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Malignant Bileaflet Mitral Valve Prolapse Syndrome in Patients With Otherwise Idiopathic Out-of-Hospital Cardiac Arrest

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Objectives The aim of this study was to investigate the prevalence of mitral valve prolapse (MVP) and its association with ventricular arrhythmias in a cohort with "unexplained" out-of-hospital cardiac arrest.

Background Ventricular arrhythmias are an important cause of sudden unexpected death in the young. The role of MVP in sudden unexpected death remains controversial.

Methods Of 1,200 patients evaluated between July 2000 and December 2009 in the Mayo Clinic's Long QT Syndrome/Genetic Heart Rhythm Clinic, all 24 (16 women, median age 33.5 years) with idiopathic out-of-hospital cardiac arrest (i.e., negative for ischemia, cardiomyopathy, and channelopathy) were reviewed.

Results All 24 patients had implantable cardioverter-defibrillators (ICDs). Out-of-hospital cardiac arrest was the sentinel event in 22 (92%). Bileaflet MVP was found in 10 (42%). Compared with patients with normal mitral valves, patients with bileaflet MVP: 1) were over-represented by women (9 of 10 [90%] vs. 7 of 14 [50%], $p = 0.04$); 2) had a higher prevalence of biphasic or inverted T waves (7 of 9 [77.8%] vs. 4 of 14 [29%], $p = 0.04$); and 3) on Holter interrogation had higher prevalence of ventricular bigeminy (9 of 9 [100%] vs. 1 of 10 [10%], $p < 0.0001$), ventricular tachycardia (7 of 9 [78%] vs. 1 of 10 [10%], $p = 0.006$), and premature ventricular contractions originating from the outflow tract alternating with the papillary muscle or fascicular region (7 of 9 [78%] vs. 2 of 10 [20%], $p = 0.02$). Over a median 1.8 years (range: 0.1 to 11.9 years) from ICD placement, 13 of 24 patients (54%) received appropriate ventricular fibrillation–terminating ICD shocks. Only bileaflet MVP was associated with ventricular fibrillation recurrences requiring ICD therapy on follow-up (logistic regression odds ratio: 7.2; 95% confidence interval: 1.1 to 48; $p = 0.028$).

Conclusions The authors describe a "malignant" subset of patients with MVP who experienced life-threatening ventricular arrhythmias. This phenotype is characterized by bileaflet MVP, female sex, and frequent complex ventricular ectopic activity, including premature ventricular contractions of the outflow tract alternating with papillary muscle or fascicular origin. (J Am Coll Cardiol 2013;62:222–30) © 2013 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) affects 300,000 to 400,000 patients in the United States, and in the majority of cases, a known cause is identified. However, there is a distinct subset of patients who experience out-of-hospital cardiac arrest (OHCA) but lack clinical evidence of either ischemic cardiomyopathy or nonischemic structural or electrical cardiomyopathies. Identifying this subset of patients with unexplained OHCA is challenging (1).

In this context, the role of mitral valve prolapse (MVP) in sudden unexpected death (SUD) and OHCA remains controversial. MVP has been reported as the only cardiac abnormality at autopsy in certain apparently healthy subjects who died suddenly or were resuscitated successfully from OHCA (2–4). SUD in patients with MVP may stem from ventricular fibrillation (VF) (4,5), but the exact etiology and risk predictors of SUD in MVP are elusive (6). Although single-leaflet MVP is present in 2.4% of the general

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population (7), the reported annual rate of SUD in patients with MVP is exceedingly low (3,4). Thus, identifying the small subset of patients with MVP who may be at increased risk for sudden death is difficult. There are case reports and small case series linking SUD and OHCA to MVP, especially in younger female patients with complex ventricular ectopic activity (2,6,8–19).

The prevalence of MVP and ventricular ectopic activity in patients with unexplained OHCA is unclear. Furthermore, there are only a few small reports comparing patients with OHCA with and without mitral valve abnormalities. We report on the prevalence of MVP in a cohort of patients with unexplained OHCA and compare the clinical phenotype of patients with and without MVP.

Abbreviations and Acronyms

LQTS = long QT syndrome
MVP = mitral valve prolapse
OHCA = out-of-hospital cardiac arrest
PVC = premature ventricular contraction
SCD = sudden cardiac death
SUD = sudden unexpected death
VF = ventricular fibrillation
VT = ventricular tachycardia

Methods

Study cohort and study design. For this institutional review board–approved study, 2 investigators (C.S.S., M.E.F.) retrospectively reviewed the electronic medical records of 1,200 consecutive patients seen in the Mayo Clinic's Long QT Syndrome/Genetic Heart Rhythm Clinic between July 2000 and December 2009. All patients who had histories of unexplained OHCA with documented cardiovascular collapse from ventricular tachycardia (VT) or VF that required defibrillation to restore sinus rhythm were included. In all patients, the etiology of OHCA remained elusive after detailed review of histories, previous medical records, and additional investigations. Patients were excluded if: 1) VF or VT was not documented; 2) VT was present without cardiovascular collapse; 3) family history was positive for channelopathy, cardiomyopathy, SUD, or OHCA; or 4) OHCA was attributable to a cardiac channelopathy, Wolff-Parkinson-White syndrome, cardiomyopathy (including arrhythmogenic right ventricular cardiomyopathy), coronary artery disease, congenital coronary artery anomalies, electrolyte derangements, or drugs or medications or was preceded by known depressed left ventricular ejection fraction. None of the included patients had any noncardiac syndromic features or documented family histories of MVP.

Clinical testing. Besides the review of the outside medical records after OHCA, all patients underwent standard investigations, including transthoracic echocardiography (20) and 12-lead electrocardiography. All patients had normal resting corrected QT intervals, and none had electrocardiographic features suggestive of Brugada syndrome or arrhythmogenic right ventricular dysplasia. Most patients underwent additional testing on a discretionary basis, guided by the circumstances of the OHCA and depending on the extent of the primary evaluation, including 24- or 48-h Holter recording, genetic testing for channelopathies, provocative intravenous procainamide or epinephrine testing, exercise stress testing, cardiac computed tomography, cardiac magnetic resonance imaging, electrophysiology study, or coronary angiography.

Overall, 20 patients (83%) had genetic testing for channelopathies ordered during the course of their primary evaluations or performed as part of their Mayo Clinic evaluations (Table 1). Seventeen patients were tested for mutations in the most common long-QT syndrome (LQTS)–associated genes by either the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory or a commercially available LQTS test (21). LQTS genetic testing was performed when a diagnosis of LQTS was considered by the referring physicians. After expert review at our institution, LQTS diagnosis was considered unlikely in this cohort of patients on the basis of detailed clinical histories; normal corrected QT intervals during the resting state, exercise, and recovery; negative results on epinephrine testing when indicated; and negative genetic test results (22,23).

Genetic testing done at the discretion of the referring physicians specifically for deleterious mutations within cardiac sodium channel and/or ryanodine receptor gene for suspected catecholaminergic polymorphic VT yielded negative results in 9 patients.

Significant coronary artery disease and presence of anomalous coronary arteries were excluded on coronary angiography and/or noninvasive imaging (computed tomography or cardiac magnetic resonance). Cardiomyopathy was excluded in part by expert review of cardiac imaging studies showing preserved left ventricular ejection fraction (>50%) and normal ventricular wall thickness.

Blinded to the specific clinical histories and echocardiographic findings, we reviewed the 12-lead electrocardiograms of all OHCA survivors. Ambulatory (24- or 48-h) Holter recordings were available for the majority of patients and were reviewed for density and site of premature ventricular contraction (PVC) origin, type of PVC (singlets, couplets, or triplets), and presence of VT. Complex ventricular ectopic activity was defined as the presence of PVC couplets, ventricular bigeminy, nonsustained VT, or sustained VT. All available 12-lead electrocardiograms were analyzed by 2 investigators (C.S.S., F.F.S.) for age-inappropriate ST-T-segment repolarization changes, including T-wave inversion or biphasic T waves, ST-segment depression or elevation, and J waves.

Blinded to the details of the individual clinical histories as well as the results of echocardiography and other tests (but unblinded to the diagnosis of OHCA), a single investigator (F.C.) retrospectively reviewed all echocardiograms performed and confirmed or revised the echocardiographic findings. The diagnosis of MVP and grading of mitral regurgitation from 1 (trivial) to 4 (severe) were according to standard guidelines. MVP was defined as systolic displacement (>2 mm) of 1 or both mitral valve leaflets into the left atrium beyond the plane of the mitral annulus in a