Nonischemic Mitral Regurgitation: Prognostic Value of Nonsustained Ventricular Tachycardia after Mitral Valve Surgery

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Key Words

Ejection fraction · Mitral regurgitation · Mitral valve surgery · Ventricular tachycardia

Abstract

Background: Nonsustained ventricular tachycardia (VT), frequent in unoperated severe mitral regurgitation (MR), confers mortality risk [sudden death (SD) and cardiac death (CD)]. The prognostic value of VT after mitral valve surgery (MVS) is unknown; we aimed to define this prognostic value and to assess its modulation by left (LV) and/or right (RV) ventricular ejection fraction (EF) for mortality after MVS. **Methods:** In 57 patients (53% females, aged 58 ± 12 years) with severe MR prospectively followed before and after MVS, we performed 24-hour ambulatory electrocardiograms approximately annually. LVEF and RVEF were determined within 1 year after MVS by radionuclide cineangiography. **Results:** During 9.52 ± 3.49 endpoint-free follow-up years, late postoperative CD occurred in 11 patients (7 SD, 4 heart failures). In univariable analysis, >1 VT episode after MVS predicted SD ($p < 0.01$) and CD (SD or heart failure; $p < 0.04$). Subnormal postoperative RVEF predicted CD ($p <$

0.04). When adjusted for preoperative age, gender, etiology or antiarrhythmics, both postoperative VT and RVEF predicted CD ($p \leq 0.05$). When postoperative VT and RVEF were both in the multivariable model, only subnormal RVEF predicted CD ($p < 0.04$). Among those with normal RVEF, VT >1 episode predicted SD ($p = 0.03$). **Conclusion:** Postoperative VT and subnormal RVEF predict late postoperative deaths in nonischemic MR. Their assessment may aid patient management.

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Introduction

Mitral valve surgery (MVS) for mitral regurgitation (MR) ameliorates congestive symptoms [1, 2] and, based on comparisons of operated and unoperated observational cohorts, appears to improve survival compared with no surgery. This apparent survival benefit seems to occur irrespective of symptom status [3, 4] and of preoperative left ventricular (LV) and/or right ventricular (RV) ejection fraction (EF) [5]. However, cardiac death (CD), frequently occurring suddenly (sudden death, SD), limits

otherwise expected survival late after MVS [3, 4, 6]. Though relatively uncommon, SD also occurs in unoperated severe MR [5, 7, 8], increasingly as LVEF deteriorates [9]. Rarely, SD occurs even among those with isolated, pure MR and normal LVEF, suggesting an underlying myocardial predisposition [9]. The effect of surgery on this predisposition is not known. Predictors of postoperative survival [10, 11] have been sought by several investigators. Preoperative LVEF and RVEF are powerful independent predictors of long-term survival after MVS [3, 7, 10, 12]. However, available data, limited largely to early postoperative events, have failed to reveal a relation between pre- or postoperative ventricular arrhythmia and postoperative outcome [13]. Nonsustained ventricular tachycardia (VT) is frequent among patients with unoperated MR [8] and may persist after MVS. Nonetheless, the relation of VT to late postoperative survival and the interaction between VT, LVEF and RVEF on survival have not been evaluated. Therefore, we undertook to determine this relation in a cohort that has undergone MVS for MR.

Methods

Patient Selection

All patients were enrolled in our prospective study of the natural progression of regurgitant valvular disease and its predictors, as previously described [7, 14]. For inclusion in the current analysis, patients must have undergone MVS for hemodynamically severe, nonischemic, pure, isolated chronic MR (verified by catheterization), 24-hour ambulatory electrocardiography (AECG) within 18 months after MVS, and follow-up after postoperative AECG. Thus, patients were excluded if they had clinically evident coronary artery disease or more than mild additional valve or other structural heart disease. Referral for MVS was determined by the patient's primary cardiologist and was unrelated to the study protocol. Initially by protocol, and subsequently as part of routine clinical evaluation, all patients in our natural history study undergo annual AECG, 2-dimensional and Doppler echocardiography, as well as rest and exercise radionuclide cineangiography (RNCA), the tests relevant for this analysis. However, patients or their primary physicians have occasionally chosen not to perform such testing in any single year.

Between February 1981 and June 2001, 96 patients in our natural history study underwent MVS. Of this group, 57 patients met the inclusion criteria. Study entry for this analysis was truncated at 2001 to allow for 10-year follow-up in all patients with this chronic disease.

Procedures

Ambulatory Electrocardiography

Two-channel, continuous 24-hour AECG was recorded from CM₁ and CM₅ leads. Recordings were scanned using several different generations of AECG scanning equipment in routine use during the study. Ventricular rhythm evaluation included quanti-

fication of the number of VT events (≥ 3 consecutive ventricular complexes; classified as nonsustained if the total run was <30 s) and number of ventricular contractions in the longest VT run on each AECG [15]. Recordings were also analyzed for atrial fibrillation (AF) and/or atrial flutter (Aflutter). AECG was performed 8.1 ± 3.3 months (range 1.5–17.0) after MVS; a subgroup (51/57 patients, 89.5%) also underwent AECG during a similar interval before operation (average 4.4 ± 4.4 months, range 0.0–17.3), permitting secondary analyses.

Radionuclide Cineangiography

RNCA was performed with the patient in supine position at rest using an ECG-gated equilibrium method analogous to that previously described [16, 17]. In these studies, red cells were labeled in vivo with stannous pyrophosphate infused intravenously prior to administration of 15–25 mCi of ^{99m}Tc . LVEF was computed by a method analogous to our previously reported count-based procedure, validated by comparison with contrast angiography [17, 18]. During the course of this study, the predominant mode of LVEF analysis changed from use of a single region of interest (ROI) at end-diastole to separate end-systolic and end-diastolic ROI; absolute values of LVEF differ depending on which procedure is used: 2 ROI values generally are 5–15% higher than 1 ROI value. Since we altered our procedure during the course of the study but already had recorded values using the original 1 ROI method, our analysis of LVEF is based on adjusted values, calculated using a random subgroup of 30 preoperative studies and a different random subgroup of 30 postoperative studies; each group was analyzed both by 1 and 2 ROI to determine the difference in values between the methods. Adjustment for values obtained with 1 ROI was determined from the paired difference between measured LVEF of 1 and 2 ROI rather than from absolute values; thus, 11% ('ejection fraction units') were added to preoperative single ROI values, and 16% were added to postoperative single ROI values. Currently, resting LVEF $<10\%$ above the lower limit of normal is considered an indication for MVS [19] and is used as a 'high risk descriptor' indicating need for MVS in this study. Subnormal RVEF was calculated and defined as $<35\%$, as in our previous publications [7, 8]. All but 1 patient underwent both pre- ($n = 57$) and postoperative ($n = 56$) RNCA; these were performed within average 0.8 ± 2.5 months (range 0.0–14.4) of preoperative AECG and within average 0.5 ± 1.8 months (range 0.0–11.9) of postoperative AECG.

Follow-Up and Definition of Endpoints

Patients were followed through November 2011 by physical examination or by telephone call or postal questionnaire to the patient, relative or physician to determine the vital status and occurrence of intercurrent events. Cause of death among decedents was determined by review of medical and vital records, supplemented by information furnished by the patients' health care provider and/or surviving family members or significant others. Average follow-up was 9.52 ± 3.49 years (range 1.98–15.5) among endpoint-free patients; 24/27 (89%) of these patients were followed for at least 5 years postoperatively. SD was defined as either witnessed unexpected arrest (resuscitated or nonresuscitated) in a patient who was previously stable or an unwitnessed unexpected death in a patient seen and apparently stable within the previous 24 h; CD was defined as death resulting from heart failure (HF), determined by the primary physician and cardiologist, in addition to all SD (myocardial infarction was also a potential endpoint, but none occurred).

Statistical Analysis

Summary data are expressed as the mean $\pm$ standard deviation or as number and percentage, as appropriate. McNemars symmetry χ^2 test was used to compare the preoperative versus postoperative presence of VT, AF or Aflutter and subnormal resting LVEF and RVEF. Pre- to postoperative differences in resting LVEF and RVEF, number of episodes of VT and maximum number of premature ventricular contractions on AECG, each evaluated as interval data, were analyzed by paired t test or the Wilcoxon rank sum test, as appropriate.

Kaplan-Meier product limit estimate curves were constructed and compared by log-rank testing to determine the relation of arrhythmia presence or systolic performance descriptors (defined postoperatively for primary analysis and preoperatively for secondary analysis) with outcomes, unadjusted for other variables. For these analyses, the distributions of the number of VT events on each AECG were analyzed in two different ways: (1) 0 versus 1 versus >1 VT events, and (2) with 0 and 1 VT events aggregated versus >1 VT events; resting RVEF was analyzed as subnormal ($<35\%$) versus normal ($\geq 35\%$), and resting LVEF was analyzed as subnormal ($<55\%$) versus normal ($\geq 55\%$). RVEF and LVEF were also analyzed as continuous variables by univariable Cox regression methodology. For the primary analysis, follow-up began on the date of the postoperative AECG or RNCA, as appropriate; for secondary analyses, follow-up began at the time of the last preoperative objective evaluation. Patients were censored from further analysis if they underwent cardiovascular reoperation ($n = 11$) or defibrillator implantation (1 patient). Patients who died due to prosthetic valve failure ($n = 1$) or of clearly noncardiac causes ($n = 5$) were also censored at the time of occurrence.

Forward stepwise multivariable Cox regression analysis (entry and removal thresholds: 0.05 and 0.10, respectively) was performed pair-wise (two variables in one model), with and without interaction terms, to define the independent or additive prognostic value of any VT or functional descriptor that predicted CD in univariable analysis. (Multivariable analysis was not undertaken for SD due to the limited number of events.) Variables entered into these models were partitioned according to the same segregation points used for univariable analysis. A series of Cox model analyses was also used to adjust for potential confounding by age, gender, etiology (mitral valve prolapse vs. other etiologies), chronic use of antiarrhythmics, valve repair versus replacement, or preoperative New York Heart Association functional class (NYHA FC). Analyses used SPSS version 15.0 (Chicago, Ill., USA). p values ≤ 0.05 were considered statistically significant; p values >0.05 but <0.1 were considered statistical trends.

Results

Cohort Characteristics

Of the 57 analyzed patients, most were middle-aged females, 35 (61%) underwent valve replacement and 22 (39%) had valve repair. Hemodynamically important nonischemic MR was secondary to mitral valve prolapse in three fourths of the patients, and rheumatic heart disease, idiopathic ruptured chordae and endocarditis in

Table 1. Baseline characteristics of the cohort

Variable	n
Average age at surgery, years	58 $\pm$ 12 [29–77]
Gender, male	27 (47)
Etiology of MR	
Mitral valve prolapse	43 (75)
Rheumatic heart disease	11 (19)
Idiopathic ruptured chordae	8 (14)
Endocarditis	1 (2)
NYHA functional class (preoperative)	
I	22 (39)
II	13 (23)
III	19 (33)
IV	3 (5)
Type of valve surgery	
Repair	22 (39)
Replacement	35 (61)
Type of prosthetic valve	
Mechanical	23 (66)
Bioprosthetic	12 (34)
Average cross-clamp time, min	75 $\pm$ 22 [16–127]
Average pump time, min	103 $\pm$ 34 [48–244]
Antiarrhythmics (preoperative)	7 (12)
Antiarrhythmics (postoperative)	10 (18)

Figures in parentheses are percentages; figures in brackets are ranges.

others (some had combined etiologies). Prior to surgery, 39% were asymptomatic (NYHA FC I); of the remaining (symptomatic) patients, most were in NYHAFC III or II (table 1). Ten patients (18%) received long-term antiarrhythmic drugs (digoxin, amiodarone, procainamide, lidocaine, disopyramide, propafenone and/or quinidine).

VT and EF before and after MVS (table 2)

VT occurred in one third of evaluable patients before MVS and in slightly more after MVS. Preoperative VT persisted after MVS in approximately half of those affected; a similar number had VT de novo after MVS. Repeated (>1) VT episodes occurred in slightly more than half of those with any VT before and in a similar proportion after the operation. Among those with VT >1 episode before the operation, VT persisted postoperatively in 3 patients (30%). AF/Aflutter was present in less than half of patients before and after MVS. LVEF and RVEF each were subnormal in approximately one quarter of patients before MVS; within 1 year after MVS, LVEF became subnormal in slightly more than half of the patients, though in most patients, RVEF returned to normal.

Fig. 1. Impact of postoperative nonsustained VT on postoperative CD. **a** VT (0 vs. 1 episode vs. >1 episode) versus survival free of SD. For the analysis of VT >1 episode versus ≤ 1 episode, $p < 0.01$; for no VT versus any VT, $p = 0.05$. **b** VT (0 vs. 1 episode vs. >1 episode) versus survival free of CD. For VT >1 episode versus ≤ 1 episode, $p = 0.04$; for no VT versus any VT, $p = 0.07$.

Table 2. Arrhythmias and EFs before and after MVS

Variable	Preoperatively	Postoperatively	p
Nonsustained VT presence	17 (33.3) ¹	19 (37.3) ^{1, 5}	NS
Median nonsustained VT events	0 [0–97, 2] ¹	0 [0–41, 2] ¹	NS
Median maximum consecutive ventricular premature complexes	2 [1–9, 4] ¹	2 [1–16, 4] ¹	NS
AF/Aflutter presence	21 (41.2) ^{1, 3}	20 (39.2) ^{1, 4}	NS
Subnormal LVEF at rest	15 (26.8) ²	30 (53.6) ²	0.001
Subnormal RVEF	12 (21.4) ²	4 (7.1) ²	0.02
Average RVEF $\pm$ SD, %	38 $\pm$ 5 [18–51] ²	43 $\pm$ 6 [30–64] ²	<0.001

Figures in parentheses are percentages; figures in brackets are ranges and the lower bound of the upper quintile. NS = Not significant.

¹ Based on 51 evaluable cases. ² Based on 56 evaluable cases. ³ AF (n = 20), Aflutter (n = 1). ⁴ AF (n = 20), Aflutter (n = 0). ⁵ Persistent nonsustained VT (n = 9), new postoperative nonsustained VT (n = 10).

Events during Follow-Up

From postoperative AECG to end of data acquisition, 16 patients died [7 suddenly, 4 due to HF, 5 due to noncardiac causes (stroke, prostate cancer, esophageal cancer, kidney failure and sepsis, 1 patient each)]. In our prospectively studied cohort, 1 death (from stroke) occurred before the initial AECG in a patient who did not qualify for this analysis.

Prediction of CD from Postoperative VT and EF

Of 19 patients with persistent or new VT after MVS, 7 died (5 suddenly, 1 due to HF, 1 noncardiac). Five deaths (4 SD, 1 HF) occurred among the 10 patients with >1 VT

event after MVS. All episodes of VT were monomorphic with the majority of patients (55%) having right bundle branch block-like QRS appearance in the V_1 Holter vector. All episodes were nonsustained and lasted an average of 2.9 ± 2.2 s and manifested an average cycle length of 448 ± 86 ms. For patients with >1 VT after MVS, the average annual risks (AARs) of SD and CD were 4.9 and 6.2%, respectively. Repeated (>1) VT episodes significantly predicted SD ($p = 0.01$) and CD ($p < 0.04$) by univariable analysis (fig. 1). Any VT marginally predicted SD ($p = 0.05$) but only trended toward predicting CD ($p = 0.07$). Neither the number of beats in the longest VT run nor the duration of that run (in seconds) predicted SD or CD.

Fig. 2. Impact of subnormal RVEF on postoperative CD. Outcomes are SD and CD (SD or HF deaths). **a** RVEF stratified as subnormal or normal versus freedom from CD. **b** RVEF versus freedom from SD. **c** Severity of RVEF depression versus rate of progression to CD among the 3 of 4 patients with subnormal RVEF who died of cardiac causes.

Fig. 3. Impact of subnormal LVEF on postoperative CD. Outcomes are SD and CD (SD or HF deaths). **a** LVEF stratified as subnormal or normal versus freedom from SD. **b** LVEF versus freedom from CD.

After MVS, all 4 patients with subnormal RVEF died (1 SD, 2 HF, 1 noncardiac). Among this group, AARs of SD and CD were 3.4 and 10.2%, respectively. Subnormal RVEF predicted CD ($p = 0.03$; fig. 2a) but not SD ($p =$ not significant; fig. 2b). Absolute magnitude of RVEF was directly correlated with postoperative survival ($p = 0.01$; fig. 2c). VT >1 episode also predicted CD ($p = 0.03$) among those with subnormal RVEF but not among those with normal RVEF ($p =$ not significant). VT >1 episode significantly predicted SD among patients with normal

RVEF ($p = 0.03$). When analysis was adjusted for variations in age, gender, MR etiology, or preoperative use of antiarrhythmics, both postoperative VT and RVEF predicted CD ($p \leq 0.05$, all adjustments). However, when postoperative VT and RVEF were considered in the same multivariable model, CD was predicted only by subnormal RVEF ($p < 0.04$), indicating its greater value versus VT for prediction of this outcome. The independent predictive value of VT >1 episode and subnormal RVEF could not be evaluated for SD due to limited events.

Among patients with subnormal LVEF after MVS, 10/30 (33.3%) patients died (6 SD, 1 HF, 3 noncardiac). LVEF did not predict SD or CD either in univariable (fig. 3) or multivariable analyses. Nonsustained VT >1 episode predicted SD among those with subnormal LVEF ($p = 0.04$) but not among those with normal LVEF ($p =$ not significant); VT >1 episode did not predict CD in either the subnormal or normal LVEF subgroups ($p =$ not significant).

Prediction of CD from Preoperative VT and EF

When defined preoperatively, presence of VT, repeated (>1) VT episodes, AF or Aflutter, LVEF and RVEF did not significantly predict postoperative SD or CD. Among those 3 patients with a VT >1 episode before and after MVS, 1 died suddenly. However, the independent predictive value of persistent VT >1 episode could not be evaluated due to the limited events.

Discussion

Our data indicate that when >1 episode of nonsustained VT is observed in a single AECG within 18 months after MVS for nonischemic MR, late postoperative cardiac mortality (especially due to SD) is significantly increased compared with absence of the arrhythmia. This is consistent with recent observations among patients with HF in the Sudden Cardiac Death in Heart Failure Trial in which >2 episodes of nonsustained VT, but not the presence of VT at baseline 24-hour AECG, predicted all-cause death [20]. Though subnormal RVEF after operation was a strong predictor of CD but not SD, among patients with normal RVEF, VT >1 episode predicted SD.

VT on AECG after MVS has not been reported previously to predict CD. However, the relatively frequent occurrence of VT in unoperated MR [8, 21], and the importance of VT and other complex ventricular arrhythmias in predicting SD in unoperated MR, described by several authors [5, 7, 8, 22, 23], suggest that the myocardial effects of MR may predispose to VT, which often progresses to death. Although LV dysfunction is an important predisposing factor for fatal outcome in patients with other diseases who manifest VT [24–27], the present data suggest that the predisposition to arrhythmia persists even after the abnormal mechanical effects of MR have been relieved.

Apparent dissociation between RVEF and LVEF for late outcome after surgery are consistent with our earlier

findings that the magnitude of preoperative RV (but not LV) dysfunction predicts late postoperative death in patients who undergo MVS when LV and RV dysfunction are established before MVS [4] and among patients who undergo surgery for concomitant MR and aortic regurgitation [14]. This suggestion is supported by our finding that subnormal RVEF after surgery is also predictive and may add to the impact of VT. However, in our study, >1 VT episode predicted SD even in patients with normal RVEF, suggesting that the myocardial predisposition to ventricular arrhythmia is not exclusively related to RV dysfunction. Although the reason for this finding is not completely understood, it may relate to an increased incidence of bundle-branch reentry VT that is observed after valve surgery [28]. This type of sustained VT has been seen predominantly in the first postoperative month in retrospective studies of patients undergoing electrophysiologic evaluation after valve surgery for suspected or documented arrhythmia [28, 29]. In contrast to these retrospective studies, we prospectively followed all patients undergoing surgery for nonischemic MR, but did not perform an electrophysiologic study to define VT types. Scar-related VT has also been associated with valve surgery, predominantly in patients with comorbid coronary heart disease (and subnormal LV function) [28, 29]. Such patients were excluded from our study.

The importance of identifying patients at risk for late postoperative CD is suggested by the studies of Hammermeister et al. [6], who found that 81 ± 4 and $79 \pm 4\%$ of patients who had undergone mechanical and bioprosthetic mitral valve replacement, respectively, died within 15 years after surgery; among these, 31 and 26% were SD. The current tendency to perform mitral valve repair rather than replacement for most patients with MR, and to perform surgery relatively earlier than in past years, has resulted in better short- and longer-term outcomes [30–33]. However, successful surgery often did not prevent preoperative VT persistence in our patients, even if LVEF was well preserved. Given the prognostic value of postoperative VT >1 episode, this finding suggests that MVS alone may be insufficient to optimally protect patients with MR, even when LVEF is preserved. Additional preventive strategies, perhaps including implantation of internal cardiac defibrillators among those at risk, may need to be considered. Our data further suggest that, in seeking patients who are at relatively high risk after the operation, rhythm analysis should be supported by RVEF determination.

Although our findings suggest that routine assessment of ventricular rhythm is important for risk stratification

after MVS, this study does not define the optimal evaluation regimen, either in terms of timing or assessment frequency. We sampled cardiac rhythm by AECG relatively infrequently. However, as a proof of principle, the magnitude of AAR for SD (4.9%) and CD (6.2%) among those with >1 VT episode on a single AECG suggests that this measure is useful. Perhaps assessment earlier than a maximum of 18 months after surgery would be more effective if remedial action is to be undertaken. Nonetheless, since only 1 death occurred in our series (from stroke) before the initial AECG, and only 1 occurred in our patients who did not qualify for this analysis, the possibility of earlier death may not negate the value of VT assessment even as late as 18 months after surgery.

We did not demonstrate a relation of postoperative LVEF with outcome. This association was expected in view of earlier findings [34] specifically relating preoperative LVEF to postoperative survival [3, 35, 36]. Inferences drawn from our data are limited by the relatively small size of our population and the relatively small range of postoperative LVEF, minimizing the likelihood of finding a relation even if it truly exists. In addition, the long recruitment interval and relatively long follow-up inevitably imply that changes in surgical techniques might have resulted in variation in our results. This is a universal problem with long-term studies but our data nonetheless suggest an important principle that has not previously been assessed.

In summary, our data suggest the importance of rhythm and RVEF determination after surgery for MR. Additional studies will be needed to optimally define the regimen for such assessment and the remedial strategies that should be developed as a result.

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