# **Robotic repair of posterior mitral valve prolapse versus conventional approaches: Potential realized**

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**Objective:** Robotic mitral valve repair is the least invasive approach to mitral valve repair, yet there are few data comparing its outcomes with those of conventional approaches. Therefore, we compared outcomes of robotic mitral valve repair with those of complete sternotomy, partial sternotomy, and right mini-anterolateral thoracotomy.

**Methods:** From January 2006 to January 2009, 759 patients with degenerative mitral valve disease and posterior leaflet prolapse underwent primary isolated mitral valve surgery by complete sternotomy (n = 114), partial sternotomy (n = 270), right mini-anterolateral thoracotomy (n = 114), or a robotic approach (n = 261). Outcomes were compared on an intent-to-treat basis using propensity-score matching.

**Results:** Mitral valve repair was achieved in all patients except 1 patient in the complete sternotomy group. In matched groups, median cardiopulmonary bypass time was 42 minutes longer for robotic than complete sternotomy, 39 minutes longer than partial sternotomy, and 11 minutes longer than right mini-anterolateral thoracotomy (P < .0001); median myocardial ischemic time was 26 minutes longer than complete sternotomy and partial sternotomy, and 16 minutes longer than right mini-anterolateral thoracotomy (P < .0001). Quality of mitral valve repair was similar among matched groups (P = .6, .2, and .1, respectively). There were no in-hospital deaths. Neurologic, pulmonary, and renal complications were similar among groups (P > .1). The robotic group had the lowest occurrences of atrial fibrillation and pleural effusion, contributing to the shortest hospital stay (median 4.2 days), 1.0, 1.6, and 0.9 days shorter than for complete sternotomy, partial sternotomy, and right mini-anterolateral thoracotomy (all P < .001), respectively.

**Conclusions:** Robotic repair of posterior mitral valve leaflet prolapse is as safe and effective as conventional approaches. Technical complexity and longer operative times for robotic repair are compensated for by lesser invasiveness and shorter hospital stay. (J Thorac Cardiovasc Surg 2011;141:72-80)

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Less invasive approaches for treating myxomatous mitral valve (MV) disease were introduced to reduce trauma while preserving the safety and quality achieved by surgery through complete sternotomy.<sup>1-5</sup> Partial sternotomy and limited right mini-anterolateral thoracotomy reduced incision size while still allowing surgery under direct visualization using conventional instruments.<sup>1,4,6</sup> Robotic MV repair represents the latest development in less invasive surgery.<sup>7,8</sup> Despite obvious potential benefits of reduced trauma and improved cosmesis, acceptance of robotic MV repair has been limited because of concern about its complexity, prolonged operative time, quality of repair, and cost.<sup>9,10</sup>

Comparisons of its safety and effectiveness with other less invasive approaches have been based on heterogeneous patient cohorts, with variable extent of myxomatous disease, and often historic rather than concurrent controls.<sup>7,11,12</sup> The purpose of this study was to provide a contemporary comparison of the safety and efficacy of robotic MV repair with those of complete sternotomy, partial sternotomy, and mini-anterolateral thoracotomy in concurrently treated patients with myxomatous MV disease limited to posterior leaflet repair.

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#### **Abbreviations and Acronyms**

- ANT = mini-anterolateral thoracotomy
- CST = complete sternotomy
- MR = mitral regurgitation
- MV = mitral valve
- PST = partial sternotomy
- ROB = robotic

#### PATIENTS AND METHODS Patients

From January 1, 2006, to January 1, 2009, 759 patients with degenerative MV disease limited to the posterior leaflet underwent primary isolated MV repair at Cleveland Clinic via complete sternotomy (CST; n = 114), partial sternotomy (PST; n = 270), mini-anterolateral thoracotomy (ANT; n = 114), or a robotic (ROB; n = 261) approach. Patients who underwent concomitant procedures were not included, with the exception of patent foramen ovale or atrial septal defect closure and left-sided ablative procedures for atrial fibrillation. Patient characteristics, including description of the extent and morphology of MV disease, are shown in Table 1. Although 17 patients had a moderate (2+) degree of mitral regurgitation (MR) on preoperative transthoracic echocardiography, all had severe MR on transesophageal or stress echocardiography.

## **Surgical Technique**

Conventional general anesthesia was used in all patients, with duallumen endotracheal intubation and isolated left lung ventilation for the ROB or ANT approach. All operations were performed on cardiopulmonary bypass at normothermia or mild hypothermia, with the use of antegrade and retrograde cold blood cardioplegia.

For CST, cardiopulmonary bypass was instituted by cannulating the distal ascending aorta and superior and inferior venae cavae, and the MV was exposed through a left atriotomy. For PST, the operation was performed through division of the upper sternum, as previously described.<sup>13</sup> ANT was performed through the fourth intercostal space with the use of femoro-femoral cardiopulmonary bypass.<sup>4</sup> ROB MV repair was accomplished with the use of robotic surgical instrumentation via a minithoracotomy or endoscopic ports.

For ANT and ROB, cardiopulmonary bypass was established by cannulating the femoral artery and vein, with optional cannulation of the superior vena cava through the right internal jugular vein. After pericardiotomy, for ANT, the ascending aorta was generally occluded with a transthoracic clamp or occasionally with an endoballoon; for ROB, the ascending aorta was occluded with an endoballoon or transthoracic clamp.

For ROB, the left arm of the robot was inserted through the third intercostal space in the anterior-axillary line and the right arm was inserted through the fifth intercostal space in the mid-axillary line. A mini-thoracotomy or working port was placed in the fourth intercostal space in the mid-axillary line, and a dynamic left atrial retractor was placed in the mid-clavicular line.

MV repair was accomplished using triangular or quadrangular resection of the prolapsed segment (Table E1). Artificial polytetrafluoroethylene chordae were used for leaflet repair in patients with extensive posterior leaflet prolapse. Edge-to-edge leaflet repair was used primarily for prolapse of lateral or medial posterior leaflet scallops. A partial flexible anuloplasty band (Cosgrove-Edwards Annuloplasty System, Edwards Lifesciences, Inc, Irvine, CA) was used in all but 1 patient, in whom the MV was replaced after failed repair.

#### Data

Preoperative and operative variables were retrieved from the Cardiovascular Information Registry, an ongoing, prospective, concurrent registry of all cardiac operations; these were augmented by data from echocardiography, cardiac anesthesia, laboratory medicine, and operating room databases. Pain scores were retrieved manually and from the Electronic Health Record. The institutional review board approved all databases for research, with patient consent waived.

#### Outcomes

*Effectiveness* of surgical approaches included evaluation of operative variables (intraoperative, cardiopulmonary bypass, and myocardial ischemia times) and efficacy of MV repair. Assessment of efficacy was based on routine predischarge transthoracic echocardiography. Severity of MR was graded as 0 = none, 1+ = mild, 2+ = moderate, 3+ = moderate) severe, and 4+ = severe. All results were interpreted on an intent-to-treat basis, with conversions in operative approach recorded and reasons analyzed separately. In addition, we analyzed differences in hematocrit and mediastinal drainage, postoperative intubation time, length of postoperative hospital stay, and pain scores.

Pain intensity was recorded as part of clinical care by nursing staff from patients' arrival in the intensive care unit to hospital discharge, using the Wong–Baker visual-analog scale.<sup>14</sup> A total of 40,755 pain scores were available for 756 patients (99.6%; Figure E1). Pain management during this time frame was uniform and included narcotic patient-controlled analgesia on the first and second postoperative days and oral analgesics and nonsteroidal anti-inflammatory agents thereafter. Because of the nature of patient-controlled analgesia, the temporal pattern of analgesia use could not be retrieved via the Electronic Health Record.

*Safety* of operative approach was assessed by comparing mortality and morbidity, defined in accordance with the Society of Thoracic Surgeons National Database (see http://www.ctsnet.org/file/rptDataSpecifications 252\_1\_ForVendorsPGS.pdf).

## **Data Analysis**

Propensity matching. A number of differences in patient characteristics precluded unadjusted comparisons of outcomes. To reduce selection bias, we used propensity matching to approximate a randomized trial.<sup>15</sup> Because our focus was on patients who received ROB MV repair, we created 3 separate propensity models for ROB versus CST, ROB versus PST, and ROB versus ANT. To construct the propensity score, we used preoperative and procedure variables (Appendix 1) and multivariable logistic regression to initially identify factors associated with ROB surgery versus CST, PST, or ANT. Having established a parsimonious model, we added other variables representing groups of patient factors that might be related to unrecorded selection factors (semi-saturated model).<sup>16</sup> A propensity score was calculated for each patient by solving the resulting propensity models for the probability of receiving ROB MV repair.<sup>17</sup> By using only the propensity score, ROB cases were matched to non-ROB cases by greedy matching.<sup>18</sup> ROB cases whose propensity scores deviated more than 0.1 from those of non-ROB cases were considered unmatched (Figure E2).

**Comparisons.** Categoric variables were compared using the chisquare or Fisher's exact test when frequency was less than 5. For continuous variables, pairwise comparisons were made using the *t* test or Wilcoxon rank-sum nonparametric test for skewed distributions and the Kruskall– Wallis test for comparisons of more than 2 groups. All analyses were performed using SAS statistical software (SAS v9.1; SAS, Inc, Cary, NC).

To compare temporal pattern of postoperative pain across time, pain scores were combined into 5 categories because of low frequency of higher pain scores: 0 (pain score 0), 1 (pain scores 1–3), 2 (pain scores 4–6), 3 (pain scores 7 and 8), and 4 (pain scores 9 and 10). These pain score categories were analyzed longitudinally for change. A nonlinear, cumulative logit mixed model was used to resolve a number of time phases in the cumulative odds domain to form a temporal decomposition model and to estimate the shaping parameters for each phase.<sup>19</sup> Each phase was independently modulated by a time function with common random intercept to accommodate the repeated nature of the data. Longitudinal cumulative

TABLE 1. Patient characteristics of al	patients according to surgical approach
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Characteristic	Complete sternotomy (total n = 114)		Partial sternotomy (total n = 270)			plateral thoracotomy tal $n = 114$ )	Robotic approach $(total n = 261)$		
	n*	No. (%) or mean ± SD	n*	No. (%) or mean ± SD	n*	No. (%) or mean ± SD	n*	No. (%) or mean ± SD	Р
Demography									
Female	114	29 (25)	270	74 (27)	114	29 (25)	261	57 (22)	.5
Age (y)	114	$61 \pm 11$	270	$57 \pm 12$	114	$55\pm11$	261	$56 \pm 11$	.0003
BMI (kg/m <sup>2</sup> )	114	$27\pm5.4$	270	$26\pm3.6$	114	$27 \pm 5.0$	261	$26 \pm 4.3$	.3
Symptoms									
NYHA functional class	114		270		114		261		.009
Ι		37 (32)		120 (44)		57 (50)		131 (50)	
II		54 (47)		128 (47)		47 (41)		97 (37)	
III		22 (19)		20 (7.4)		10 (8.8)		31 (12)	
IV		1 (0.88)		2 (0.74)		0 (0)		2 (0.77)	
LVEF (%)	111	$59\pm5.7$	269	$60 \pm 4.6$	114	$59 \pm 4.4$	258	$60 \pm 4.4$	.1
Heart failure	114	22 (19)	270	20 (7.4)	114	4 (3.5)	261	19 (7.3)	<.0001
Cardiac morbidity									
MR grade	114		270		114		261		.9
2+†		4 (3.5)		6 (2.2)		3 (2.6)		4 (1.5)	
3+		17 (15)		45 (17)		22 (19)		46 (18)	
4+		93 (82)		219 (81)		89 (78)		211 (81)	
Atrial fibrillation/flutter	114	8 (7.0)	270	4 (1.5)	112	2 (1.8)	259	13 (5.0)	.02
Previous MI	114	8 (7.0)	270	6 (2.2)	114	5 (4.4)	261	4 (1.5)	.02
Noncardiac comorbidity									
Carotid disease	114	12 (11)	270	26 (9.6)	114	4 (3.5)	261	29 (11)	.1
Stroke	114	2 (1.8)	270	6 (2.2)	114	1 (0.88)	261	3 (1.1)	.7
PAD	114	3 (11)	270	26 (9.6)	114	4 (3.5)	261	29 (11)	.1
Hypertension	113	52 (46)	267	109 (41)	110	51 (46)	255	102 (40)	.5
Diabetes									
Insulin treated	113	0 (0)	265	1 (0.38)	108	0 (0)	254	0 (0)	.6
Non-insulin treated	113	6 (5.3)	265	8 (3.0)	108	3 (2.8)	254	5 (2.0)	.4
Creatinine (mg/dL)	114	$0.98\pm0.19$	270	$1.0\pm0.76$	114	$0.99\pm0.18$	261	$0.99\pm0.2$	.1
Smoking	113	38 (34)	265	74 (28)	108	32 (30)	255	88 (35)	.4
COPD	114	10 (8.8)	270	9 (3.3)	114	4 (3.5)	261	10 (3.8)	.09

*BMI*, Body mass index; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *MR*, mitral regurgitation; *NYHA*, New York Heart Association; *PAD*, peripheral arterial disease; *SD*, standard deviation. \*Patients with data available. †See text for details.

logistic regression for repeated measurements (SAS PROC NLMIXED) was used to implement the temporal decomposition model.<sup>20,21</sup> Prevalence of each pain score category over time was estimated by averaging patient-specific profiles.

#### Presentation

Continuous variables are summarized by mean  $\pm$  standard deviation or by median and 15th and 85th percentiles, consistent with  $\pm$  1 standard deviation. Categoric data are summarized by frequencies and percentages.

# RESULTS

#### Effectiveness

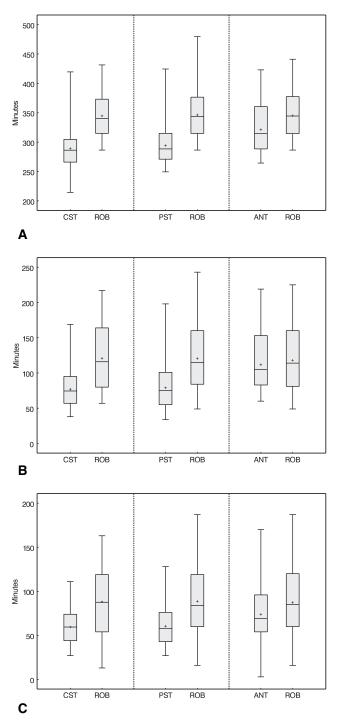
MV repair was accomplished in all patients except 1 patient in the CST group (Table E1).

Among matched patients, the ROB group had the longest operative times (median, 387 minutes), 109, 110, and 60 minutes longer than the CST, PST, and ANT groups (all P < .0001), respectively (Figure 1). The ROB group also had the longest cardiopulmonary bypass times (median

116 minutes), 42, 40, and 10 minutes longer than for the CST, PST, and ANT groups (all P < .007), respectively (Figure E3). Median myocardial ischemia time for the ROB group was 85 minutes, 28, 26, and 19 minutes longer than for the CST, PST, and ANT groups (all P < .0001), respectively. These times have all steadily decreased across time (Figure E4).

Quality of MV repair was similar among matched groups, with more than 95% of patients having no or mild residual MR on postoperative (predischarge) transthoracic echocardiogram (P = .6, .2, and .1, respectively; Table 2).

Conversion for the ROB approach was 9.1% (24/261), compared with 2.6% (7/270) for PST and 2.6% (3/114) for ANT. Thirteen of the 24 conversions occurred before robot docking because anatomic factors precluded safe peripheral cannulation (small or arteriosclerotic femoral vessels; Table 3). Four of the conversions occurred after docking but



**FIGURE 1.** Intraoperative times (minutes) according to approach, propensity-matched patients. *A*, Total operative time. *B*, Cardiopulmonary bypass time. *C*, Myocardial ischemic time. *ANT*, Mini-anterolateral thoracotomy; *CST*, complete sternotomy; *PST*, partial sternotomy; *ROB*, robotic surgery.

before atriotomy because of inability to arrest the heart with endoballoon-administered cardioplegia. Seven of the conversions occurred after atrial incision because of bleeding, inability to arrest the heart, or repair failure.

# Safety

There were no operative deaths. Complications defined by the Society of Thoracic Surgeons were similar among matched groups (Table 4). Reoperation for postoperative bleeding and blood product use were similar among groups. Despite differences in size and location of incisions, pain scores after ROB surgery were similar to those in the CST and PST groups, with 70% of patients reporting no or little pain by the fourth postoperative day (Figure E5), but lower than after ANT procedures. The lowest prevalence of new postoperative atrial fibrillation/flutter (24%) was observed in the ROB group, 14% (P = .5), 13% (P = .002), and 7% (P = .3) lower than the CST, PST, and ANT groups, respectively.

Among matched patients, the ROB group had the shortest postoperative hospital stay (median, 4.2 days), 1.0, 1.6, and 0.9 days less than the CST, PST, and ANT groups (all P < .001).

# DISCUSSION

Invasiveness of MV surgery is to a large degree related to incisional trauma. Size of all surgical incisions is determined by the need for (1) direct visualization of the operative field and (2) enough space for the surgeon's hands and instruments to perform the operation. Extent of reduction in incision size and associated surgical trauma to patients with partial sternotomy and right thoracotomy were limited by the need for direct visualization and use of standard surgical instrumentation. Introduction of video-assisted mitral surgery via mini-thoracotomy has proven to be safe and effective, but has gained limited following because of difficulties in manipulating long-shafted instruments in a 2-dimensional operative field and lack of surgical assistance.<sup>1,4</sup> A robotic surgical system, with its 3-dimensional high-definition imaging and sophisticated articulated microinstrumentation, favorably influences both determinants of surgical invasiveness and allows MV repair to be conducted with the least degree of surgical trauma.<sup>7,8,12</sup> Despite initial favorable reports, concerns about complexity and cost of the procedure, as well as its quality and safety, have limited its acceptance.<sup>9,10</sup> This study provides a contemporary concurrent evaluation of safety and efficacy of robotic MV repair versus those obtained with complete sternotomy and alternative less invasive approaches.

#### **Key Findings**

Our study demonstrates that robotically assisted MV repair is as safe and effective as repair accomplished though complete sternotomy, partial sternotomy, and mini-right thoracotomy. Complexity of the robotic procedure is reflected in longer operative times; however, less invasiveness resulted in less morbidity and shorter hospital stay. ACD

TABLE 2. Efficacy of mitral valve repair, assessed by grade of postoperative mitral regurgitation measured by predischarge transthoracic echocardiography\*

	Complete sternotomy vs robotic approach (106 matched pairs)†		Partial ster robotic a (223 match	pproach	Mini-anterolateral thoracotomy vs robotic approach (113 matched pairs)†		
	Complete sternotomy	Robotic approach	Partial sternotomy	Robotic approach	Mini-anterolateral thoracotomy	Robotic approach	
Mitral regurgitation grade	No. (%)	No. (%)	No. (%)	<b>No.</b> (%)	<b>No.</b> (%)	<b>No.</b> (%)	
0/1+	102 (99)	101 (98)	218 (99)	213 (97)	111 (99)	107 (96)	
2+	1 (0.97)	2 (1.9)	2 (0.91)	6 (2.7)	1 (0.89)	5 (4.5)	
Р	.6	)	.2		.1		

\*Each of the 3 comparisons in the table reflects separately propensity-matched patient groups. †Entries not adding to total matched pairs represent missing data.

TABLE 3. Conversions in all patients according to s	surgical approach
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			Reason for conversion							
			Failed repair using							
Time of conversion	No.	Bleeding	initial approach	Patient anatomy	Inability to arrest	Other				
Partial sternotomy										
Before atrial incision	6	3	_	1	_	2				
After atrial incision	1	1	_	_	_	_				
Mini-anterolateral thoracotomy										
Before atrial incision	2	_	_	2	_	_				
After atrial incision	1	_	_	_	_	1				
Robotic approach										
Before docking robot	13	_	_	13	_	_				
After docking robot but before atrial incision	4	_	_	1	3	_				
After atrial incision	7	3	2	—	2					

# Efficacy

Longer operative times for robotic MV repair are the result of greater complexity of anesthesiologic preparation of the patient and greater operative complexity. Placement of a double-lumen endotracheal tube and echo-guided percutaneous insertion of the retrograde cardioplegia catheter are time-consuming and responsible for one third of the time difference between complete sternotomy (the shortest) and robotic approaches. Although cardiopulmonary bypass and myocardial ischemic times were statistically significantly longer for patients undergoing robotic surgery than in other groups, these differences were smaller and clinically less relevant than in previously published series on robotic MV repair.<sup>7,12,22</sup> Shorter myocardial ischemic time in our series is a result of simplified leaflet repair techniques and a novel anuloplasty technique that uses running mattress suture for faster insertion of the anuloplasty band.<sup>23,24</sup> Although these times are still somewhat longer than for conventional procedures, they are comparable to those reported for conventional less invasive MV operations. Furthermore, prolonged operative times for robotic repair reflect a learning curve inevitably present in adopting new surgical techniques.<sup>25</sup>

Conversion to alternative approaches was highest in the robotic group; most conversions were due to size and mor-

phology of femoral vessels that precluded safe peripheral cannulation. Those patients were mostly converted to PST, another less invasive approach that allows safe establishment of cardiopulmonary bypass via central cannulation. These findings have affected our preoperative workup, and we now routinely perform computed tomography of the aorta and duplex ultrasound of the femoral vessels to assess their diameter and degree of arteriosclerosis. Several conversions were due to failure to adequately arrest the heart with the aortic endoballoon, with secondary difficulties in adequately delivering antegrade cardioplegia. Asymmetry in balloon design, which opposes the central lumen of the cardioplegia delivery catheter against the aortic wall, resulted in inadequate rate of antegrade cardioplegia delivery. Recent changes in catheter design have resolved this problem. Conversions from the robotic approach after the robotic instruments were inserted into the chest were rare and did not result in compromised valve repair or adverse outcomes.

Although we use the robotic approach for all patients with MV prolapse regardless of complexity and extent of disease, we limited this study to patients undergoing isolated posterior leaflet repair to ensure comparable complexity of myxomatous MV disease. MV repair quality in this group mirrors our results obtained with conventional

	Complete sternotomy vs robotic approach (106 matched pairs)			Partial sternotomy vs robotic approach (223 matched pairs)			Mini-anterolateral thoracotomy vs robotic approach (113 matched pairs)		
	Complete sternotomy	Robotic approach		Partial sternotomy	Robotic approach		Mini-anterolateral thoracotomy	Robotic approach	
Morbidity	No. (%)	No. (%)	Р	No. (%)	No. (%)	Р	No. (%)	No. (%)	Р
Reoperation for bleeding	4 (3.8)	4 (3.8)	1.0	11 (4.9)	19 (4.5)	.8	2 (1.8)	7 (6.2)	.09
Blood product use									
RBC (units)			.1			.2			.5
0	90 (85)	98 (92)		202 (91)	199 (89)		107 (95)	101 (89)	
1	9 (8.5)	3 (2.8)		11 (4.9)	10 (4.5)		3 (2.7)	5 (4.4)	
2	6 (5.7)	2 (1.9)		9 (4.0)	7 (3.1)		1 (0.88)	2 (1.8)	
$\geq 3$	1 (0.94)	3 (2.8)		1 (0.45)	7 (3.1)		2 (1.8)	5 (4.4)	
Platelets	5 (4.7)	5 (4.7)	> .9	11 (4.9)	15 (6.7)	.4	0 (0)	10 (8.8)	.001
Cryoprecipitate	0 (0)	1 (0.94)	.3	0 (0)	3 (1.3)	.08	0 (0)	1 (0.88)	.3
Stroke	1 (0.94)	2 (1.9)	.6	7 (3.1)	6 (2.7)	.8	0 (0)	2 (1.8)	.2
New-onset atrial fibrillation/flutter	32 (30)	28 (26)	.5	78 (35)	49 (22)	.002	29 (26)	22 (19)	.3
Hypoperfusion	12 (11)	9 (8.5)	.5	26 (12)	25 (11)	.9	11 (9.7)	12 (11)	.8
Ventilated $> 24$ h	3 (2.8)	2 (1.9)	.6	5 (2.2)	11 (4.9)	.1	1 (0.88)	4 (3.5)	.2
Pleural effusion	9 (8.5)	0 (0)	.002	19 (8.5)	4 (1.8)	.001	2 (1.8)	2 (1.8)	1.0
All STS reported complications	10 (9.4)	9 (8.5)	.8	22 (9.9)	24 (11)	.8	3 (2.7)	14 (12)	.006

TABLE 4. Safety of mitral valve repair as reflected in postoperative morbidity and blood product requirements\*

RBC, Red blood cells; STS, Society of Thoracic Surgeons. \*As in Table 2, each of the 3 comparisons reflects separately propensity-matched patient groups.

approaches and compares favorably with data from previous robotic studies.<sup>26</sup> We believe that excellent 3-dimensional visualization of the operative field and superior handling of robotic instruments allow excellent quality of MV repair.

# Safety

Safety of robotic MV repair has been well documented in prior studies; however, a recent Society of Thoracic Surgeons' survey revealed increased risk of neurologic complications in patients undergoing less invasive MV surgery.<sup>27</sup> The choice of surgical approach in our study did not affect occurrence of neurologic, renal, or respiratory complications, confirming the safety of robotically assisted surgery. We believe that neurologic complications after less invasive MV surgery are in large part due to retrograde embolism of arteriosclerotic material from the descending aorta and iliac and femoral vessels. Preoperative computed tomography of the descending aorta and duplex ultrasound studies of the femoral vessels allow detection of patients with important arteriosclerosis for whom an alternative operative approach should be chosen.

Fewer occurrences of atrial fibrillation in the robotic group likely reflect a lesser degree of atrial trauma. This is because MV repair is approached robotically through an incision on the right lateral chest wall, permitting exposure of the MV in its normal anatomic position. This requires a small left atriotomy and minimal manipulation of surrounding atrial tissue that may result in low occurrence of postoperative atrial fibrillation. In conventional operations via median or partial sternotomy, exposure of the MV is accomplished via left atriotomy or transseptally. Large atrial incisions are needed in both cases because the MV must be brought into the surgeon's view from its natural position facing the right side of the chest. We postulate that resulting substantial trauma of atrial tissue increases the potential for postoperative atrial fibrillation. This is most obvious in the partial sternotomy group, in which extensive incision through the atria and interatrial septum is needed for MV exposure. In contrast, MV repair through median sternotomy was most commonly performed via left atriotomy, thus limiting dissection of atrial tissue and resulting in postoperative atrial fibrillation occurrence comparable to that of robotic repairs.

Although some studies have reported a decrease in pain after minimally invasive surgery, we could not demonstrate differences in postoperative pain scores in our patients except for those having a mini-anterolateral incision.<sup>26,28</sup> This may be explained by the relatively small patient populations studied and excellent pain management, with near complete pain relief by the fourth postoperative day.

Shorter hospital stay after robotic MV repair, despite longer operative times and a similar degree of postoperative discomfort, is most likely due to a combined result of lower occurrence of atrial fibrillation and common complications such as pleural effusions and hemothorax.

## **Strengths and Limitations**

This is a single-institution clinical study with analysis of outcomes limited to hospital course. However, the Cleveland Clinic has one of the largest MV repair volumes, with all surgeons highly experienced in repair techniques. The type of MV operation was reflective of surgeons' preference and not standardized. A strength of this heterogeneity in approach, however, is that we were able to evaluate approaches concurrently. We tried to compensate for bias in patient selection by propensity matching patients with similar comorbidities and similar extent of MV disease. Long-term follow-up is needed to fully evaluate comparative effectiveness of robotic MV repair.

# CONCLUSIONS

Robotically assisted MV repair represents the least invasive form of MV surgery without a compromise in quality of valve repair or patient safety, and should therefore be considered for all patients with severe myxomatous MV disease and posterior leaflet prolapse. Ongoing refinements of robotic instrumentation and development of ancillary technologies will facilitate wider adoption of this technique in contemporary surgical practice.

#### References

- Chitwood WR Jr, Wixon CL, Elbeery JR, Moran JF, Chapman WH, Lust RM. Video-assisted minimally invasive mitral valve surgery. *J Thorac Cardiovasc Surg.* 1997;114:773-82.
- McClure RS, Cohn LH, Wiegerinck E, Couper GS, Aranki SF, Bolman RM 3rd, et al. Early and late outcomes in minimally invasive mitral valve repair: an eleven-year experience in 707 patients. *J Thorac Cardiovasc Surg.* 2009;137: 70-5.
- Mihaljevic T, Cohn LH, Unic D, Aranki SF, Couper GS, Byrne JG. One thousand minimally invasive valve operations: early and late results. *Ann Surg.* 2004;240: 529-34.
- Schroeyers P, Wellens F, De Geest R, Degrieck I, Van Praet F, Vermeulen Y, et al. Minimally invasive video-assisted mitral valve surgery: our lessons after a 4-year experience. *Ann Thorac Surg.* 2001;72:S1050-4.
- Seeburger J, Borger MA, Falk V, Kuntze T, Czesla M, Walther T, et al. Minimal invasive mitral valve repair for mitral regurgitation: results of 1339 consecutive patients. *Eur J Cardiothorac Surg.* 2008;34:760-5.
- Gillinov AM, Cosgrove DM, Blackstone EH, Diaz R, Arnold JH, Lytle BW, et al. Durability of mitral valve repair for degenerative disease. *J Thorac Cardiovasc Surg.* 1998;116:734-43.
- Chitwood WR Jr, Rodriguez E, Chu MW, Hassan A, Ferguson TB, Vos PW, et al. Robotic mitral valve repairs in 300 patients: a single-center experience. *J Thorac Cardiovasc Surg.* 2008;136:436-41.
- Mohr FW, Falk V, Diegeler A, Walther T, Gummert JF, Bucerius J, et al. Computer-enhanced "robotic" cardiac surgery: experience in 148 patients. *J Thorac Cardiovasc Surg.* 2001;121:842-53.
- Diodato MD Jr, Damiano RJ Jr. Robotic cardiac surgery: overview. Surg Clin North Am. 2003;83:1351-67. ix.
- Robicsek F. Robotic cardiac surgery: quo vadis? J Thorac Cardiovasc Surg. 2003;126:623-4.
- Folliguet T, Vanhuyse F, Constantino X, Realli M, Laborde F. Mitral valve repair robotic versus sternotomy. *Eur J Cardiothorac Surg*, 2006;29:362-6.
- 12. Murphy DA, Miller JS, Langford DA, Snyder AB. Endoscopic robotic mitral valve surgery. *J Thorac Cardiovasc Surg.* 2006;132:776-81.
- Cosgrove DM 3rd, Sabik JF, Navia JL. Minimally invasive valve operations. *Ann Thorac Surg.* 1998;65:1535-9.
- Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Pediatr* Nurs. 1988;14:9-17.
- Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat Med.* 2007;26:20-36.
- Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg. 2002; 123:8-15.
- Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41-55.
- Bergstralh EJ, Konsanke JL. Computerized matching of cases to controls. Technical Report #56: Mayo Foundation; 1995.

- Blackstone EH, Rajeswaran J. A non-linear cumulative logit mixed model with time varying phases and coefficients. XXIII International Biometric Conference; Montreal; 2006.
- Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. J Thorac Cardiovasc Surg. 2001;122: 430-9.
- 21. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of Longitudinal Data. 2nd ed. New York: Oxford University Press; 2002.
- Nifong LW, Chitwood WR, Pappas PS, Smith CR, Argenziano M, Starnes VA, et al. Robotic mitral valve surgery: a United States multicenter trial. *J Thorac Cardiovasc Surg.* 2005;129:1395-404.
- George KM, Mihaljevic T, Gillinov AM. Triangular resection for posterior mitral prolapse: rationale for a simpler repair. J Heart Valve Dis. 2009;18:119-21.
- Mihaljevic T, Jarrett CM, Gillinov AM, Blackstone EH. A novel running annuloplasty suture technique for robotically assisted mitral valve repair. *J Thorac Cardiovasc Surg.* 2010 Feb 25 [ePub ahead of print].
- Tatooles AJ, Pappas PS, Gordon PJ, Slaughter MS. Minimally invasive mitral valve repair using the da Vinci robotic system. *Ann Thorac Surg.* 2004;77: 1978-84.
- Svensson LG, Atik FA, Cosgrove DM, Blackstone EH, Rajeswaran J, Krishnaswamy G, et al. Minimally invasive versus conventional mitral valve surgery: a propensity-matched comparison. *J Thorac Cardiovasc Surg.* 2010;139: 926-32. e1-2.
- Gammie JS, Zhao Y, Rankin JS, O'Brien S, Griffith BP. Utilization and outcomes of less invasive mitral valve operations in North America. Society of Thoracic Surgeons 47th annual meeting. San Diego; 2010.
- Aklog L, Adams DH, Couper GS, Gobezie R, Sears S, Cohn LH. Techniques and results of direct-access minimally invasive mitral valve surgery: a paradigm for the future. *J Thorac Cardiovasc Surg.* 1998;116:705-15.

# Discussion

**Dr Vivek Rao** (*Toronto, Ontario, Canada*). The authors are to be congratulated. There is clearly a patient- and provider-driven desire to move toward minimally invasive surgery. Many studies, including several from the Cleveland Clinic, have shown that this can be done. I am pleased that the authors have now focused their attention on whether or not this should be done.

I want to point out a few caveats. This is a study performed by a large-volume center by several experienced valve surgeons. Their outstanding clinical results include zero mortalities in 750 mitral repairs and only 1 failure to repair a valve. Before we start taking this procedure home to our own institutions, we have to keep that in mind that in these excellent hands their results are spectacular. Despite those spectacular clinical outcomes, there were certain drawbacks to MV surgery done with robotic assistance. Clearly, as you have shown, operative times are longer, cardiopulmonary bypass times are longer, and ischemic times are longer, and this in a cohort of patients who had relatively easy MVs to repair, isolated posterior leaflet prolapse. Are these differences magnified when we start to challenge the more complex MV?

Third, you indicated there was no significant difference in bleeding or transfusion requirements among the groups; however, it was interesting to note that massive transfusion requirements, defined as more than 3 units of packed red blood cells, was actually higher in the robotic group. Does that mean that when things go bad with robotic surgery, things go really bad?

I also point out that the length of stay reductions that we observed were less than overwhelming, an average of 1 median day less, and what you did not present but was present in your article was that there was actually no difference in pain scores between robotic surgery and even complete sternotomy, and that was somewhat surprising to me. That leads me to question a few things about your study from a philosophical nature. What is the real goal of robotic minimally invasive surgery? Is it to improve the quality and the physiologic recovery of patients or is it for cosmesis? If the former, a simple walk through our exhibit hall will show many companies that show sternal fixation devices that allow patients to go home 2 to 3 days after surgery, which would be a dramatic improvement compared with even the excellent results that you show here.

Last, I caution people in compromising the integrity of their overall medical management simply to achieve minimally invasive surgery. If we can achieve similar results with good physiologic recovery with a full sternotomy and perform all the technical procedures that are needed to be done on a patient, I think that should be paramount. There is a tendency in the real world to compromise our patients by doing, for example, a percutaneous stent to the left anterior descending artery to facilitate port-access MV surgery and perhaps not do what is in the best interest of our patients.

Once again, these are philosophical questions at most, and I thank the Association for the privilege of discussing this article.

**Dr Mihaljevic.** Your first question is whether this is a cosmesis versus quality. Our entire study was designed to show that there was no compromise in quality. We report essentially 100% mitral valve repair rate with zero mortality. It is difficult to argue that there is a compromise in quality with such results.

It is also difficult to show, as you said, a spectacular reduction in hospital length of stay for operations that normally do not require a long hospital stay anyhow. So it is not to be expected that a patient after general anesthetic and cardiopulmonary bypass is going to leave the hospital on postoperative day 2 no matter what we do, and you are right about that. I think one of the real advantages of this approach, which is not analyzed in this study, is the fact that these patients do return to their regular activities of daily life substantially faster than those who have a complete sternotomy, and that has been our experience.

Now, as I said, when it comes to the bleeding, yes, we have had, obviously, conversions. You have to understand that these are the patients whom we analyzed with an intent to treat, so we have not tried to hide the complications that occur with occasional conversions, but those were rare and they have not compromised the overall outcome of our patients in this study, as I hope that this is well documented with our results and analysis.

**Dr Harold Roberts** (*Lauderdale Lakes, Fla*). I have a couple of questions, and one of them is, indeed, your bypass and ischemic times were longer in this subset of patients. Have you in fact broken down with time to see if there has been improvement in this overall, because I know in my own experience that the times in the first few cases have dramatically improved over the last several months.

**Dr Mihaljevic.** That is true. In regard to ischemic and cardiopulmonary bypass time, I would just like to remind you that the absolute crossclamp time, the length of the crossclamp time, is 80 minutes for all-comers, including those first patients who clearly had somewhat longer bypass times, but none of our patients required excessively long crossclamp times in excess of 120 minutes. If you compare this with even most recently published series on complete sternotomy or mini-anterolateral thoracotomy, you will find that these absolute times are shorter than any of the previously published series. And, of course, as we became more facile, the crossclamp times have become shorter and shorter, so that our crossclamp time now averages approximately 70 minutes regardless of the complexity of MV repair that we need to do with the robot.

**Dr Roberts.** Two more questions. In light of your initial success with a P2 prolapse, have you tried to do more complex repairs with this approach? Finally, I noticed you had a significant conversion rate when you found heavily diseased or inadequate vessels. I think that a useful adjunct, and I wonder if you had incorporated this, is to now use preoperative computed tomography angiography. You can know exactly what size cannulas are going to work and which patients should not undergo operation because of atheromatous debris.

**Dr Mihaljevic.** To answer your first question, we use the robotic approach for any patients with myxomatous MV disease regardless of the MV disease complexity. And, yes, we have changed our preoperative approach. Now we use a computer-assisted tomography scan and a femoral ultrasound to identify those patients who have aortoiliac or femoral artery disease.

**Dr Ralph Damiano** (*St. Louis, Mo*). I disclose I am a consultant for AtriCure and Medtronic. I was wondering why you confined the study just to posterior leaflet disease. In your conclusion you say that robotics is safe and effective for all myxomatous disease. Maybe you could clarify this comment with your present experience. Are there patients with complex disease for whom you do not recommend a robotic approach? Are your results generalizable to more complex mitral repair?

**Dr Mihaljevic.** We have purposely defined this cohort as a cohort of patients when we did the repair to the posterior leaflet. It doesn't mean that these patients did not have a bileaflet prolapse based on the preoperative echo, and quite a few patients, as you know, who have a bileaflet prolapse can be repaired by taking care of the posterior leaflet prolapse and putting in an annuloplasty ring. So we wanted to have this cohort stratified in such a way that it reflects accurately the procedural complexity. I think your comment is relevant.

I have to say today in our current practice, as I mentioned before, robotic MV repair is offered to all patients with myxomatous MV disease regardless of the complexity of their disease.

**Dr Damiano.** I noticed you did not present any cost data. Did you look at whether there were increased hospital costs by using a robotic system?

**Dr Mihaljevic.** The purpose of this study is to assess the procedural safety and efficacy. We are actively looking into cost, and not only cost of hospitalization but the costs and benefits of this procedure that extend beyond the hospital stay, and we hope to have data to present soon, but just to share with you that there is a minor difference in hospital cost.

**Dr Damiano.** In the patients who underwent mini-anterolateral thoracotomies, what was your surgical technique? What was the size of the thoracotomy? Did you try to avoid rib spreading? Did you use specialized instrumentation? You can make a very small incision with current techniques.

**Dr Mihaljevic.** Yes, it is a very small incision, anterolateral thoracotomy, sometimes without rib spreading, sometimes with rib spreading, long-shafted instruments, most of the times direct transthoracic crossclamping, occasional endo balloon.

**Dr Antonio Laudito** (*Wichita, Kan*). I was a bit surprised, and I would like to know what you think. One of the minimal approaches to attack the MV that Dr Larry Cohn proposes is the lower inferior sternotomy, and, despite that, you presented the upper part. The

lower inferior, kind of a minimally invasive, approach depends on you. You use the same perfusion, cannulation, cardioplegia strategy as in median sternotomy. You don't need double lumen. It is a simple approach if you are on top of the MV. And I was wondering, what do you think about this approach that I didn't see mentioned?

**Dr Mihaljevic.** Having been trained at the Brigham, I am perfectly familiar with it. A partial sternotomy does the same thing. With the partial upper sternotomy, it is direct central cannulation, usual instruments. It is just a preferred approach at the Cleveland Clinic. But I am familiar with Dr Cohn's approach and have done it many times.

**Dr Robert Higgins** (*Chicago, 1ll*). Impressive data. Do you have any information about the completeness of follow-up, your mortality after hospitalization, and the efficacy of the repair beyond hospitalization?

**Dr Mihaljevic.** We are going to have a complete 2-year followup soon. As you may have noticed, this cohort included patients up to January of 2009, so we will have 2-year completeness data soon. We have not had a single mortality beyond the usual 30 days, an inhospital mortality, that we know for a fact.

Dr Higgins. And the completeness of your follow-up?

**Dr Mihaljevic.** As I said, we have not completed a 2-year follow-up because this is a recent study.

**Dr David Adams** (*New York, NY*). I am an inventor of annuloplasty rings with Edwards Lifesciences.

Tommy, I rise to congratulate you. This is a master series by master surgeons. Your robotic series over a 2-year period is really unbelievable, an amazing amount of work. I have 2 short questions. One, you didn't show us a summary of techniques. Have you altered your techniques of valve repair based on robotics, for instance, less resection, less sliding plasty, more polytetrafluoroethylene? Second, it looks like from your data that at least in well-selected patients with degenerative and predominantly posterior leaflet prolapse you could offer many different incision options reproducibly. So institutionally how are you approaching that? Obviously different surgeons have different skill sets and biases. Are you offering approaches to all patients or is that still surgeon based? I think it is an interesting thing for you to comment on. Congratulations on your fine series.

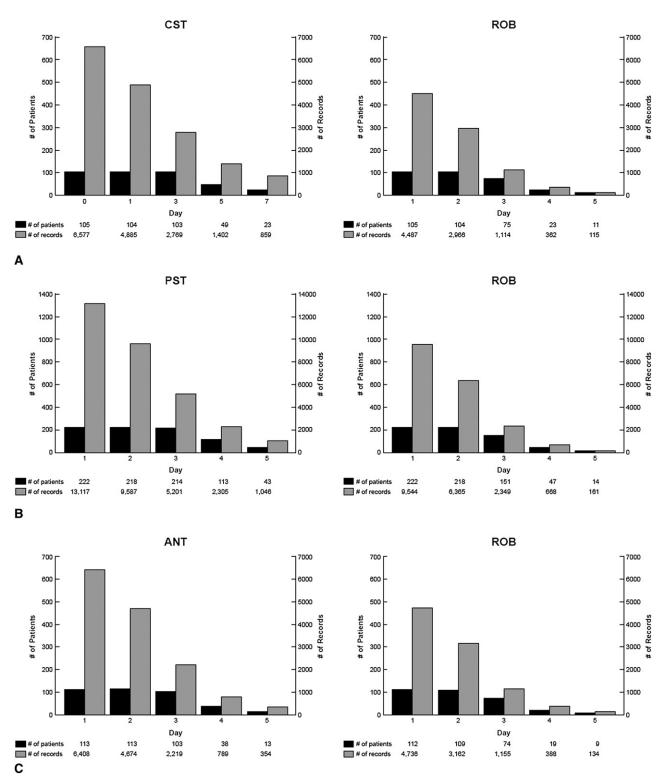
**Dr Mihaljevic.** To answer your question first, yes, just like any other surgical technique, our repair techniques have evolved over time. Generally speaking, for patients who have a limited MV prolapse, we would use resectional techniques; for those who have a more diffuse MV prolapse, whether it is the bileaflet or the posterior leaflet, we tend toward no resection and placement of artificial chordae, and it has been a more common practice in the recent year, also.

When it comes to offering a patient an appropriate procedure, we offer the patient an entire spectrum of the procedure and essentially tailor the procedure to the patient. We always tell a patient that our primary goal is to do a safe and effective operation and our secondary goal is to do it through the smallest incision possible, and if we cannot do a safe and effective operation through a small incision, we will use an incision that will allow us to do a safe operation.

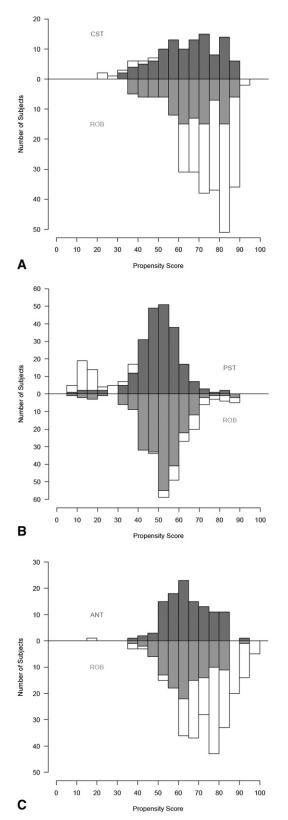
Demographics	Age,*' $\ddagger$ ¶ sex, $\dagger$ ' $\S$ ¶ height (cm), weight (kg),* body surface area (m <sup>2</sup> ), body mass index (kg/m), $\S$ '¶
Cardiac morbidity	Atrial fibrillation, <sup>‡</sup> '¶ ventricular arrhythmia, heart failure
Noncardiac comorbidity	Chronic obstructive pulmonary disease, hypertension, peripheral arterial disease,    renal disease, diabetes, stroke, smoking†‡
Laboratory medicine	Blood urea nitrogen (mg/dL),§*¶ cholesterol (mg/dL),†*§ low-density lipoprotein (mg/dL), high-density
	lipoprotein (mg/dL), creatinine (mg/dL), hematocrit (%),†"   bilirubin (mg/dL),§ triglycerides (mg/dL)
Preoperative symptoms	New York Heart Association functional class (I–IV),* <sup>.</sup> § <sup>.</sup> ¶
Experience	Interval (years) from January 2006 to index operation
Preoperative echocardiogram values	MV regurgitation,†§ aortic valve regurgitation,†§ left atrial diameter (cm), left atrial systolic area (cm <sup>2</sup> ), LV systolic dysfunction (1 = none, 2 = mild, 3 = moderate, 4 = severe), LV inner diastolic diameter (cm), LV end-diastolic volume (mL),† LV inner systolic diameter (cm),§ LV end-systolic volume (mL), LV fractional shortening, LV ejection fraction (%),† posterior wall thickness (cm),‡ intraventricular septal wall thickness (cm), LV relative wall thickness (mm), LV mass (g),† tricuspid valve regurgitation velocity (m/s), right ventricular systolic pressure (mm Hg)
MV pathology	MV calcification, <sup>†</sup> posterior chordal rupture

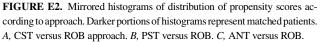
#### **APPENDIX 1. Variables used in the analyses**

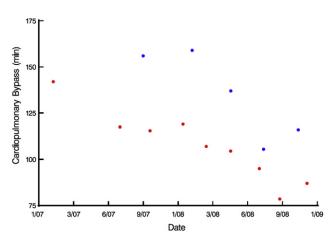
ANT, Mini-anterolateral thoracotomy; CST, complete sternotomy; LV, left ventricular; MV, mitral valve; PST, partial sternotomy; ROB, robotic surgery. \*Variables in CST versus ROB parsimonious model. †Variables in CST versus ROB saturated model. ‡Variables in PST versus ROB parsimonious model. §Variables in PST versus ROB saturated model. ||Variables in ANT versus ROB parsimonious model. ¶Variables in ANT versus ROB saturated model.



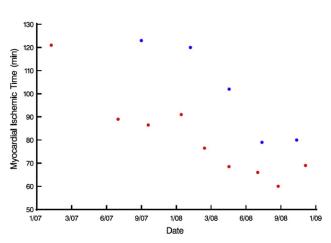
**FIGURE E1.** Number of patients with pain score measurements available postoperatively and number of pain score measurements available for analysis (*black bars* = patients; *grey bars* = pain score measurements). *A*, CST versus ROB. *B*, Partial sternotomy versus ROB. *C*, ANT versus ROB.



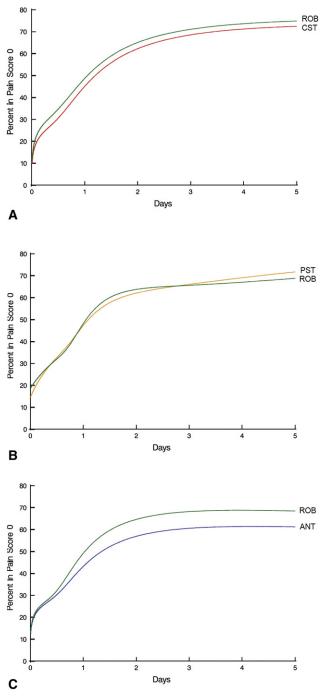




**FIGURE E3.** Cardiopulmonary bypass time across date of operation for the 2 surgeons performing robotic repair of posterior MV prolapse. Grouped mean times (*red* and *blue dots*) represent approximately 20 patients grouped at the midpoint of calendar dates.



**FIGURE E4.** Myocardial ischemic time across date of operation for the 2 surgeons performing robotic repair of posterior MV prolapse. Grouped mean times (*red* and *blue dots*) represent approximately 20 patients grouped at the midpoint of calendar dates.



**FIGURE E5.** Percentage of patients who are pain free postoperatively according to surgical approach: propensity-matched patients.

Procedure	Complete sternotomy $(n = 114)$	$\begin{array}{l} \mbox{Partial sternotomy} \\ (n=270) \end{array}$	$\label{eq:mini-anterolateral} \begin{array}{l} \mbox{Mini-anterolateral thoracotomy} \\ (n=114) \end{array}$	Robotic approach $(n = 261)$	Р
MV procedure					
Anuloplasty	113 (99)	270 (100)	114 (100)	261 (100)	
+Leaflet resection	105 (93)	257 (95)	112 (98)	243 (93)	.2
Triangular	31 (27)	115 (43)	48 (42)	161 (62)	<.0001
Quadrangular	74 (65)	142 (53)	64 (56)	82 (31)	<.0001
+ Chordal procedure	5 (4.4)	5 (1.9)	0 (0)	8 (3.1)	.1
+Edge-to-edge	4 (3.5)	15 (5.6)	3 (2.6)	26 (10)	.02
MV replacement	1 (0.88)	0 (0)	0 (0)	0 (0)	.1
Concomitant procedure					
ASD or PFO closure	7 (6.1)	23 (8.5)	7 (6.1)	34 (13)	.07
Left-sided ablative lesions for AF	31 (27)	5 (1.9)	7 (6.1)	22 (8.4)	<.0001

#### TABLE E1. Operative procedure according to surgical approach

AF, Atrial fibrillation; ASD, atrial septal defect; MV, mitral valve; PFO, patent foramen ovale.