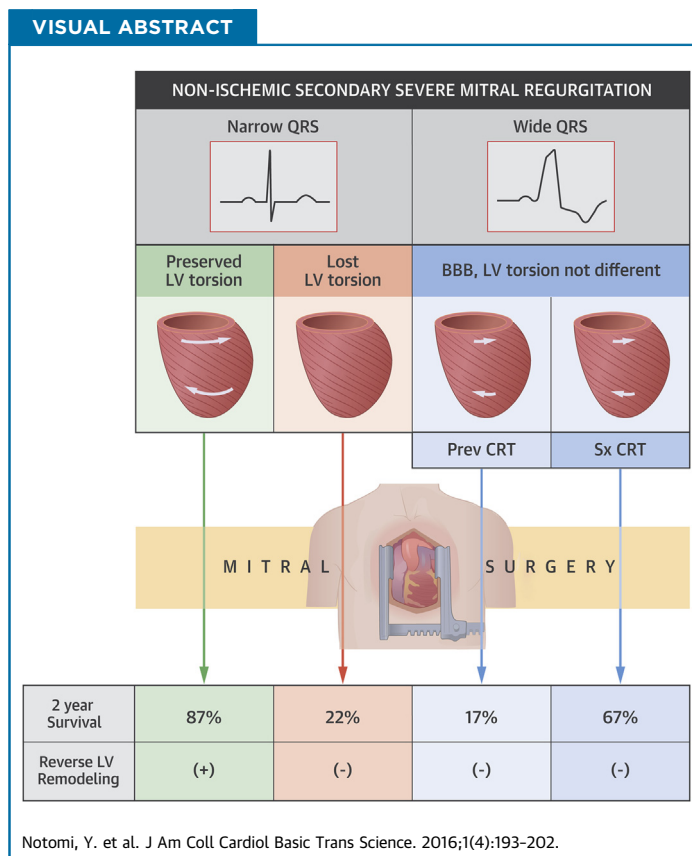




CLINICAL RESEARCH

Pre-Operative Left Ventricular Torsion, QRS Width/CRT, and Post-Mitral Surgery Outcomes in Patients With Nonischemic, Chronic, Severe Secondary Mitral Regurgitation

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HIGHLIGHTS

- Determining which patients with NICSMR will benefit from MS is a clinical dilemma.
- LV torsion (which is a shear strain, not volume strain such as ejection fraction and originates in LV myocardial architectures) may reveal the myopathic conditions and reflect intra-LV electrical conduction.
- The LV torsional profile predicted post-MS outcomes in NICSMR patients with a narrow QRS but not in those with a wide QRS.
- The findings may help to resolve the clinical dilemma and identify appropriate candidates for mitral surgery (and other resources) in patients with NICSMR.

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SUMMARY

The selection of appropriate candidates for mitral surgery among symptomatic patients with nonischemic, chronic, secondary severe mitral regurgitation (NICS MR) remains a clinical challenge. We studied 50 consecutive symptomatic NICS MR patients for a median follow-up of 2.5 years after mitral surgery and concluded that the pre-operative 2-dimensional speckle tracking echocardiography-derived left ventricular torsional profile and QRS width/ cardiac resynchronization therapy are potentially important prognostic indicators for post-surgery survival and reverse remodeling. (J Am Coll Cardiol Basic Trans Science 2016;1:193-202) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

In 2008, U.S. guidelines (1) stated, “Determining the surgical candidacy of the symptomatic patient with mitral regurgitation (MR) and far-advanced left ventricular (LV) dysfunction is a common clinical dilemma.” Even today, as stated in the current U.S. guidelines published in 2014 (2), mitral surgery for severely symptomatic patients with nonischemic, chronic, severe secondary mitral regurgitation (NICS MR) is a Class IIb recommendation with Level of Evidence (LOE): B. Because the primary cause of this condition is cardiomyopathy, “restoration of mitral valve competence is not by itself curative; thus, the best therapy for chronic secondary MR is much less clear than it is for chronic primary MR” (2). The guidelines additionally stated, “Prognosis is poor for both ischemic and nonischemic MR, but ischemic MR lends itself to the possibility of revascularization and potential improvement in LV function if CAD has led to large areas of hibernating viable myocardium” (2). This statement suggests that the prognosis of NICS MR after mitral surgery (in which some patients improve, whereas others die) depends more on the effectiveness of volume unloading as a result of the surgery, that is, the “reverse remodeling viability” (3) of the compromised LV myocardium.

Strategies for risk stratification by applying viability indexes beyond LV size and ejection fraction may play a critical role in enabling patients and attending physicians to understand the risk, prognosis, and available resources (i.e., guideline-directed medical therapy [GDMT], transcatheter mitral valve repair system, mitral surgery, ventricular assistance device [VAD]/transplantation, or palliative care). Most previous reports (4-9) on mitral surgery for dilated poor LV function, however, have neither focused on NICS MR (mostly ischemic etiology) nor reflected the results of recent advancements, such as cardiac resynchronization therapy (CRT), which is a Class I recommendation

with a Level of Evidence: A (2) for NICS MR patients with appropriate indications (10). As a result, patients are offered CRT before mitral surgery or receive a CRT system at the time of mitral surgery. The characteristics and prognosis of these patients also remain unclear.

Left ventricular torsion (LV-Tor), which originates in the myocardial architecture and conduction system, may be a sensitive indicator of cardiomyopathy and disturbances of intra-LV conduction. LV-Tor may therefore be considered a viability index, as suggested by “force-dependent” LV strain (11). In contrast, right ventricular pacing and biventricular pacing generally result in decreases in LV-Tor (12); it has therefore also been suggested that LV torsional mechanics is not an essential component of LV function in left bundle branch block (LBBB) or during CRT (13).

SEE PAGE 203

Therefore, we investigated whether pre-operative LV-Tor and QRS width/CRT use can predict post-operative survival and LV reverse remodeling in patients with NICS MR and can ultimately identify an optimal clinical approach to identifying the appropriate treatment in patients with NICS MR.

METHODS

STUDY DESIGN. From September 2006 to August 2012, 50 consecutive patients with NICS MR who were scheduled for mitral surgery at the Hayama Heart Center, Kanagawa, Japan, were included in this observational study, which was approved by the local ethics committee. NICS MR stands for *nonischemic, chronic, severe secondary mitral regurgitation*. The term *nonischemic* in this study refers to idiopathic cardiomyopathy, as defined by the World Health Organization/International Society and Federation of Cardiology Task Force (14,15). All patients included were in an advanced symptomatic state (New York

ABBREVIATIONS
AND ACRONYMS

CRT = cardiac resynchronization therapy

EDV = end-diastolic volume

EF = ejection fraction

ESD = end-systolic dimension

GDMT = guideline-directed medical therapy

LBBB = left bundle branch block

LV = left ventricle/ventricular

NICS MR = nonischemic chronic secondary mitral regurgitation

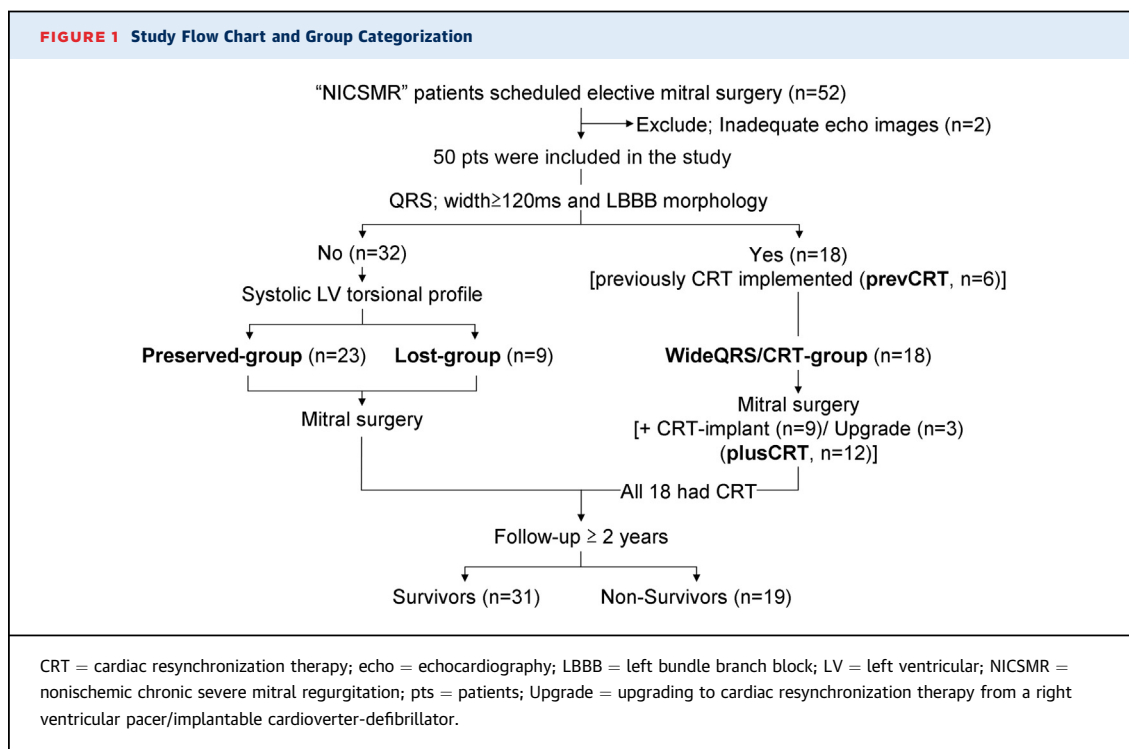
Heart Association functional class III or IV), had already received the maximum GDMT for more than 6 months, had no prior surgical history, and provided written informed consent before inclusion in the study. The study flow chart and group categorization are shown in **Figure 1**. On the basis of the pre-operative baseline LV-Tor profile and QRS width (<120 or ≥120 ms), we divided the 50 patients into 3 groups: the Preserved, Lost, and WideQRS/CRT groups. The WideQRS/CRT group was subdivided into the PrevCRT (patients who received CRT before the mitral surgery) and PlusCRT (patients who were given CRT at the time of the mitral surgery) groups. All patients in the WideQRS/CRT group received CRT after the mitral surgery. We followed the clinical/survival status and echocardiographic variables of the 50 patients for at least 2 years after the mitral surgery.

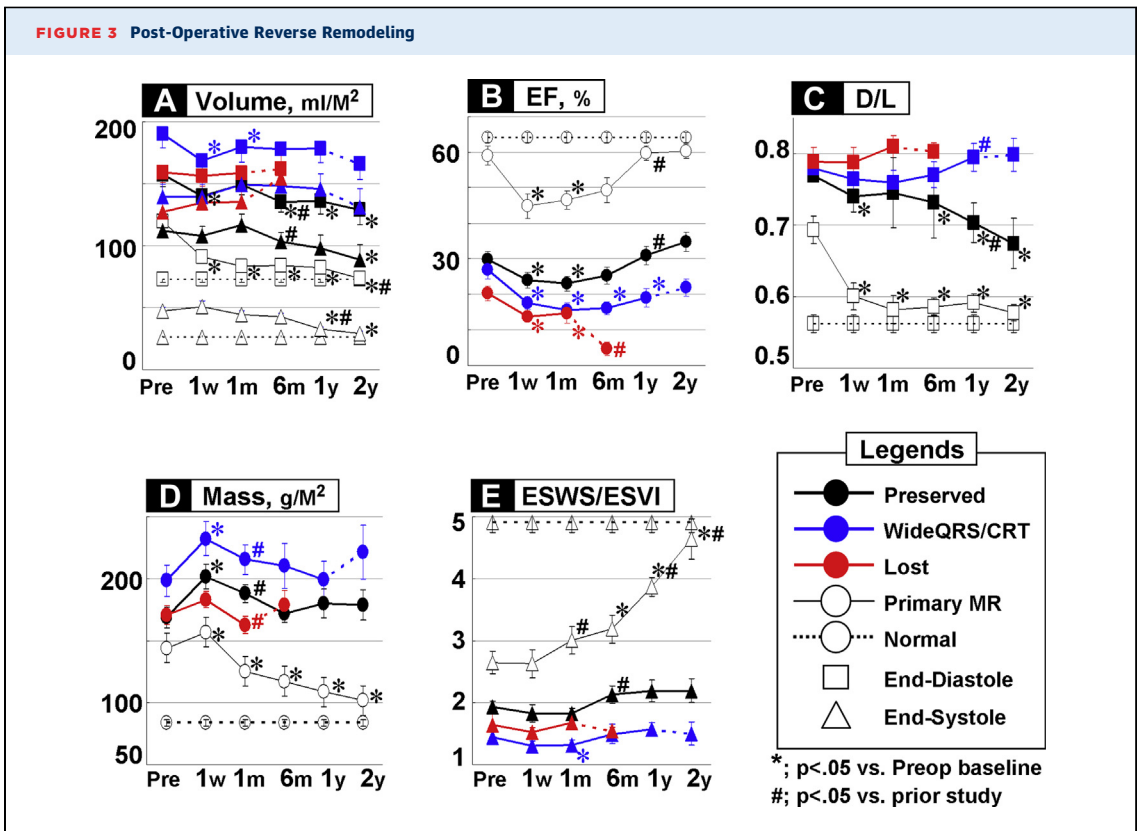
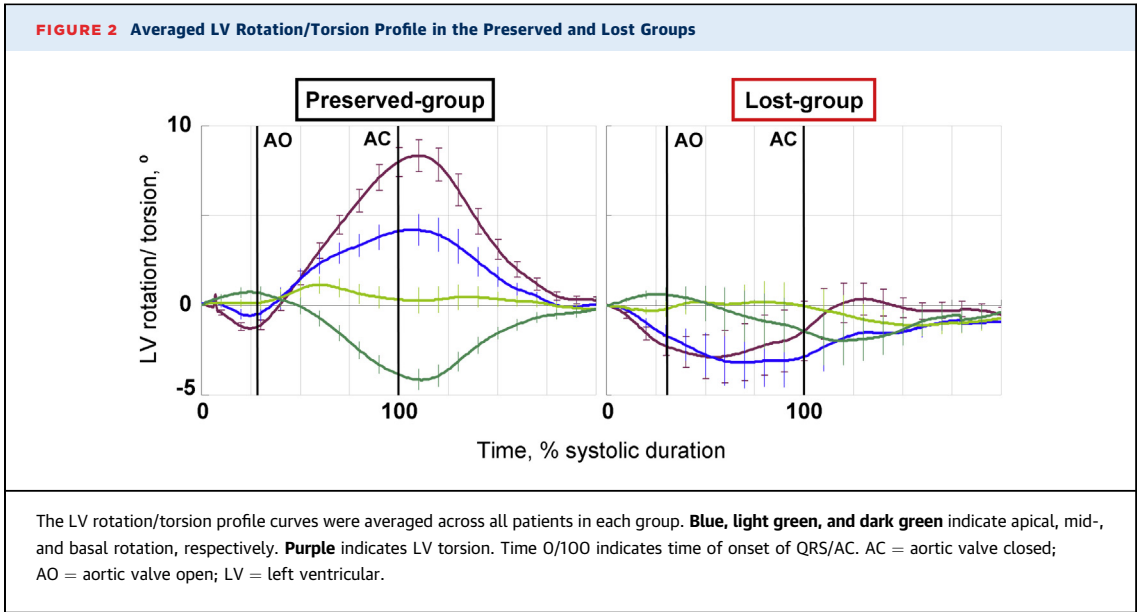
SURGICAL PROCEDURES. Surgical correction of MR was performed with preservation of the subvalvular apparatus, which acts as a modulator of contractility and LV-Tor (16). Mitral valve (MV) repair was performed with annuloplasty (Carpentier-Edwards Physio or Physio II Annuloplasty Ring [Edwards Lifesciences, Irvine, California]; median ring size: 28 mm) with or without second chordal cutting and/or adding artificial chordae tendineae. According to the U.S. guidelines (2), MV repair was preferred

over MV replacement if possible; replacement was performed in 9 patients (18%) on the basis of the surgeons' intraoperative preference, and tricuspid surgery (annuloplasty with or without edge-to-edge repair) was performed in 29 patients (58%) who also had severe functional tricuspid regurgitation or tricuspid annulus dilation. For patients in the PlusCRT subgroup, an epicardial LV lead was placed intraoperatively and optimal CRT was performed immediately after the surgery.

ECHOCARDIOGRAPHIC ANALYSIS. All 2-dimensional (2D) echocardiographic measurements (including MR quantification according to the proximal isovelocity surface area method with angle correction) followed the recommendations of the American Society of Echocardiography and American Heart Association/American College of Cardiology (2,17). Conventional 2D, Doppler, and speckle tracking echocardiography (STE) were performed using commercially available equipment and analyzed on a workstation (Vivid7 or E9 with an M4S or M5S [1.5 to 4.3 MHz and 2.2 to 5.0 MHz] transducer and EchoPAC, GE Healthcare, Horten, Norway) as previously reported (12,18-20). LV contractility/elasticity was determined with the end-systolic wall stress and volume ratio (ESWS/ESVI) (21-24).

Definitions of "preserved" and "lost" LV torsion. Using the systolic torsional profiles analyzed by 2D-STE, we





The LV volume (A) and EF (B) were calculated with the area-length method. 1 week, 1 month, 6 months, 1 year, and 2 years indicate 1 week, 1 month, 6 months, 1 year, and 2 years after mitral surgery, respectively. The **dotted line in the graphs** indicates the number of remaining survivors was less than one-half of the initial number of patients (i.e., more than one-half died at that time). *Significantly different from baseline (Pre). #Significantly different from the prior study. D/L (C) = ratio of left ventricular diameter and length; EF = ejection fraction; ESWS/ESVI (E) = end-systolic wall-stress per indexed end-systolic volume (mm Hg/ml/m²); Mass (D) = indexed LV mass (g/m²); MR = mitral regurgitation; Pre = pre-operative baseline data.

divided narrow QRS patients into 2 groups: the *Preserved* and *Lost* (LV-Tor) groups. *Preserved* was defined as a preserved normal systolic torsional profile and positive net torsion (i.e., apical to basal rotation) through the systole following reverse torsion in the very early phase. Positive rotation or torsion was indicated by a counterclockwise direction when the LV was viewed from the apex. In most cases, this condition was the result of positive apical and negative basal rotation. *Lost* was defined as a loss of the normal systolic torsional profile, which was typically due to large negative apical rotation and small basal negative rotation. As a result, the LV-Tor profiles of the lost torsion patterns were negative (persistent reverse net torsion) during systole (Figure 2). All of the apical short-axis images were assessed for the appropriateness of the scanned level (Supplemental Table 1).

STATISTICAL ANALYSIS. The normality of the variables was assessed with the Kolmogorov-Smirnov test. Continuous variables are expressed as the mean ± SD if normally distributed or by the median (interquartile range) for variables with a skewed distribution. On the basis of the normality of the variables, the parametric or the nonparametric test was chosen as appropriate. Categorical variables are expressed as counts and percentages. The error bars in the LV torsional profiles and Figure 3 are shown as the mean ± SE. Comparisons between survivors and nonsurvivors were made using the Student *t* test or the Mann-Whitney *U* test. Categorical variables were analyzed using the chi-square test or Fisher exact test (when the expected cell frequency was <5). The categorical variables were analyzed with residual analysis to identify the category responsible for a chi-square statistic. Multiple comparisons were made among the 3 groups using analysis of variance or the Kruskal-Wallis test with Sheffé's post-hoc analysis. Kaplan-Meier curves were constructed to show patients' survival after the mitral surgery over time. The index date was the date of the surgery. The primary endpoints were analyzed until death (all causes), the implantation of VAD, or the study termination date. Survival among groups was compared using the log-rank test. Changes in variables from baseline to follow-up were analyzed using paired *t* tests or Wilcoxon matched-pairs analysis.

Statistical analysis was performed with the Statistical Package for Windows (Excel Statistics 2012, Social Survey Research Information Co., Ltd., Tokyo, Japan) and R software version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed *p* value <0.05 was considered significant.

RESULTS

The study was terminated in September 2014. We followed up with 42 patients (84%) at the Hayama Heart Center; the other patients' data were provided by their primary attending physicians. The median follow-up term was 2.5 years (interquartile range: 0.9 to 4.5 years).

PRE-OPERATIVE VARIABLES. The baseline pre-operative variables of the entire cohort and the 2-year survivors/nonsurvivors after mitral surgery are shown in Table 1.

Pre-operative clinical status did not differ between post-operative survivors and nonsurvivors except when CRT had previously been used. The Society of Thoracic Surgeons scores among the Preserved, Lost, and WideQRS/CRT groups were also similar

TABLE 1 Pre-Operative Variables

	Whole Cohort (n = 50)	2 Years After Mitral Surgery		p Value
		Survivors (n = 31)	Nonsurvivors (n = 19)	
Clinical indexes				
Age, yrs	62 ± 11	63 ± 10	62 ± 12	0.81
Female	15 (30)	11 (35)	4 (21)	0.35
Body surface area, m ²	1.59 ± 0.20	1.63 (1.47-1.77)	1.57 (1.43-1.66)	0.30
Body mass index, kg/m ²	21 ± 3	21 ± 3	20 ± 3	0.16
Atrial fibrillation/flutter	13 (26)	10 (32)	3 (16)	0.32
QRS width, ms	116 (98-136)	103 (96-135)	118 (100-152)	0.33
Previous CRT	6 (12)	1 (3)	5 (26)	0.024
NYHA functional class	3.6 ± 0.5	3.5 ± 0.5	3.7 ± 0.5	
III	20 (40)	17 (55)	13 (68)	0.39
IV	30 (60)	14 (45)	6 (32)	
STS score	1.20 (0.95-2.14)	1.15 (0.91-1.82)	1.24 (0.99-3.01)	0.23
Echocardiographic indexes				
LV end-diastolic dimension/BSA, cm/m ²	4.6 ± 0.6	4.5 (4.1-5.0)	4.8 (4.3-4.9)	0.07
LV end-diastolic volume/BSA, ml/m ²				
Biplane	132 (111-145)	124 (107-140)	142 (129-165)	0.005
Area-length	170 ± 46	162 ± 47	181 ± 43	0.17
LV ejection fraction, %				
Biplane	27 ± 8	27 ± 9	26 ± 6	0.80
Area-length	24 (20-36)	27 (20-37)	23 (20-26)	0.18
LV shape, diameter/length	0.77 ± 0.07	0.76 ± 0.07	0.79 ± 0.07	0.12
LV mass/BSA, g/m ²	180 ± 45	174 ± 44	189 ± 46	0.25
LV torsion, °	4.6 ± 6.0	6.1 ± 4.7	2.0 ± 7.3	0.018
Left atrial volume/BSA, ml/m ²	80 (55-131)	74 (54-105)	99 (75-136)	0.23
MR volume/BSA, ml/m ²	31 ± 8	31 ± 8	31 ± 7	0.90
Effective regurgitant orifice area of the MR, cm ²	0.41 (0.31-0.50)	0.35 (0.31-0.49)	0.46 (0.34-0.54)	0.09

Values are mean ± SD, n (%), or median (interquartile range). Society of Thoracic Surgeons score was calculated on version 2.81. Values in bold indicate a significant *p* value (*p* < 0.05).

BSA = body surface area; CRT = cardiac resynchronization therapy; LV = left ventricular; MR = mitral regurgitation; NYHA = New York Heart Association.

(median 1.15, 1.23, and 1.32, respectively; $p = 0.42$; in general, a difference between the study groups could not be found in the pre-operative variables) (Supplemental Table 2).

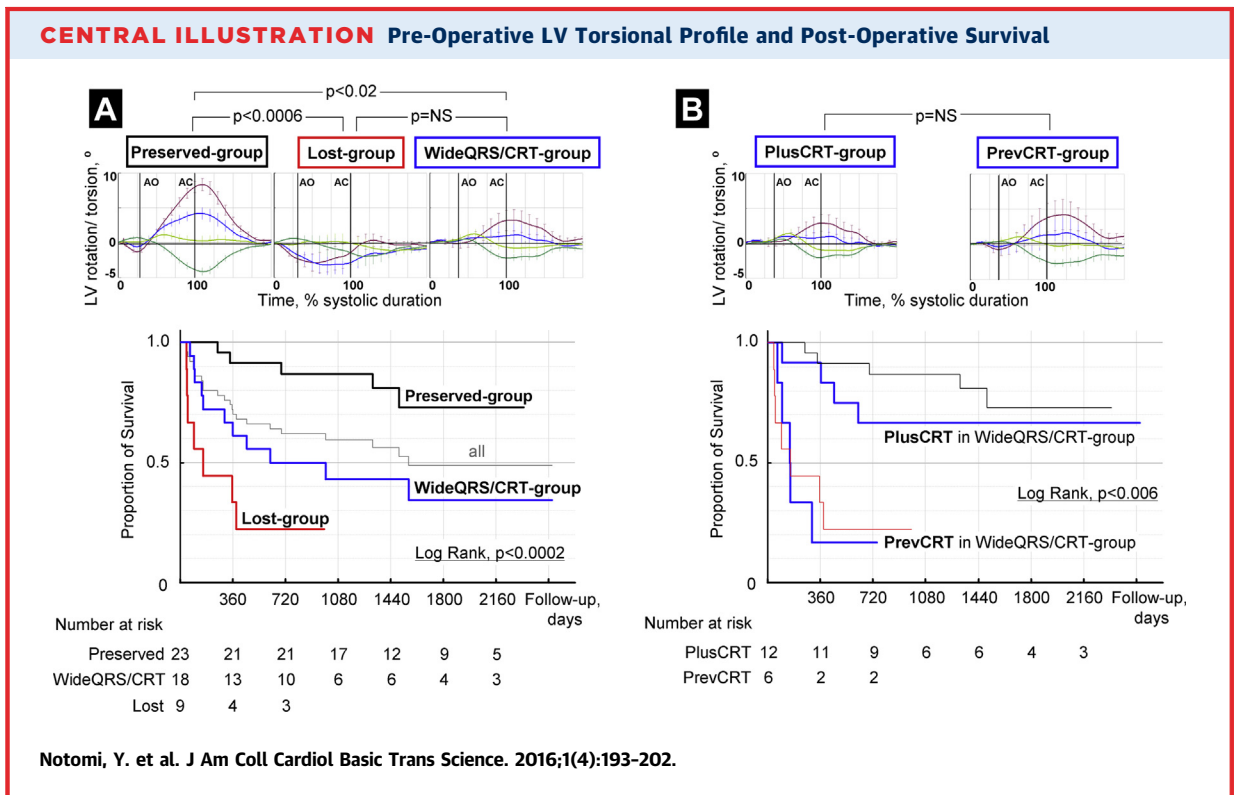
Baseline LV size, shape, and mass tended to be larger and more spherical in nonsurvivors; however, there was no statistical difference except in the LV volume estimated by the biplane disk summation. The LV ejection fraction and MR severity were virtually identical among the groups; the LV torsion, however, was higher in survivors.

POST-OPERATIVE SURVIVAL. During the study period, there was no operative mortality; 19 patients reached the primary endpoint: 12 died of congestive heart failure, 1 received VAD implantation, 4 died suddenly, and 2 died of noncardiac causes (1 from pneumonia and 1 from infectious spondylitis). These 2 noncardiac deaths occurred in the Preserved group.

The Central Illustration shows the LV torsional profiles and Kaplan-Meier curves for the endpoint in the 3 categorized groups (panel A) and in the subgroups of the WideQRS/CRT group (panel B).

In panel A, the end-systolic LV torsion was significantly higher in the Preserved group ($8.2 \pm 3.6^\circ$) than in the Lost ($-1.4 \pm 5.0^\circ$) and WideQRS/CRT ($3.2 \pm 6.1^\circ$) groups, but there was no significant difference between the Lost and WideQRS/CRT groups. The log-rank test indicated a significant difference in the 2-year survival among the 3 groups (87%, 22%, and 50%; log-rank $p < 0.0002$). There was also a significant difference between the Preserved and WideQRS/CRT groups ($p < 0.007$) but not between the WideQRS/CRT and Lost groups ($p = 0.067$, but statistical power 0.39). In panel B, although the LV torsional profile was not significantly different between the subgroups (end-systolic torsion: $2.7 \pm 5.4^\circ$ in PlusCRT and $4.5 \pm 6.4^\circ$ in PrevCRT; $p = 0.45$), the PrevCRT group showed significantly worse 2-year survival than the PlusCRT group (17% vs. 67%; log-rank $p < 0.006$).

Congestive heart failure hospitalization was very frequent in patients in the Lost group (67%) but relatively infrequent in the Preserved group (9%). Moderate or higher MR recurrence after mitral repair was observed in 2 patients in the Preserved group and



(A and B) The legends of upper graphs of LV torsional profile are the same as in Figure 1. (A) LV torsional profiles and Kaplan-Meier curves in the 3 groups. In the lower Kaplan-Meier graphs, the gray line indicates the survivor curve for all 50 patients. (B) LV torsional profiles and Kaplan-Meier curves in the subdivided 2 groups from the WideQRS/CRT group. In the lower Kaplan-Meier graphs, the thin black and red lines are superimposed on the Preserved and Lost group curves in A for comparison (not all statistical analyses are shown, due to a similar trend and a small number).

1 patient each in the Lost and WideQRS/CRT groups during follow-up; this was treated medically in all cases.

POST-OPERATIVE REVERSE REMODELING. Figure 3 shows the degree and course of the LV reverse remodeling in each of the 3 groups.

To better understand the reverse remodeling after mitral surgery, we also analyzed the comparative data of age- and sex-matched 18 normal subjects and 12 patients with primary MR.

Figure 3A. At 1 week and 1 month, decreased LV size as a result of volume unloading with mitral surgery was observed in all groups except for the Lost group. After 1 to 6 months, in the Preserved group, the LV end-diastolic volume (EDV) gradually decreased, whereas the LV end-systolic volume slowly and significantly decreased after 2 years compared with the baseline ($19 \pm 39\%$ reduction from baseline; $p = 0.027$), but it remained high ($112 \pm 47 \text{ ml/m}^2$ to $89 \pm 48 \text{ ml/m}^2$). The LVEDV in the primary MR group returned to a normal level sooner than in the other groups. No significant LV volume reduction was observed in the WideQRS/CRT or Lost groups after 2 years. Even the PlusCRT subgroup of the WideQRS/CRT group did not manifest significant reverse remodeling; the end-systolic volume/body surface area values were baseline: $141 \pm 51 \text{ ml/m}^2$; 1 year: $152 \pm 41 \text{ ml/m}^2$ ($p = 0.09$); and 2 years: $136 \pm 36 \text{ ml/m}^2$ ($p = 0.32$ vs. baseline).

Figure 3B. LV function tended to show a mild transient decrease from 1 week to 6 months after surgery in all groups, and thereafter returned to a normal level in the primary MR group and to the baseline level in the Preserved group at 6 months. The Preserved group showed delayed and insignificant improvement over the course of 2 years, whereas the other groups did not.

Figure 3C. The LV shape gradually became more elliptical toward normal only in the Preserved group (but still spherical at 2 years), whereas the shape rapidly normalized in primary MR.

Figure 3D. Transient LV mass increment at 1 week (suggesting the effect of cardioplegia) was observed in all groups except for the Lost group. The LV mass returned to the baseline level at 1 month and was stable thereafter, except in the primary MR group. The primary MR group continued to exhibit regression of the LV mass to the normal level over 2 years, whereas the Preserved group did not show similar regression.

Figure 3E. The LV contractility/elastance of the primary MR group was normalized over a period of 2 years, but the NICSMR groups did not increase more than the baseline.

It should be mentioned that most trends of reverse remodeling in the WideQRS/CRT group were not found to be dissimilar to those in PrevCRT and/or PlusCRT patients. One reason for this finding is that most patients in the PrevCRT subgroup died within 1 year.

DISCUSSION

The main findings of the current study are as follows:

1. For patients with NICSMR and a narrow QRS width, preserved LV-Tor may be a better predictor of post-mitral surgery survival; conversely, lost LV-Tor may imply a poor post-surgical outcome. Importantly, pre-operative LV size, EF, and geometric shape were not significantly different between 2-year survivors and nonsurvivors in our cohort.
2. The post-surgical survival results were intermediate in patients with a wide (LBBB pattern) QRS. This group was divided into 2 subgroups for discussion because patients who had previously undergone CRT had significantly poorer survival, and those with newly performed CRT at the time of surgery had relatively better survival after mitral surgery, although the 2 subgroups had a similar LV-Tor.
3. Therefore, lost LV-Tor and previously administered CRT appeared to be markers of poor survival after mitral surgery in patients with NICSMR.
4. Reverse remodeling was observed only in the preserved LV-Tor group. Hence, lost LV-Tor and wide QRS (even in the PlusCRT subgroup) were markers of no reverse remodeling viability.

In short, as a clinical scenario, patients with NICSMR who have lost LV-Tor and a narrow QRS width or previous CRT implementation appeared to benefit less from mitral surgery; however, for patients with preserved LV-Tor and a narrow QRS, mitral surgery seemed to be an acceptable option. Thus, the assessment of LV-Tor may be useful for the prediction of post-mitral surgery outcomes in patients with a narrow QRS but not in those with a wide QRS, including patients with previous CRT implementation.

Hereafter, we discuss the pathophysiological rationale and clinical relevance of the current study.

LV-TOR AND REVERSE REMODELING: RECOVERY, REMISSION, OR PLASTIC. Although patients in the Preserved group showed a significant reverse “chamber” remodeling after MR elimination, the LV mass did not regress (keeping the initial mass volume) over 2 years; consequently, it re-remodeled toward concentric LV geometry. This re-remodeling appeared to lead to a decrease in wall stress without an increase in ESWS/ESVI during the 2 years of

follow-up. This finding was in contrast to the reverse remodeling course of primary MR, which showed a decrease in both chamber and mass and could truly be called “recovery” (improvement of the myocytes’ contractility). The Preserved group, therefore, appeared to be in “remission” (maintaining initial contractility) rather than recovery (25). To normalize the LV performance, with weak and compromised myocardium/myocytes this “re-remodeling” would be required. Thus, patients with preserved torsion would receive minimal (survival) benefit from volume unloading treatment.

In addition, the “plastic region” (25) might be characterized in the Lost group by no significant LV-Tor (hence, no chamber elliptization during systole) (Supplemental Table 3), poor post-surgical survival, and no reverse remodeling, in which the LV myocardium was irreversibly damaged and did not have the ability to respond to the volume-unloading treatment. The LV in the Lost group also appeared to be entirely pre-load dependent; it did not decrease in LVEDV after surgery (instead exhibiting re-dilation). The LV in the Lost group may have sustained irreversible myocellular damage in the plastic or “creep” region (irreversible “slippage” between myofibrils [26]) and did not achieve “remission” after mitral surgery. Thus, the lost LV-Tor profile might be a sign of requiring a ventricular assistance device.

Together, our results suggest the hypothesis that LV torsion may indicate the contractility/elastance (which enables reverse remodeling) of the LV compromised myocardium in NICS MR patients. LV-Tor was modestly but significantly correlated with ESWS/ESVI in our cohort ($r^2 = 0.17$; $p = 0.003$).

CRT IN NICS MR. Pathophysiology. It has been suggested that LV torsional mechanics require a normal synchrony (normal and rapid LV activation sequence) and that LV rotation mechanics may not be an essential component of LV function in cases of LV dyssynchrony and epicardially paced resynchronization (13). In other words, LV in LBBB and CRT contracts without torsional mechanics, which is a physiological advantage on the basis of the architecture. This contraction may be why the WideQRS/CRT group showed unusual LV torsional profiles, which required the creation of another group.

The mechanical discoordination indexes CURE (circumferential uniformity ratio estimate) (27) and ISF (internal stretch fraction) (28), calculated by the numerical data derived from 2D-STE, showed borderline discoordination values in both the PrevCRT and PlusCRT subgroups (Supplemental Table 4). Thus, the PrevCRT subgroup maintained some degree of discoordination, whereas the PlusCRT group did not

exhibit severe discoordination. This difference may explain why volume unloading (mitral surgery) and resynchronization would not be effective for promoting reverse remodeling in both subgroups. Additionally, favored reverse remodeling might be prevented by surgical factors such as systemic inflammatory response or myocardial oxidative stress/free radical injury with cardiopulmonary bypass, cardioplegia, and complete cardiac arrest. Hence, implementation of CRT before mitral surgery on the basis of appropriate indications would be needed, as suggested in the guidelines.

CORRECTION OF UNIMPROVED MR AFTER CRT IN NICS MR.

Although the effect of CRT on secondary MR was clear, MR persists in 30% to 40% of CRT patients (29–31) in the real world. The natural history of CRT nonresponders (nonfunctional MR improvers) is poor, with a reported 2-year mortality of 50% (29,30) and 3-year mortality up to 70% (31). In the present study, surgical correction of unimproved MR after CRT in NICS MR was unsuccessful. A recent report on the MitraClip (Abbott Vascular, Santa Clara, California), however, has demonstrated excellent results in such patients and “it emphasized the need to stratify early after CRT those patients who may either develop FMR or in whom FMR is unlikely to change (decrease) as well as need to consider additional therapeutic options such as (mitral) surgery or MitraClip treatment” (32).

STUDY LIMITATIONS AND FUTURE DIRECTIONS. We should address several limitations of this observational study, which was conducted at a single center.

Although consecutive patients were selected from a real-world clinic, the patient population was small and the follow-up term was short. A larger number of WideQRS/CRT group patients, specifically, should be included in the future to obtain more robust conclusions.

The mean effective regurgitant orifice area/regurgitant volume/regurgitant fraction was 0.41 cm²/48 ml/60% in the entire cohort. Because the current Western guidelines (2,33) indicate a value >0.2 cm²/ >30 ml/ $>50\%$ as severe, the symptoms of many patients observed in this study might have been too severe (or too late) at the time of referral to surgery. Unexpectedly, LV size, EF, and shape were not post-operative discriminators in this study. No assumption method using robust high-resolution 3-dimensional imaging (echocardiography or CMR) modalities can accurately assess the MR and LV volume (34–36).

Although it was beyond the scope of the current study, it is of note that nonsurvivors in our

cohort tended to have a larger right ventricle (possibly related to more required tricuspid surgery and higher levels of brain natriuretic peptide) (Supplemental Table 5). Right ventricular size was weakly inversely related to LV-Tor ($r^2 = 0.10$; $p = 0.026$). A multivariate Cox analysis in an appropriately sized randomized study might be able to determine the significance and independence of those indexes with sufficient statistical power. In the current study, the small sample precluded the ability to adjust for potential confounding factors when analyzing survival.

We did not include a medically treated control group. A randomized prospective trial of mitral surgery and GDMT in far-advanced LV dysfunction and heart failure has not been explored to date. It may be appropriate to determine the best clinical approach for NICS MR patients with the results of an analysis of quality-adjusted life-years and incremental cost-effectiveness in such trials. VAD as a destination therapy generally leads to 70% survival at 2 years (37), which may serve as a measure of survival success for other resources. The ongoing COAPT study (NCT01626079) involving patients with NICS MR with and without CRT will shed light on this issue. Finally, to treat primary myopathy, regenerative therapy to attain myocardial “recovery” would potentially facilitate therapeutic responses in NICS MR patients.

CONCLUSIONS

In patients with NICS MR, the LV torsional profile assessed with 2D-STE discriminated post-mitral surgery outcomes in patients with a narrow QRS but not in those with a wide QRS, and previously

implemented CRT appeared to be a marker of poor post-surgical survival.

The National Institutes of Health Fact Sheet (38) states that among adults, the 5-year relative survival rate for all cancers combined is now approximately 68%, whereas it was 50% in our entire cohort. Determining the safest and most effective management for NICS MR patients is the goal. The findings of this study may help to resolve this clinical dilemma and identify appropriate candidates for mitral surgery in patients with NICS MR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Preservation of the LV systolic torsional profile may be a helpful predictor for post-mitral surgery survival and reverse remodeling in patients with NICS MR who have a narrow QRS. Patients who received CRT prior to mitral surgery had poor post-surgery survival, whereas those who received CRT at the time of mitral surgery had better survival but no reverse remodeling.

TRANSLATIONAL OUTLOOK: Further randomized controlled trials are needed to determine whether clinical stratification with an LV torsional profile and QRS width/CRT use is associated with better, longer-term clinical outcomes after mitral surgery (and other resources) in patients with NICS MR.

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- KEY WORDS** cardiac resynchronization therapy, LV reverse remodeling, LV torsion, mitral surgery, nonischemic chronic secondary mitral regurgitation
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- APPENDIX** For supplemental tables, please see the online version of this article.