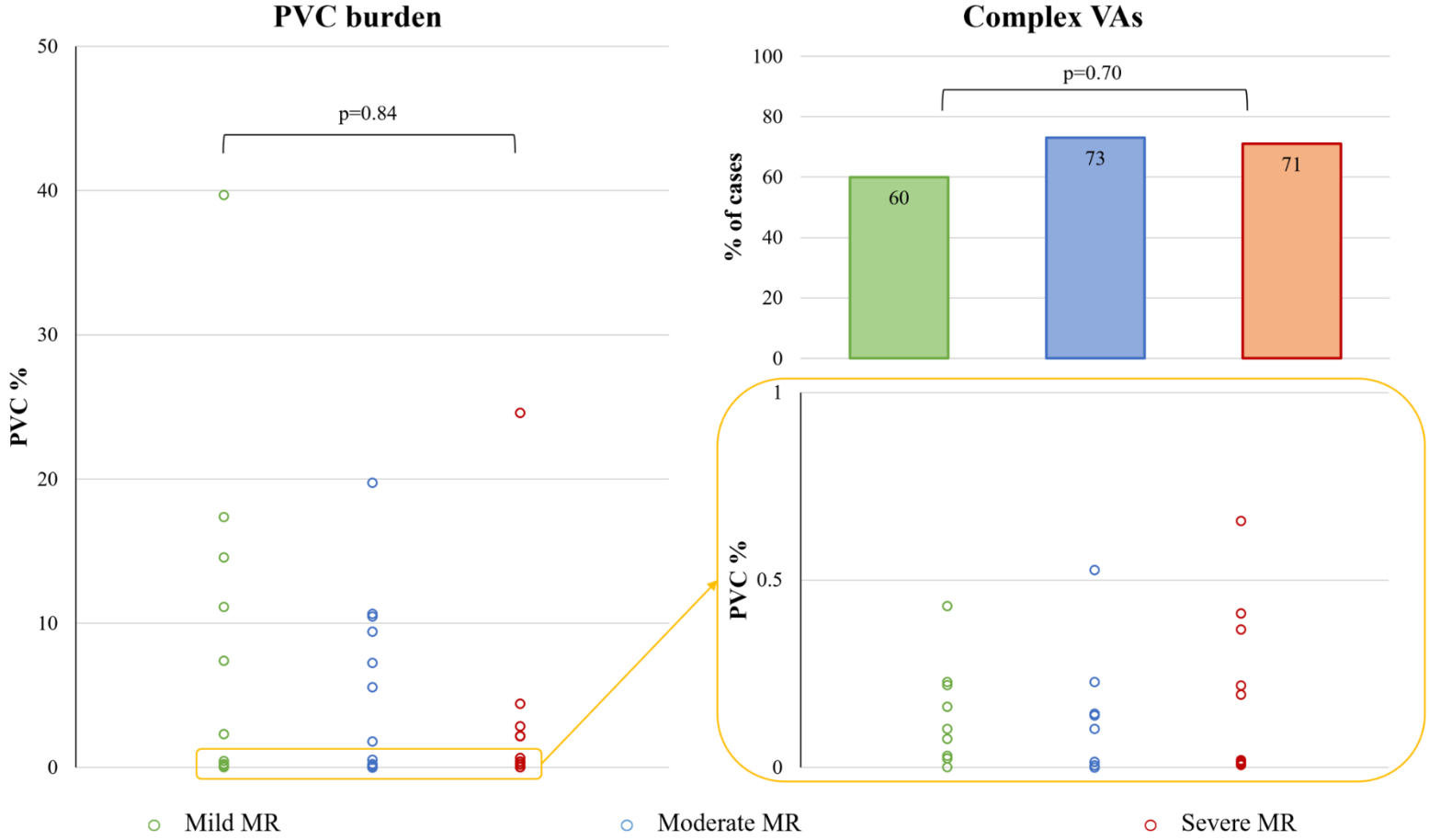
6.7.3 *VAs according to LGE and MAD status for surgical cases*

	Pre-operative		**Post-operative**			
	PVC%	Lown grade ≥4	PVC%	p-value*	Lown grade ≥4	p-value†
LGE+ (n=9)	0.22 (0.01-1.4)	6 (67%)	0.78 (0.09-3.3)	0.03	9 (100%)	0.25
LGE- (n=4)	0.52 (0.10-8.1)	3 (75%)	0.17 (0.01-1.3)	0.72	1 (25%)	0.48
MAD+ (n=5)	0.66 (0.27-6.4)	5 (100%)	0.32 (0.02-6.5)	0.69	3 (60%)	0.48
MAD- (n=9)	0.22 (0.01-1.3)	5 (56%)	0.69 (0.09-2.4)	0.14	8 (89%)	0.25

*Compared to pre-operative parameters using Wilcoxon sign-rank test
†Compared to pre-operative parameters using McNemar's test

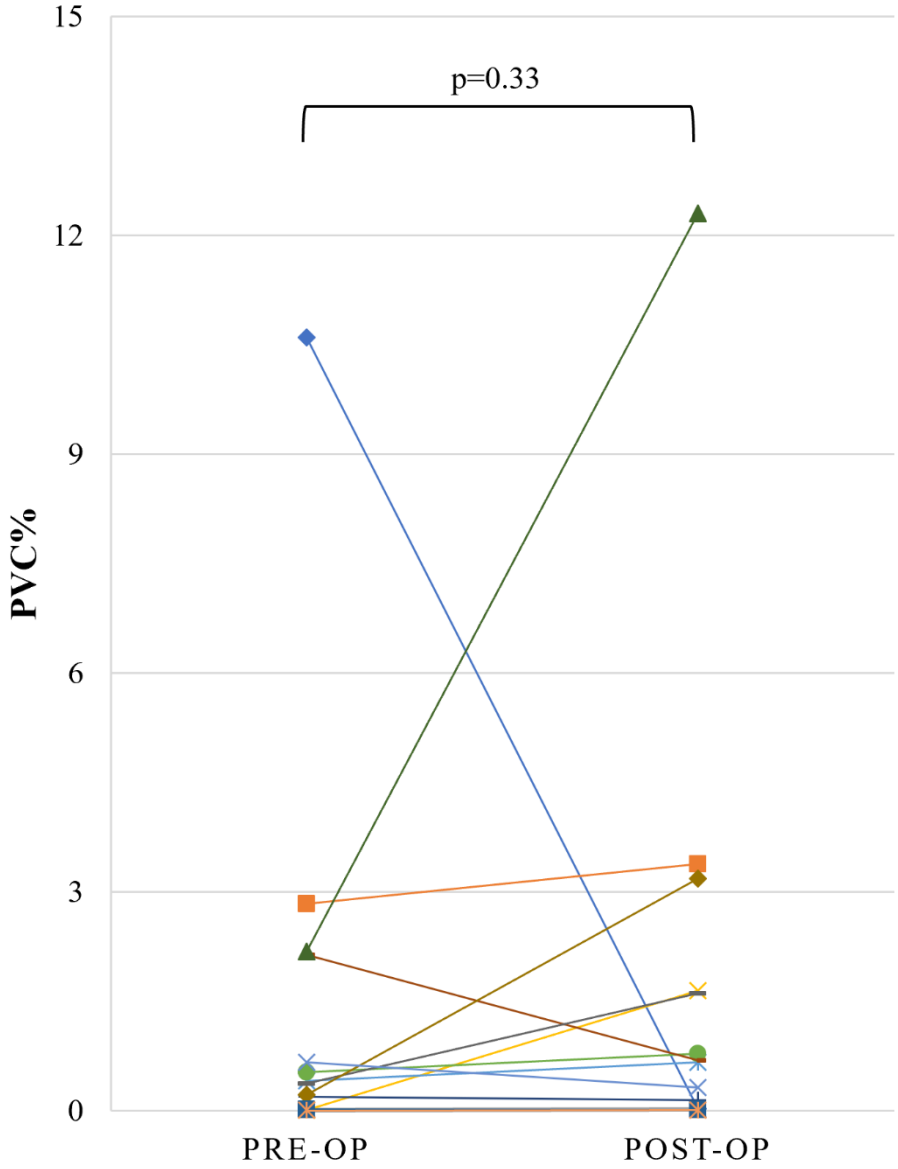
6.8 Figures

6.8.1 *VAs according to MR severity*



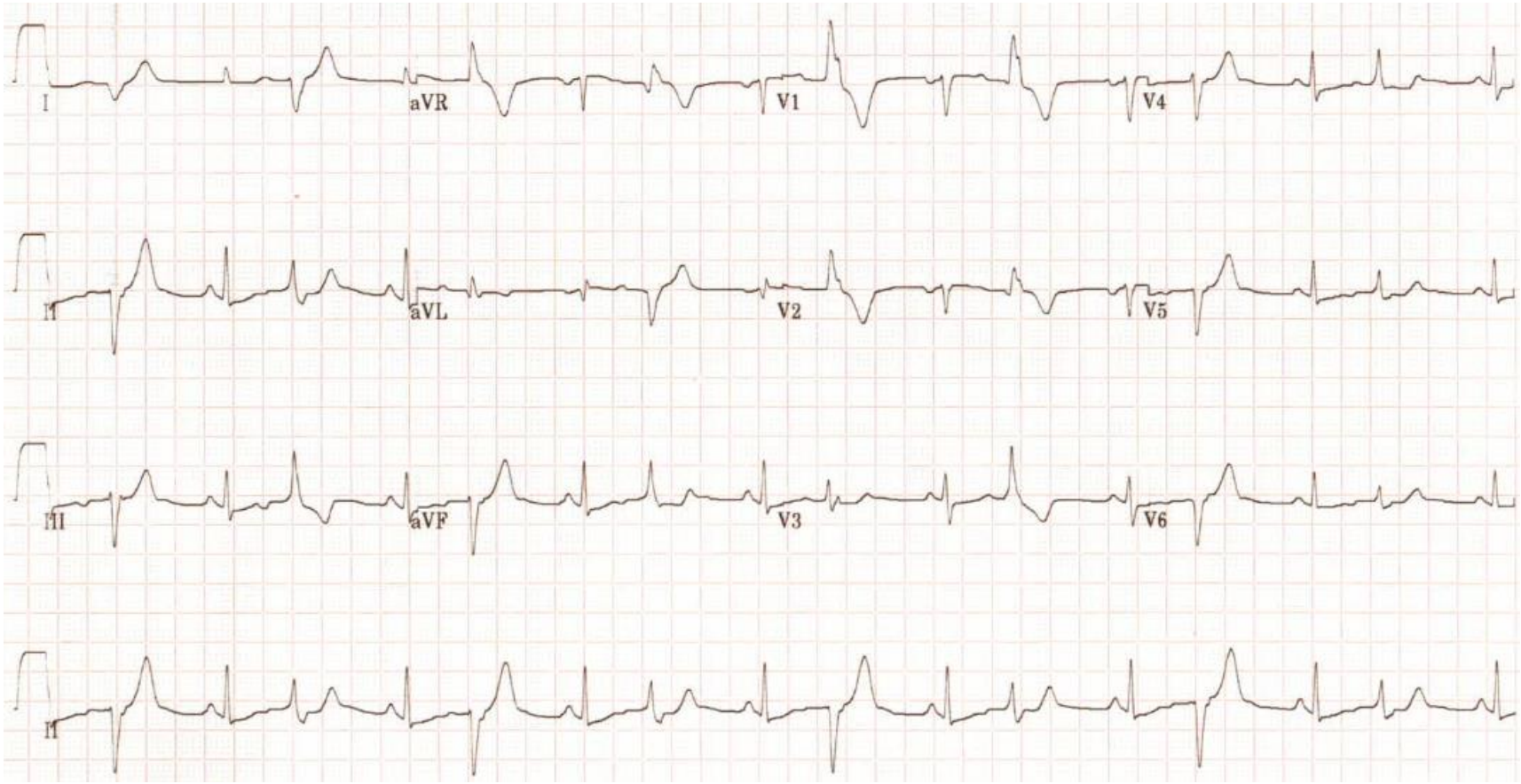
PVC burden compared using Kruskal-Wallis test
Complex VAs compared using chi-square test

6.8.2 *PVC burden for surgical BiRMVP cases*



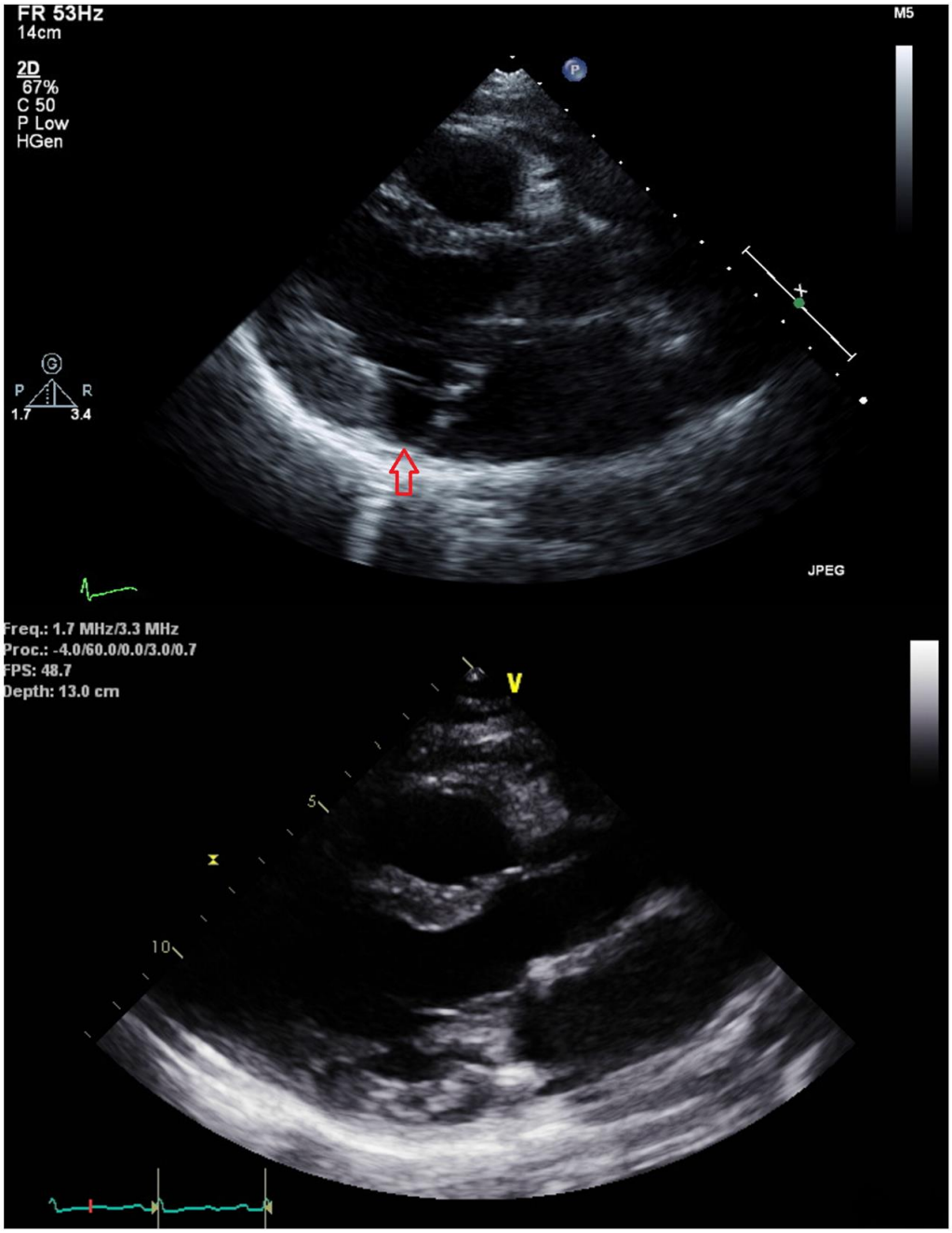
Each line represents PVC burden of a patient pre-operatively and post-operatively
PVC burdens compared using Wilcoxon sign-rank test

6.8.3 *12-Lead ECG with PVCs*



ECG showing sinus rhythm with ventricular bigeminy of 2 morphologies. PVC1 is left ventricular with superior axis, possibly originating from the posteromedial papillary muscle. PVC2 is left ventricular with inferior axis, possibly originating from the mitral annulus or anterolateral papillary muscle.

6.8.4 *Mitral annular disjunction*



Top image is pre-operative echocardiogram showing MAD (red arrow) and bottom image is post-operative echocardiogram showing the same view after MV repair and annuloplasty ring insertion.

6.9 Supplemental Materials

6.9.1 *Other MVP surgical cases*

Case	**Age/ Sex**	**MAD**	**LGE**	**MV surgery**	**Additional surgery**	**Pre-operative parameters**				**Post-operative parameters**					
						MR	AAD	PVC%	Lown grade	MR	AAD	PVC%	p-value*	Lown grade	p-value†
15‡	79M	N	N	Repair	LAA, cryo, TV	Sev	Metoprolol	0.023	4a	Nil	Metoprolol	0.74		5	
16‡	58M	N	N	Repair	Nil	Sev	Nil	0.0022	1	Nil	Nil	0.010		5	
17§	60M	N	Y	Repair	Nil	Sev	Nil	0.075	4a	Mild	Nil	0.088		5	
18§	69M	N	N	Repair	CABG x2	Sev	Nil	0.18	5	Mild	Metoprolol	0.11	0.14	4a	1.0
19§	62M	N	N	Replace	LAA, CABG x1	Mod	Sotalol	0.0011	1	Nil	Sotalol	0		0	
20§	55M	N	NA	Repair	Nil	Sev	Nil	0.0029	4a	Mild	Nil	0		0	
21‡	57M	N	Y	Repair	CABG x3	Mod	Metoprolol	0.011	1	Nil	Metoprolol	0.033		3	
22§	79M	N	N	Repair	Nil	Mod	Nil	0.037	3	Nil	Metoprolol	0.10		3	
23§	79F	N	Y	Replace	Nil	Mod	Nil	0.14	3	Mild	Metoprolol	3.78		4a	

AAD, anti-arrhythmic drugs; CABG, coronary artery bypass graft; LAA, left atrial appendage (closure); LGE, late gadolinium enhancement; MAD, mitral annular disjunction; TV, tricuspid valve (annuloplasty)

*Compared to pre-operative parameters using Wilcoxon sign-rank test

†Compared to pre-operative parameters using McNemar's test

‡Non-redundant MVP

§Posterior leaflet redundant MVP

CHAPTER 7

Summary

MVP is a common cardiac valve condition which has been associated with the occurrence of SCD through the development of malignant VAs, however this link is predominantly based on case reports. The underlying cardiac histopathological changes described in individuals with iMVP-SCD are lacking from adequately controlled data, while little is known regarding the distribution of histological fibrosis in these cases. Electrophysiological cardiac rhythm information in these patients is limited to reports utilizing short-term cardiac rhythm monitoring strategies, while the importance of mitral regurgitation with respect to VAs in MVP requires clarification. This thesis investigated the complex relationship between MVP, VAs and SCD.

The apparent link between MVP and SCD has been predominantly been based on individual case reports and series. Chapter 2 systematically reviewed all reported cases of MVP with SCD or cardiac arrest in the literature. Relevant clinical characteristics include a predominantly young, female population with frequent PVCs, bileaflet involvement and cardiac arrest occurring as a result of VF. Leaflet redundancy was shown as the only independent predictor of SCD in MVP. The estimated incidence of SCD in MVP is approximately 1.5 times compared to the general population, although this is likely significantly higher in those with leaflet redundancy.

Reported histopathological changes in individuals with MVP and sudden death include greater cardiac mass, increased mitral annulus size and left ventricular fibrosis although

such findings are confounded by a lack of adequate control cases. Furthermore, there are a paucity of cases describing cardiac arrest rhythm in individuals with autopsy confirmed iMVP. Chapter 3 described histopathological findings and cardiac arrest rhythm in individuals with iMVP and SCD compared to matched control groups. Salient results included increased cardiac mass, mitral annulus size and left ventricular fibrosis in individuals with iMVP, with VF being the predominant cardiac arrest rhythm. Findings from this chapter indicate that individuals with iMVP have left ventricular substrate abnormalities on histopathological examination providing a plausible link to the development of malignant VAs resulting in SCD.

Detailed left ventricular assessment for transmural and circumferential fibrosis along with characterization of right ventricular fibrosis may provide additional insights into the potential pathogenic role of cardiac fibrosis in individuals with iMVP-SCD. Chapter 4 comprehensively and systematically quantified left and right ventricular fibrosis in individuals with iMVP-SCD compared to a matched control group. Salient results included more left ventricular and interventricular septum fibrosis in iMVP-SCD cases with a significant endocardial-epicardial fibrosis gradient within the lateral and posterior walls. Findings from this chapter indicate that individuals with iMVP have both localised and generalised left ventricular histological fibrosis and that non-uniform left ventricular remodelling may be important in the pathogenesis of SCD.

There is limited data regarding long-term continuous cardiac rhythm monitoring for VAs in patients with MVP. Chapter 5 compared the incidence of VAs detected with continuous cardiac rhythm monitoring in patients with MVP and controls, and

examined whether certain factors predicted for the development of VAs within the MVP group. Salient results included a higher overall incidence of VAs in patients with MVP compared to control groups and that presence of late gadolinium enhancement on cardiac MRI predicted for the development of VAs in those with MVP. Findings from this chapter demonstrate that patients with MVP are at high risk for VAs even compared to traditional higher risk cohorts whilst affirming the predictive importance of cardiac fibrosis for VAs in a living cohort of patients with MVP.

The importance of mitral regurgitation with regards to VAs in patients with redundant leaflet MVP requires clarification. Furthermore, whether amelioration of mitral regurgitation with surgery impacts VA burden in these patients requires prospective evaluation. Chapter 6 evaluated the role of mitral regurgitation and mitral valve surgery with regards to VAs in patients with redundant leaflet MVP. Salient results included that the severity of mitral regurgitation did not affect VA burden in patients with redundant leaflet MVP while mitral valve surgery did not change VA burden in unselected patients with MVP. Findings from this chapter confirm that the degree of mitral regurgitation is not linked to development of VAs in a higher risk subset of patients with MVP. Furthermore, despite previous case reports of improved VA burden post mitral valve surgery, we demonstrate that is not applicable to an unselected cohort of patients.

CHAPTER 8

Future Directions

Findings from this thesis provide several novel insights into the pathogenesis of ventricular arrhythmias and sudden cardiac death in individuals with mitral valve prolapse. However, further work is required to better understand this complex relationship and develop frameworks for identifying those with MVP who are at highest risk of SCD events allowing the potential for therapeutic interventions.

This thesis provided a comprehensive summary of published cases of MVP and SCD reporting clinical characteristics, predictors and estimated incidence. However, to better understand the complex relationship between MVP and SCD, standardised reporting of clinical, electrophysiological, echocardiographic and other cardiac imaging variables with documentation of long terms outcomes is required.

Certain histopathological findings of individuals with MVP and SCD were demonstrated in this thesis. Further work should focus on delineating fibrosis distribution longitudinally within the left ventricle (at the base and apex) to confirm our postulation of non-uniform left ventricular remodelling. Additionally, correlation is required between identified histological fibrosis with non-invasive fibrosis characterization via cardiac MRI.

This thesis also showed an increased incidence of VAs in patients with MVP, although this did not translate to episodes of sustained VAs. Future studies which are able to

provide continuous cardiac monitoring to a larger group of patients with redundant leaflet MVP may provide clarification regarding whether non-sustained VAs results in sustained VAs or SCD in this group of patients. In doing so, contemporary predictors for sustained VAs or SCD may be added to that of leaflet redundancy.

Finally, potential therapeutic interventions to reduce VAs and prevent SCD are required including non-pharmacological, pharmacological and interventional measures. Whilst pharmacological treatments such as magnesium, beta-blockers and amiodarone are indicated in certain subsets of patients with VAs, there is a distinct lack of evidence with regards to patients with MVP and VAs. Furthermore, invasive electrophysiological interventions, implantable cardioverter defibrillator insertion and cardiac surgery have also been studied in selected patients with VAs with limited data available for MVP patients. Larger scale, prospective studies of these measures in a high-risk cohort of patients with MVP would ultimately allow for physicians to provide appropriate and considered care for patients with MVP.

CHAPTER 9

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