

The Effect of Concomitant Radiofrequency Ablation and Surgical Technique (Repair Versus Replacement) on Release of Cardiac Biomarkers During Mitral Valve Surgery

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All patients undergoing heart surgery experience a certain amount of nonspecific myocardial injury documented by the release of cardiac biomarkers and associated with poor outcome. We investigated the role of unipolar radiofrequency ablation of atrial fibrillation on the release of cardiac biomarkers in 71 patients undergoing mitral valve surgery and concomitant left atrial ablation case-matched with 71 patients undergoing isolated mitral surgery. The study was powered to detect a 3 ng/mL difference. There was no difference between the 2 groups in terms of cardiac troponin I (10 ± 5.3 versus 12 ± 10.4 ng/mL; $P = 0.7$) or creatine kinase-MB (50 ± 21.8 versus 57 ± 62.0 ng/mL; $P = 0.5$) release. Postoperative peak cardiac troponin I levels

had univariate associations with the duration of cardiopulmonary bypass ($P = 0.002$) and aortic cross-clamping ($P = 0.001$) and with the surgical technique (15 ± 12 ng/mL for mitral valve replacement versus 9 ± 4.8 for mitral valve repair; $P = 0.0007$) at univariate analysis. Mitral valve replacement was the only independent predictor of postoperative peak release of cardiac troponin I identified with multivariate analysis ($P = 0.005$). Radiofrequency ablation of atrial fibrillation does not significantly increase cardiac biomarker release compared with isolated mitral surgery; mitral valve repair is associated with less release of cardiac biomarkers compared with mitral valve replacement. (Anesth Analg 2005;101:24-9)

A measurable degree of myocardial injury is expected among patients undergoing cardiac surgery. This injury is an epiphenomenon of the procedure itself in most cases, but significant myocardial damage may occur in some patients (1). This perioperative myocardial damage is the result of either a focal myocardial infarction in a single coronary artery territory or a diffuse myocardial injury that is generally more difficult to recognize and that can lead to postoperative ventricular dysfunction and heart failure (2). The European Society of Cardiology and the American College of Cardiology (3) suggested troponin as the preferred indicator of myocardial injury, but its increase does not define the mechanism of injury in the context of cardiac surgery (4).

Regardless of the mechanism of injury, however, a high postoperative peak of cardiac troponin I (cTnI) is

associated with an increased risk of short- and long-term death and also with nonfatal cardiac events within 2 yr after cardiac surgery (5-8).

Surgical ablation of atrial fibrillation (AF) using the epicardial radiofrequency (RF) approach allows recovery of sinus rhythm and atrial function in the large majority of patients with AF who undergo open-heart surgery (9). The efficacy of RF ablation is related to its role in creating linear scars within the atrial wall by means of thermally-induced coagulative necrosis (10). Therefore, concomitant AF ablation using RF during open heart surgery could possibly influence postoperative release of cardiac necrosis biomarkers; indeed a significant release of cardiac necrosis biomarkers in patients undergoing transcatheter RF ablation has been shown (11,12). There are no published data about the release of cardiac necrosis biomarkers after surgical ablation of AF.

We investigated the role of surgical RF ablation of AF in causing the postoperative release of cardiac necrosis biomarkers cTnI and creatine kinase-MB (CK-MB).

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Methods

This was a single-center case-matched study performed at IRCCS San Raffaele Hospital of Milan, Italy during January 2001 to July 2003. The study group consisted of 71 consecutive patients undergoing mitral valve surgery associated with RF ablation of AF; during the same period, 71 patients who underwent isolated mitral valve surgery were selected as controls. The selection of patients in the control group was based on a 1:1 case-control study. For each case in the study group, a control patient was randomly matched as follows: same age, same sex, and same surgical technique (either mitral repair or mitral valve replacement [MVR]).

The study was conducted in accordance with the Helsinki declaration and approved by the Ethics Committee of our institution; written informed consent was obtained. Exclusion criteria consisted of minor age.

The operation was performed through median sternotomy. No ischemic preconditioning was performed. Cardiopulmonary bypass (CPB) was instituted in all patients by gravity drainage of blood into a open venous reservoir with use of a roller peristaltic pump through a heat exchanger integrated with a hollow fiber membrane oxygenator with phosphorylcholine coating (Avant D903; PHISIO, DIDECO, Mirandola, Italy), an arterial filter, and a mean flow rate of 2.4 L/min/m². Intermittent cold (4°C) blood cardioplegia was infused by means of heat exchanger and 2 roller pumps according to Buckberg et al.'s protocol (13). Mild hypothermia was used. All patients received an intraoperative infusion of tranexamic acid (1 g over 20 min before skin incision, followed by a continuous infusion of 400 mg/h until completion of surgery) according to our institutional protocol (14). At the end of surgery patients were maintained sedated, mechanically ventilated, and transferred to the intensive care unit (ICU). Tracheal extubation and discharge from ICU followed clinical criteria.

Measured outcome included hours of mechanical ventilation, cardiac events (defined as the occurrence of low cardiac output syndrome secondary to ventricular dysfunction requiring large doses of inotropes or intraaortic balloon pumping for more than 24 h), (15) and duration of ICU and hospital stay.

Patients with AF undergoing elective MVR or repair were also given combined intraoperative left atrial RF ablation. All ablations were performed with a temperature-controlled linear RF catheter (Cobra, Boston Scientific). The settings we adopted were 3 min at 80–85°C for epicardial ablations and 2–2.5 min at 70–75°C for endocardial ablations. Bilateral ablation around the orifices of the right and left pulmonary vein couples was performed epicardially on CPB, as was as an ablation from the left pulmonary veins to

the left atrial appendage. After aortic cross-clamping, two linear ablations were performed endocardially: one was between the two encirclings on the posterosuperior atrial wall; the other ablation connected the left appendage to the posterior aspect of the mitral annulus. The auricle was then excluded using a double-layer running 4–0 polypropylene suture. The ablation technique has been previously described in detail (16).

During the perioperative period, 4 blood samples were drawn from each patient for estimation of cTnI and CK-MB; samples were obtained the day before surgery, at ICU arrival, and after 4 h and 18 h. For the purposes of the analysis the peak level of each biomarker was used. Blood was collected in plastic tubes with clot activator (Becton Dickinson Vacutainer Systems; Sparks, MD) and was centrifuged (2500g for 15 min.) before analysis. cTnI and mass creatine kinase MB isoenzyme (CK-MB) were assayed with Dimension XPand (Dade-Behring Diagnostic). The cTnI and CK-MB method is a one-step enzyme immunoassay based on the sandwich principle. For cTnI, sensitivity of the assay was 0.04 ng/mL. The cross-reactivity to other myofibrillar proteins found in human muscle tissue was either minimal or undetectable. The sensitivity of the CK-MB (mass assay) was determined to be 0.5 ng/mL. There was no significant cross-reactivity to CK-BB or CK-MM isoenzyme. The reference interval in our center was 0–7 ng/mL for CK-MB and 0–1.5 ng/mL for cTnI.

Sample size calculations were based on a two-sided α error of 0.05 and 80% power. We anticipated a postoperative peak cTnI release of 12 ± 6.3 ng/mL and assumed a 3 ng/mL difference between patients with or without RF as being clinically significant. We calculated that we would need a sample size of 71 patients per group. Therefore, the total study population was $2 \times 71 = 142$ patients. Data were analyzed by use of Epi Info 2002 software (Centers for Disease Control, Atlanta, GA) and SAS software, version 8 (SAS Institute, Cary, NC). Patients were case-matched by age, sex, and surgical technique (mitral repair and MVR) with patients who did not receive ablation of AF. Preoperative patient characteristics and individual risk factors, intraoperative course, and operative outcomes were compared by univariate analysis. Data are reported as percentage or as mean \pm SD or, for variables not normally distributed, as median and 25th–75th percentiles.

All data analysis was performed according to a pre-established analysis plan. Dichotomous data were compared by using χ^2 test with the Yates corrected χ^2 tests or Fisher's exact test when appropriate. Continuous measures were compared by analysis of variance or the Mann-Whitney *U*-test when appropriate. Two-sided significance tests were used throughout the analysis.

Table 1. Preoperative Characteristics, Surgical Procedure, and Intraoperative Data

	RF (n = 71)	No RF (n = 71)	P value
Age (yr)	59 (10)	58 (13)	0.6
Female gender	37 (52)	43 (61)	0.4
Reoperation	6 (9)	10 (14)	0.4
Mitral valve replacement	25/71 (35)	18/71 (25)	0.3
CPB time (min)	105 (23.8)	70 (22.6)	<0.0001
Aortic cross-clamp (min)	72 (18.7)	52 (16)	<0.0001

Values are mean (SD) or n (%).
RF = radiofrequency; CPB = cardiopulmonary bypass.

Stepwise multivariate linear regression analysis (entry values $P < 0.05$, exit values $P < 0.05$) was used to determine independent predictors of cTnI release and results are reported as odds ratios (OR) with 95% confidence intervals.

Results

In the study period 142 patients were investigated: 71 patients undergoing mitral valve surgery and RF ablation case-matched with 71 undergoing isolated mitral surgery. Preoperative characteristics, surgical procedure, and intraoperative data are described in Table 1. Postoperative outcomes (ICU stay, hospital stay, postoperative cardiac events) are illustrated in Table 2. No in-hospital death was observed.

No patient had baseline cTnI levels above our preset discrimination level of 0.04 ng/mL, and no patient had measurable CK-MB levels.

There were no significant differences between the RF and the non-RF groups in peak cTnI (10 ± 5.3 versus 12 ± 10.4 ng/mL; $P = 0.7$; Fig. 1) or CK-MB (50 ± 21.8 versus 57 ± 62.0 ng/mL; $P = 0.5$) release in spite of a longer CPB (105 ± 23.8 versus 70 ± 22.6 min; $P < 0.0001$) and aortic cross-clamp (72 ± 18.7 versus 52 ± 16.0 min; $P < 0.0001$) duration in the RF group. When other perioperative causes of cTnI release were studied, CPB ($P = 0.002$, $r^2 = 0.06$) and aortic cross-clamping duration ($P = 0.001$, $r^2 = 0.06$) and the type of mitral surgery (15 ± 12 ng/mL for MVR versus 9 ± 4.8 ng/mL for mitral repair; $P = 0.001$; Fig. 2) were associated with postoperative peak cTnI at univariate analysis. MVR was the only independent predictor of cTnI release at multivariate analysis ($P = 0.005$). These results were confirmed when peak CK-MB release was evaluated with univariate and multivariate analysis.

MVR released more cTnI than mitral valve repair even if the duration of CPB did not differ significantly between MVR and mitral repair (Table 3).

Patients who suffered postoperative cardiac events released more cardiac necrosis biomarkers than those with an uneventful course (18 ± 14.2 versus 10 ± 6.2 ng/mL of cTnI; $P = 0.004$; Fig. 3).

Table 2. Postoperative Outcomes

	RF	No RF	P value
Cardiac events	8 (11)	12 (16)	0.5
ICU stay (days)	1 (1-2)	1 (1-1)	0.9
LOS (days)	5 (4-6)	6 (5-7)	0.02

Values are median (interquartile range) or n (%).
ICU = intensive care unit; LOS = length of stay; RF = radiofrequency.

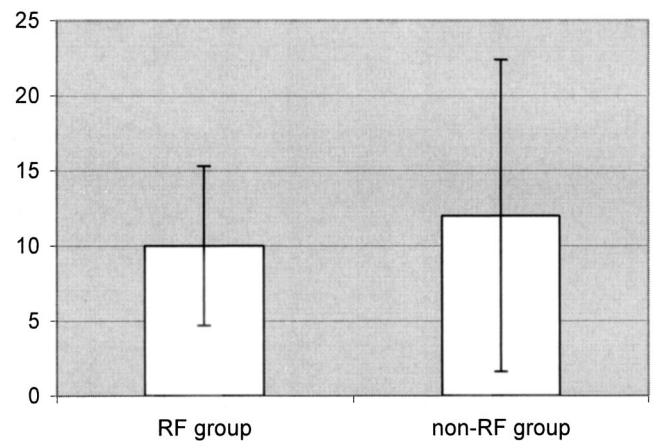


Figure 1. Peak postoperative cardiac troponin I (ng/mL) in patients who received surgical radiofrequency (RF) ablation of atrial fibrillation ($P = 0.7$).

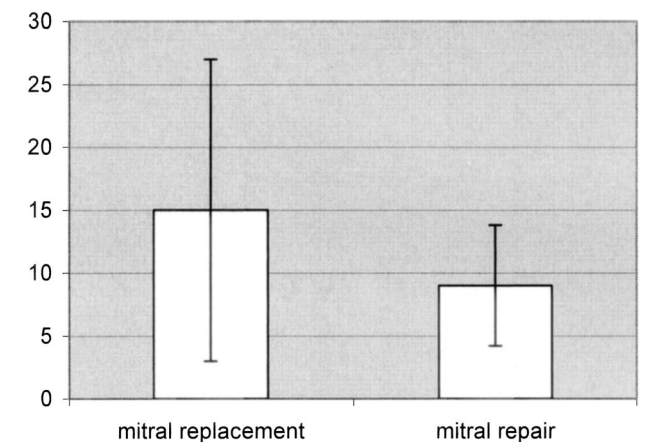


Figure 2. Peak postoperative cardiac troponin I (ng/mL) in patients who underwent either mitral valve replacement or repair ($P < 0.0001$).

Table 3. Cardiac Biomarkers Peak Postoperative Values, Cardiopulmonary Bypass and Aortic Cross-Clamping Time

	Mitral Replacement	Mitral Repair	P Value
Radiofrequency group			
CtnI	13 ± 5.9	9 ± 4.5	0.005
CK-MB	58 ± 21.0	45 ± 20.6	0.007
CPB time	101 ± 23.2	112 ± 23.7	0.07
Cross-clamp time	77 ± 17.4	69 ± 18.8	0.06
Non-Radiofrequency group			
CtnI	18 ± 17.5	9.4 ± 5.1	0.001
CK-MB	85 ± 103.9	48 ± 36.0	0.03
CPB time	73 ± 29.7	69 ± 19.9	0.4
Cross-clamp time	54 ± 25.8	51 ± 12.2	0.4

CtnI = cardiac troponin I; CPB = cardiopulmonary bypass.

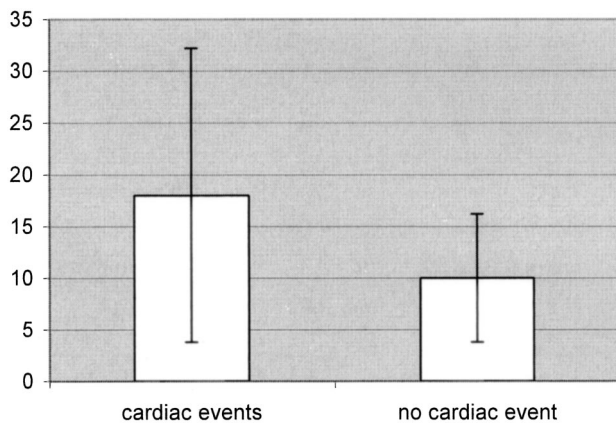


Figure 3. Peak postoperative cardiac troponin I (ng/mL) in patients who had cardiac events versus patients who had an uneventful postoperative course ($P = 0.0004$).

Discussion

This is the first study to investigate the role of unipolar RF ablation of AF on the release of myocardial necrosis biomarkers after cardiac surgery; our results show that patients undergoing RF do not have any increased release of CK-MB or cTnI compared with isolated mitral procedures. Furthermore, this study demonstrates that mitral valve repair is associated with less release of cardiac biomarkers as compared with MVR, and it confirms that a high postoperative peak of cardiac necrosis biomarkers is associated with increased risk of cardiac events (1,3,6-9).

Madrid et al. (11) studied CK-MB and cTnI serum levels in 51 patients who underwent percutaneous RF ablation; they showed a pathologic value of cTnI in 92% of the patients in the ablation group and a moderate level of correlation between the number of RF pulses and cTnI release. Peak cTnI ranged from 1.5 ± 0.83 ng/mL to 6.0 ± 5.7 ng/mL depending on the type of arrhythmia ablated.

Manolis et al. (12), measuring blood levels of cTnI after transcatheter RF ablation in 118 patients, confirmed that the degree of myocardial injury (2.2 ± 2.46

ng/mL 4-24 hours after the end of the procedure) in patients who underwent transcatheter RF ablation is more accurately assessed by cTnI than by CK-MB and that the cTnI levels correlate with the number of RF lesions.

RF catheter ablation is a highly effective treatment for AF (17,18). There are no published data about the release of cardiac necrosis biomarkers after surgical ablation of AF. It is a common belief that after RF ablation there is always a release of cTnI as a result of the small localized myocardial necrosis. Because cTnI has a sensitivity and a specificity close to 100% in detecting myocardial necrosis, our findings show that the amount of cardiac biomarker release caused by the thermal injury related to the surgical RF approach is small and undetectable within the background of biomarker release during cardiac surgery.

It is possible that epicardial application of unipolar RF on the beating heart have somehow reduced the depth of the lesions and thus the amount of cardiac biomarker release. In fact, under these conditions, blood flow in the atrial chamber cools the endocardial layer of the atrial wall, thus hindering penetration of the lesion. Nevertheless it should be considered that all patients having ablation in this series were also given 2 endocardial linear ablations at least 4-5 cm long to complete the lesion set.

This study suggests that myocardial biomarker release after cardiac surgery is associated with the surgical technique: MVR releases significantly more cTnI and CK-MB than mitral valve repair. The different release patterns of the biochemical markers CK-MB and cTnI in patients undergoing different types of cardiac surgery is not a new finding (19,20). Lasocki et al. (6) found that different surgical procedures were associated with different cTnI release, but they also found that combined surgery and mitral valve repair were associated with the largest postoperative cTnI concentrations and no difference in cTnI between patients scheduled for coronary artery bypass graft (CABG) surgery or valve replacement. This conflicting result could be explained by considering that

Lasocki et al. (6) grouped together aortic valve replacement and MVR. By contrast, in our study MVR was characterized by the largest cardiac biomarker release. This phenomenon may be secondary to the lesser amount of heart manipulation during the reparative approach to the mitral valve; furthermore, mitral repair does not usually involve any procedure on the subvalvular apparatus (21-25). The observed differences in postoperative enzyme levels between MVR and repair seen in our study could indicate a possible difference in the response to ischemia and reperfusion. As a result of geometric and related functional changes caused by transection of the subvalvular apparatus in MVR there is an anomalous left ventricle response to early reperfusion; partial or total chordal transection results in significant increase in end-systolic circumferential wall stress and geometric distortion (22,25). Mitral reconstruction, compared with MVR, results in a marked reduction in end-systolic stress and maintenance of more ellipsoidal chamber geometry.

A Consensus Conference (4) has redefined the diagnostic criteria for myocardial infarction in every context except cardiac surgery, where there is still much debate (24,25). In fact, measurement of cTnI may be helpful for establishing the prognosis; a high postoperative peak of cTnI is associated with increased risk of death, death from cardiac causes, and with nonfatal cardiac events within 2 yr after CABG surgery (6,8,9). In addition, cTnI concentration measured 20 h after the end of surgery is an independent predictor of in-hospital death after cardiac surgery, and increased concentrations of cTnI are also associated with death resulting from a cardiac cause and with major postoperative complications (7). Our study shows that a high postoperative peak of cardiac necrosis biomarkers is associated with an increased risk of cardiac events, although this increased peak of postoperative cTnI release is not attributable to the effects of RF ablation of AF, and that RF ablation of AF does not affect short-term outcome.

There are some limitations to this report. It was not possible to introduce any randomization in the study. It is certain that minor myocardial injury may occur during RF ablation of AF. Nonetheless this myocardial injury is neither clinically nor statistically significant in the context of mitral valve surgery, where numerous important causes of troponin release coexist.

The etiology of perioperative cTnI release after cardiac surgery has not yet been studied in detail despite its importance. Clinicians need to consider two primary possible etiologies for increased cardiac markers after cardiac surgery: either the increased marker reflects an acute myocardial infarction or the cardiac biomarker increase is related to other factors. Discriminating between these two possibilities may represent a substantial challenge. Our study shows that RF ablation of AF does not significantly affect peak cTnI

release. Furthermore, this study shows that mitral valve repair releases less cardiac biomarkers compared with MVR surgery.

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References

1. Greenon N, Macoviak J, Krishnaswamy P et al. Usefulness of cardiac troponin I in patients undergoing open heart surgery. *Am Heart J* 2001;141:447-55.
2. Costa MA, Carere RG, Lichtenstein SV, et al. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the Arterial Revascularization Therapies Study (ARTS). *Circulation* 2001;104:2689-93.
3. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined- a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.
4. Jannuzzi JL, Lewandrowski K, MacGillivray TE, et al. A comparison of cardiac troponin T and creatine kinase-MB for patient evaluation after cardiac surgery. *J Am Coll Cardiol* 2002;39:1518-23.
5. Fellahi J, Gue X, Richomme X, et al. Short- and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing coronary artery bypass grafting. *Anesthesiol* 2003;99:270-4.
6. Lasocki S, Provenchere S, Benessiano J, et al. Cardiac troponin I is an independent predictor of in-hospital death after adult cardiac surgery. *Anesthesiol* 2002;97:405-11.
7. Lehrke S, Steen H, Sievers HH, et al. Cardiac troponin T for prediction of short- and long-term morbidity and mortality after elective open heart surgery. *Clin Chem* 2004;50:1560-7.
8. Kathiresan S, Servoss SJ, Newell JB, et al. Cardiac troponin T elevation after coronary artery bypass grafting is associated with increased one-year mortality. *Am J Cardiol* 2004;94:879-81.
9. Williams MR, Stewart JR, Bolling SF, et al. Surgical treatment of atrial fibrillation using radiofrequency energy. *Ann Thorac Surg* 2001;71:1939-44.
10. Cox JL. Atrial fibrillation II: rationale for surgical treatment. *J Thorac Cardiovasc Surg* 2003;126:1693-9.
11. Madrid AH, del Rey MJ, Rubi J, et al. Biochemical markers and cardiac troponin I release after radiofrequency catheter ablation: approach to size of necrosis. *Am Heart J* 1998;136:948-55.
12. Manolis AS, Vassilikos V, Maounis T, et al. Detection of myocardial injury during radiofrequency catheter ablation by measuring serum cardiac troponin I levels: procedural correlates. *J Am Coll Cardiol* 1999;34:1099-105.
13. Buckberg GD, Beyersdorf F, Allen BS, Robertson JM. Integrated myocardial management: background and initial application. *J Card Surg* 1995;10:68-89.
14. Casati V, Gerli C, Franco A, et al. Tranexamic acid in off-pump coronary surgery: a preliminary, randomized, double-blind, placebo-controlled study. *Ann Thorac Surg* 2001;72:470-5.
15. Crescenzi G, Bove T, Pappalardo F, et al. Clinical significance of a new Q wave after cardiac surgery. *Eur J Cardiothorac Surg* 2004;26:1001-4.
16. Benussi S, Nascimbene S, Agricola E, et al. Surgical ablation of atrial fibrillation using the epicardial radiofrequency approach: mid-term results and risk analysis. *Ann Thorac Surg* 2002;74:1050-6.
17. Raman J, Ishikawa S, Storer MM, et al. Surgical radiofrequency ablation of both atria for atrial fibrillation: results of a multicenter trial. *J Thorac Cardiovasc Surg* 2003;126:1357-66.

18. Chiappini B, Martin-Suarez S, LoForte A, et al. Surgery for atrial fibrillation using radiofrequency catheter ablation. *J Thorac Cardiovasc Surg* 2003;126:1788-91.
19. Swaanenburg JC, Loeff BG, Volmer M, et al. Creatine kinase MB, troponin I, and troponin T release patterns after coronary artery bypass grafting with or without cardiopulmonary bypass and after aortic and mitral valve surgery. *Clin Chem* 2001;47:584-7.
20. Crescenzi G, Cedrati V, Landoni G, et al. Cardiac biomarker release after CABG with different surgical techniques. *J Cardiothorac Vasc Anesth* 2004;18:34-7.
21. Lee EM, Shapiro LM, Wells FC. Importance of subvalvular preservation and early operation in mitral valve surgery. *Circulation* 1996;94:2117-23.
22. Goldfine H, Aurigemma GP, Zile MR, Gaash WH. Left ventricular length-force-shortening relations before and after surgical correction of chronic mitral regurgitation. *J Am Coll Cardiol* 1998;31:180-5.
23. Bolling SF, Deeb MG, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. *J Thorac Cardiovasc Surg* 1995;109:676-83.
24. Svedjeholm R, Dahlin LG, Lundberg C, et al. Are electrocardiographic Q-wave criteria reliable for diagnosis of perioperative myocardial infarction after coronary surgery? *Eur J Cardiothorac Surg* 1998;13:655-61.
25. Hodakowski GT, Craver JM, Jones EL et al. Clinical significance of perioperative Q-wave myocardial infarction: the Emory Angioplasty versus Surgery Trial. *J Thorac Cardiovasc Surg* 1996; 112:1447-54.