Published in final edited form as:
Circulation. 2008 October 14; 118(16): 1619–1625. doi:10.1161/CIRCULATIONAHA.108.790162.

Milrinone Use is Associated With Postoperative Atrial Fibrillation Following Cardiac Surgery

Gregory A. Fleming, M.D.[1], **Katherine T. Murray, M.D.**[2], **Chang Yu, Ph.D.**[3], **John G. Byrne, M.D.**[4], **James P. Greelish, M.D.**[4], **Michael R. Petracek, M.D.**[4], **Steven J. Hoff, M.D.**[4], **Stephen K. Ball, M.D.**[4], **Nancy J. Brown, M.D.**[2,*], and **Mias Pretorius, MBChB, MSCI**[5,*]

[1]Division of Pediatric Cardiology, Department of Pediatrics, Vanderbilt University Medical School, Nashville, TN

[2]Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical School, Nashville, TN

[3]Department of Biostatistics, Vanderbilt University Medical School, Nashville, TN

[4]Department of Cardiac Surgery, Vanderbilt University Medical School, Nashville, TN

[5]Department of Anesthesiology, Vanderbilt University Medical School, Nashville, TN

Abstract

Background—Postoperative atrial fibrillation (AF), a frequent complication following cardiac surgery, causes morbidity and prolongs hospitalization. Inotropic drugs are commonly used perioperatively to support ventricular function. This study tested the hypothesis that the use of inotropic drugs is associated with postoperative AF.

Methods and Results—We evaluated perioperative risk factors in 232 patients who underwent elective cardiac surgery. All patients were in sinus rhythm at surgery. Sixty-seven (28.9%) patients developed AF a mean of 2.9±2.1 days after surgery. Patients who developed AF stayed in the hospital longer (P<0.001) and were more likely to die (P=0.02). Milrinone use was associated with an increased risk of postoperative AF (58.2% versus 26.1% in non-users, P<0.001). Older age (63.4 ±10.7 versus 56.7±12.3 years, P<0.001), hypertension (P=0.04), lower preoperative ejection fraction (P=0.03), mitral valve surgery (P=0.02), right ventricular dysfunction (P=0.03), and higher mean pulmonary artery pressure (PAP) (27.1±9.3 versus 21.8±7.5 mmHg, P=0.001) were also associated with postoperative AF. In multivariable logistic regression, age (P<0.001), ejection fraction (P=0.02), and milrinone use (odds ratio 4.86, 95% CI 2.31-10.25, P<0.001) independently predicted postoperative AF. When data only from patients with pulmonary artery catheters were analyzed and PAP was included in the model, age, milrinone use (odds ratio 4.45, 95% CI 2.01-9.84, P<0.001), and higher PAP (P=0.02) were associated with an increased risk of postoperative AF. Adding other potential confounders or stratifying analysis by mitral valve surgery did not change the association of milrinone use with postoperative AF.

Conclusion—Milrinone use is an independent risk factor for postoperative AF following elective cardiac surgery.

Correspondence and Reprints: Nancy J. Brown M.D. 550B RRB Vanderbilt University Medical Center Nashville, TN 37232 Fax: (615) 343-2551 Phone: (615) 343-8701 E-mail: nancy.j.brown@vanderbilt.edu.
*The contributions of these two authors were equivalent

Conflict of Interest: None of the authors has a conflict of interest.

Clinical Trial Registration Information: NCT00141778 http://www.clinicaltrials.gov/ct2/show/NCT00141778

Keywords

atrial fibrillation; surgery; inotropic agents

Atrial fibrillation (AF), the most common complication after cardiac surgery, is associated with significant morbidity, increased mortality, longer hospital stay, and higher hospital costs.[1-4] Numerous risk factors for developing postoperative AF have been identified, including advanced age, previous history of AF, male gender, decreased left ventricular ejection fraction, left atrial enlargement, mitral valve surgery, chronic obstructive pulmonary disease, chronic renal failure, diabetes mellitus, postoperative withdrawal of β-blockers or angiotensin converting enzyme (ACE) inhibitors, and obesity.[1-7] In contrast, postoperative treatment with β-blockers or amiodarone, potassium supplementation, and preoperative treatment with statins has been associated with a reduced the risk of developing postoperative AF.[3, 8] The pathophysiology of postoperative AF is complex and involves an interaction between surgical trauma, activation of the inflammatory response, preexisting atrial pathology, and increased adrenergic tone.[9] Because ventricular dysfunction is common following cardiac surgery, inotropic drugs are often necessary to improve hemodynamic status; however, the effect of inotropic drugs on postoperative AF has not been extensively studied. For example, the use of low dose dopamine or dobutamine in the postoperative period has been associated with an increased risk of developing postoperative AF.[10, 11] Milrinone has been reported to be associated with a lower risk of postoperative AF compared to dobutamine use, but milrinone increases the risk of atrial arrhythmias in patients with acute exacerbation of chronic heart failure.[11, 12]

The aim of this analysis was to test the hypothesis that the use of inotropic drugs is associated with an increased risk of postoperative AF in cardiac surgery patients participating in an ongoing randomized, double blinded, placebo controlled trial.

Methods

Subjects included in this analysis were participants in the ongoing Atrial Fibrillation and Renin Angiotensin Aldosterone System (RAAS) study (ClinicalTrials.gov Identifier: NCT00141778). This study is approved by the Vanderbilt University Institutional Review Board for Research on Human Subjects and conducted according to the Declaration of Helsinki. All patients provided written informed consent. Briefly, the trial is designed to test the hypothesis that interruption of the RAAS, by either angiotensin converting enzyme (ACE) inhibition (ramipril) or aldosterone receptor antagonism (spironolactone), decreases the incidence of AF following elective cardiac surgery. Patients are eligible for the study if they are undergoing elective coronary artery bypass graft (CABG) or valvular surgery and are in sinus rhythm. Exclusion criteria include chronic AF, an ejection fraction less than 30 per cent, evidence of coagulopathy, emergency surgery, serum creatinine greater than 1.6 mg/dL, and hyperkalemia with potassium greater than 5.0 meq/L. One week to four days prior to surgery, patients are randomized to treatment with placebo, spironolactone (25 mg/day), or ramipril (1.25 mg the first two days followed by 2.5 mg/day). Randomization is stratified by age, prior statin use, and prior ACE inhibitor, angiotensin receptor blocker (ARB), or mineralocorticoid receptor (MR) antagonist use. Preexisting ACE inhibitor, ARB, or MR antagonist use is stopped at randomization. The primary endpoint of the study is the occurrence of electrocardiographically confirmed AF at any time following the end of surgery until hospital discharge. Secondary endpoints include intraoperative mean arterial pressure, intraoperative and postoperative requirements for vasopressors, death, length of hospital stay, and serum potassium and creatinine concentrations.

Study Population

The analysis population is comprised of all subjects included in the first interim analysis of the Atrial Fibrillation and RAAS study. Three-hundred and twenty-eight subjects were consented and screened for the study prior to the analysis. Fifty-eight subjects were excluded from the study for the following reasons: twenty-four subjects had surgery emergently, at another location, or did not require surgery; four subjects had an ejection fraction less than 30 per cent; nine subjects were unable to stop their current medications; three subjects had hyperkalemia; two subjects had an elevated serum creatinine; two subjects had chronic AF; one subject previously had angioedema with an ARB; and the remaining nine subjects were judged unable to follow the protocol. Thirty-eight subjects withdrew from the study for personal reasons prior to starting the study drug. Thus, 236 subjects were randomized. Of these, an additional four subjects did not undergo surgery, such that the final data set consisted of 232 adult subjects.

There were no differences in age, gender, race, body mass index (BMI), blood pressure, heart rate, history of diabetes, history of hypertension, history of smoking, types of procedures, or in the pre-study use of ACE inhibitors, ARBs, beta blockers, or statins between those subjects who were consented and not studied and the 232 subjects studied. Those not studied were more likely to be taking spironolactone ($P<0.001$), had a significantly lower ejection fraction ($P=0.049$), and had a higher baseline serum potassium ($P=0.03$), reflecting the exclusion criteria of the study.

Patient Treatment

Anesthetic and surgical management were conducted according to institutional protocols. Briefly, patients received general endotracheal anesthesia, consisting of induction with a combination of thiopental, midazolam, fentanyl, or etomidate and maintenance with isoflurane, pancuronium, and fentanyl. Monitoring included standard modalities [electrocardiogram (ECG), temperature, invasive blood pressure, pulse oximetry, and gas monitoring], plus central venous pressure or pulmonary artery catheter monitoring, and transesophageal echocardiography. Aprotinin was used for repeat sternotomy procedures and those involving more than one open chamber procedure, but its use was discontinued following release of study results by Mangano et al.[13] showing increased mortality in patients treated with aprotinin. ε-Aminocaproic acid (ε-ACA) was used for first-time sternotomy operations in patients without a history of venous thrombosis or unstable coronary syndromes. Anticoagulation for cardiopulmonary bypass (CPB) consisted of 400 U/kg unfractionated porcine heparin. Temperature management involved cooling to 28° to 30°C, temperature uncorrected blood gas management (alpha stat), and cold anterograde and retrograde cardioplegia techniques. At the conclusion of CPB, anticoagulation was reversed with 250 mg protamine, with an additional 50 mg administered in the following 10 minutes in the presence of ongoing microvascular bleeding. Vasopressors and inotropes were used for separation from CPB for the following criteria: left ventricular ejection fraction less than 40 per cent, CPB time longer than 120 minutes, a cardiac index less than $2 L/min/M^2$ or evidence of new onset left ventricular dysfunction by transesophageal echocardiogram. Use of inotropes and/or vasopressor in the postoperative period was at the discretion of the intensive care physicians. Milrinone was preferentially used if the post-bypass left ventricular ejection fraction was less than 30 per cent, for evidence of right ventricular dysfunction, or for pulmonary hypertension. Milrinone was started as a continuous infusion at a dose of 0.5 μg/kg/min and adjusted at the discretion of the supervising physician. Norepinephrine was used to offset milrinone-induced vasodilation. Metoprolol 12.5mg twice a day was given if heart rate was greater than 60 and systolic blood pressure greater than 100 mmHg starting on postoperative day one. Patients were monitored continuously on telemetry throughout the postoperative period until discharge. ECG's were obtained for any rhythm changes detected on telemetry monitoring, and in addition, ECG's

were performed preoperatively and daily starting on postoperative day one. All ECGs and rhythm strips were reviewed in a blinded fashion by a cardiac electrophysiologist.

Statistical Analysis

There were a total of 67 AF events in the study cohort. Initial univariate analysis was performed to determine risk factors associated with the development of postoperative AF, as well as risk factors associated with treatment with milrinone on the day of surgery. Univariate analyses were performed using student's t-test or Mann-Whitney U test, when data was not normally distributed, for continuous variables and chi square test for categorical variables. Data are presented as mean ± standard deviation (SD). Risk for developing AF was then evaluated by logistic regression. Variables with $P < 0.1$ by univariate analysis, as well as known risk factors for AF, were considered for logistic regression modeling. The number of variables included in the model was based on the criteria of one variable per 10 events,[14] which allowed seven variables in the final model. Only variables considered to be the most important confounders were used. Although current smoking showed a trend toward association with postoperative AF ($P<0.1$) by univariate analysis, it was not felt to be a strong confounder on the effect of milrinone on AF, and the final model included age, gender, history of hypertension, mitral valve surgery, baseline ejection fraction, preoperative β-blocker use, and treatment with milrinone on the day of surgery. An additional model was performed that included mean pulmonary artery pressure (PAP) in addition to the previous variables; however, because not all patients underwent pulmonary artery catheter placement, this model excluded 45 patients. Potentially significant confounding variables, including right ventricular dysfunction, postoperative left ventricular dysfunction, statin use, perioperative treatment with norepinephrine, and perioperative treatment with dobutamine were analyzed with the main logistic regression model by adding each variable, one at a time, to the main model. Due to the large number of potential confounding variables associated with milrinone treatment, we also conducted a propensity score analysis using logistic regression on age, gender, hypertension, baseline ejection fraction, mitral valve surgery, preoperative use of β-blockers, preoperative use of statins, CPB time, perioperative treatment with dobutamine, and perioperative treatment with norepinephrine. Because the number of patients treated perioperatively with dopamine and epinephrine was so small and there was no association of the use of these pressors with AF in this study, we did not include these variables in our logistic regression or propensity score analyses. Data are reported as the estimated odds ratios (ORs) and 95% confidence intervals (CIs) (with a value of $P<0.05$ considered statistically significant). Data were analyzed using SPSS (Version 15.1, SPSS, Chicago, IL), and the propensity score analyses were performed using SAS for Windows (Version 9, Cary, NC). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Subject Characteristics Associated with Milrinone Use

Baseline characteristics of patients according to treatment with milrinone on day of surgery are presented in Table 1. There was a trend toward increased milrinone use in women. Patients treated with milrinone were less likely to be diabetic. Preoperative statin use was significantly lower in patients treated with milrinone, but the use of other preoperative medications was similar between patients treated with milrinone and those not treated with milrinone. The rate of milrinone use was not significantly different among the mock-unblinded study groups (data not shown).

Table 2 presents intraoperative characteristics in patients according to whether or not they were treated with milrinone on the day of surgery. Milrinone was started in the operating room in

28.4% of patients and was used in a total of 35.3% of patients on the day of surgery. Patients who received milrinone perioperatively were more likely to have had on-pump surgery, were more likely to have had mitral valve surgery, had longer pump times, were more likely to be treated with norepinephrine and epinephrine postoperatively, and were less likely to be treated with dobutamine and dopamine postoperatively. The mean PAP at the end of surgery was significantly higher in patients who received milrinone. Data from intraoperative transesophageal echocardiography were available for 192 subjects. Right ventricular dysfunction as well as postoperative left ventricular dysfunction (postoperative EF<35%) were associated with milrinone use.

Subject Characteristics Associated with Postoperative Atrial Fibrillation

Sixty-seven (28.9%) patients developed postoperative AF at a mean of 2.9±2.1 days (median of 2 days) after surgery. Patients who developed postoperative AF stayed in the hospital longer (8.5±11.6 days versus 5.1±2.0 days, P<0.001) and were more likely to die in the hospital (4.5% versus 0%, P=0.02). Baseline characteristics of patients with or without postoperative AF appear in Table 3. Patients who developed postoperative AF were significantly older, were more likely to have a history of hypertension, and had a lower preoperative left ventricular ejection fraction. Women tended to be overrepresented in the AF group. Preoperative medications were similar between groups with a trend toward higher preoperative β-blocker use in the AF group. Race, blood pressure, BMI, and preoperative laboratory measurements were similar between groups.

Table 4 indicates intraoperative patient characteristics in patients with or without postoperative AF. Milrinone use on the day of surgery was associated with an increased risk of postoperative AF (58.2% versus 26.1%, P<0.001). Milrinone use on the day of surgery was also associated with an increased risk of postoperative amiodarone or sotalol use (37.8% versus 11.3%, P<0.001). In addition, mitral valve surgery and a higher mean PAP measured at the end of surgery were associated with an increased risk of postoperative AF. Right ventricular dysfunction was associated with postoperative AF, whereas postoperative left ventricular dysfunction (postoperative EF<35%) was not.

The use of inotropes other than milrinone was similar between groups; however, there was a non-significant trend toward increased norepinephrine use in patients who developed postoperative AF. The groups were similar with regard to other surgical procedures and whether or not they had surgery on cardiopulmonary bypass or off-pump. Blood product transfusions were similar between groups.

Logistic Regression Models

In a multivariate logistic regression model that included age, gender, history of hypertension, baseline ejection fraction, mitral valve surgery, and treatment with milrinone on the day of surgery; only milrinone use, increasing age, and lower baseline ejection fraction were significantly associated with the development of postoperative AF (Table 5). The Hosmer and Lemeshow test for goodness of fit accepted this model (P=0.83). Because increased mean PAP, right ventricular dysfunction, left ventricular dysfunction, decreased dobutamine use, decreased preoperative statin use and increased norepinephrine use were associated with milrinone treatment, we evaluated the possible confounding by these variables in logistic regression models that included each of these variables. When the mean PAP, measured at the end of surgery, was added to the model, only milrinone use (odds ratio 4.44, 95% CI 2.01-9.83; P<0.001), higher mean PAP (odds ratio 1.06, 95% CI 1.01-1.11; P=0.02), and older age were associated with an increased risk of postoperative AF. Adding right ventricular dysfunction to the model did not change the effect of milrinone on postoperative AF (odds ratio 5.59, 95% CI 2.34-13.37; P<0.001), and the effect of right ventricular dysfunction was not significant

(odds ratio 1.24, 95% CI 0.43-3.63; P=0.69). Also, the addition of left ventricular dysfunction to the model did not change the effect of milrinone on postoperative AF (odds ratio 6.35, 95% CI 2.62-15.39; P<0.001), and the effect of left ventricular dysfunction was not significant (P=0.33). When treatment with dobutamine was added to the main logistic regression model, the effect of milrinone on AF was slightly increased (odds ratio 5.91, 95% CI 2.65-13.17; P<0.001), and treatment with dobutamine did not significantly increase the risk of postoperative AF (odds ratio 2.30, 95% CI 0.85-6.18; P=0.10). Adding norepinephrine treatment to the model did not change the effect of milrinone on postoperative AF (odds ratio 4.56, 95% CI 2.13-9.75; P<0.001), and the effect of norepinephrine was not significant (odds ratio 1.31, 95% CI 0.59-2.93; P=0.51). When statin use was added to the model, the effect of milrinone on postoperative AF also did not change significantly (odds ratio 4.91, 95% CI 2.31-10.43; P<0.001). Statin use tended to decrease the risk of postoperative AF (odds ratio 0.5, 95% CI 0.23-1.07; P=0.07).

After adjusting for the propensity score, the effect of milrinone on AF remained significant (odds ratio 3.64, 95% CI 1.76-7.56, P<0.001). The balance of the distribution of all the covariates used in constructing the propensity score between milrinone-users and non-users was satisfactory within the lower and upper half of the propensity score subgroups, except for mitral valve surgery due to its strong relationship with milrinone use. For this reason, we examined the relationship between milrinone use and postoperative AF after stratifying subjects according to whether or not they had had mitral valve surgery (Figure 1). The results were consistent with the multivariate logistic regression model (Cochran-Mantel-Haenszel common odds ratio for milrinone use 3.88, 95% CI 1.97-7.66, P<0.001; odds ratio for milrinone use in the mitral valve surgery stratum 5.00, 95% CI 1.67-15.00, P=0.003; and odds ratio for milrinone use in the non-mitral valve surgery stratum 3.16, 95% CI 1.32-7.59, P=0.008).

Discussion

We assessed risk factors for postoperative AF in an ongoing randomized clinical trial designed to assess the effect of ACE inhibition or aldosterone receptor antagonism versus placebo on postoperative AF. The data confirm previous studies indicating an association of increased age, decreased ejection fraction, and pulmonary hypertension with postoperative AF. Perioperative milrinone use was associated with a 2- to 4-fold increased risk of postoperative AF, even after controlling for potential confounders.

Sympathetic activation predicts postoperative AF whereas beta adrenergic blockers effectively decrease the incidence of postoperative AF.[15-17] Perioperative use of dopamine or dobutamine is associated with an increased risk of postoperative AF following cardiac surgery.[10, 11] Short-term intravenous milrinone use has been associated with an increased risk of atrial arrhythmias during treatment of acute exacerbation of chronic heart failure.[12] In contrast, Fenek at al [11] reported a decreased incidence of postoperative AF in cardiac surgery patients randomized to milrinone compared to those randomized to dobutamine; however, there was no placebo control group. In addition, AF was not a primary endpoint of this study, and the incidence of postoperative AF, at five to 18 per cent, may have been underestimated.

Milrinone and inotropes such as dopamine and dobutamine may increase the risk of AF by increasing cyclic adenosine monophosphate (cAMP), leading to an increase in intracellular calcium concentration. Dopamine and dobutamine increase cAMP production by activating the β1-adrenergic receptor, whereas milrinone decreases cAMP degradation by inhibiting phosphodiesterase. Activation of protein kinase A (PKA) by cAMP leads to phosphorylation of ion channel subunits involved in multiple cardiac currents, including the slowly-activating delayed rectifier (I_{Ks}) and L-type calcium current.[18, 19] The mechanisms whereby PKA activation promotes AF may include abbreviation of atrial refractoriness and triggered activity

in pulmonary veins.[18, 20] Recent data indicate that phosphodiesterase inhibition may significantly enhance PKA-mediated phosphorylation in the heart, compared to β-adrenergic stimulation.[21]

Because this study was observational and not randomized, confounding by indication may have contributed to the increased risk of postoperative AF among milrinone-treated patients. Norepinephrine and epinephrine, sympathomimetics often given to counteract the hypotensive effect of milrinone, were administered more often in milrinone-treated patients than in those who did not receive milrinone. In contrast, patients treated with milrinone were less likely to receive dopamine or dobutamine. Patients treated with milrinone had a higher PAP, longer bypass times, and a number of other clinical characteristics that may have predisposed them to postoperative AF. For example, pulmonary hypertension is associated with an increased morbidity and mortality following cardiac surgery.[22, 23] PAP predicts risk of AF following mitral valve surgery in patients with a prior history of AF as well as in patients following closure of secundum atrial septal defects.[24, 25] Milrinone-treated patients were less likely to have taken statins prior to surgery. Statin use has been reported to protect against postoperative AF in observational studies as well as in a randomized, placebo-controlled trial,[8, 26] and we also observed a trend toward a protective effect of preoperative statin use. Controlling for each of these confounding variables using multivariate regression, using propensity score analysis, and stratifying by mitral valve surgery did not change the association between perioperative milrinone use and postoperative AF. Nevertheless, other factors may exist that are associated with the use of milrinone in certain patients that were not measured and were not controlled for in our analysis.

Despite the limitations presented by an observational study, the absolute rate of postoperative AF among patients treated with milrinone in the perioperative period raises concern. Approximately 500,000 patients undergo cardiac surgery each year in the United States, and milrinone is commonly used for the treatment of postoperative ventricular failure.[27, 28] In this single-center study, thirty-five per cent of patients received milrinone in the perioperative period. Based on the incidence of postoperative AF observed in the milrinone-treated versus non-exposed patients, similar rates of treatment with milrinone nationally could result in an excess of 56,000 cases of postoperative AF per year. If even a fraction of these is attributable to milrinone use rather than to underlying disease, this represents a significant health concern.

In summary, milrinone, a phosphodiesterase inhibitor that increases cardiac cAMP, has been associated with increased risk of AF in a randomized trial in patients with congestive heart failure.[12] In the present study, we found that perioperative milrinone use was associated with an increased incidence of postoperative AF, even after controlling for potential confounders. Because of the possible impact of selection bias on these observational data, randomized clinical trials are needed to confirm or refute this finding. Given the magnitude of the effect of milrinone on AF risk, however, the potential impact on morbidity and health care costs is large.

Clinical Perspective

Approximately 500,000 patients undergo cardiac surgery in the United States each year. Postoperative atrial fibrillation is a common complication following surgery and causes morbidity and prolongs hospitalization. Milrinone use on the day of surgery was associated with an increased risk of postoperative atrial fibrillation even after controlling for other risk factors such as age, ejection fraction, and increased pulmonary artery pressure. These findings have clinical and financial implications. Milrinone was administered in thirty-five per cent of patients in this single-center study. Based on the incidence of postoperative atrial fibrillation in the milrinone-treated versus non-exposed patients, similar rates of milrinone use nationally could result in an excess of 56,000 cases of postoperative atrial fibrillation per year, with an

attendant excess in postoperative stroke and prolongation of hospital stay. Randomized, prospective studies are needed to assess further the risk of postoperative atrial fibrillation associated with milrinone use.

Acknowledgments

We would like to thank Carol Meisch, RN, Delia Woods, RN, and Anthony DeMatteo for their nursing assistance and for database management.

Financial Support: This study was supported by National Heart, Lung, and Blood Institute grants 077389, 085740, and RR024975.

References

1. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, Collins JJ Jr. Cohn LH, Burstin HR. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation 1996;94:390–397. [PubMed: 8759081]
2. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, Browner WS. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. Jama 1996;276:300–306. [PubMed: 8656542]
3. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT. A multicenter risk index for atrial fibrillation after cardiac surgery. Jama 2004;291:1720–1729. [PubMed: 15082699]
4. Almassi GH, Schowalter T, Nicolosi AC, Aggarwal A, Moritz TE, Henderson WG, Tarazi R, Shroyer AL, Sethi GK, Grover FL, Hammermeister KE. Atrial fibrillation after cardiac surgery: a major morbid event? Ann Surg 1997;226:501–511. [PubMed: 9351718]discussion 511-503
5. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 1993;56:539–549. [PubMed: 8379728]
6. Banach M, Rysz J, Drozdz JA, Okonski P, Misztal M, Barylski M, Irzmanski R, Zaslonka J. Risk factors of atrial fibrillation following coronary artery bypass grafting: a preliminary report. Circ J 2006;70:438–441. [PubMed: 16565561]
7. Echahidi N, Mohty D, Pibarot P, Despres JP, O'Hara G, Champagne J, Philippon F, Daleau P, Voisine P, Mathieu P. Obesity and metabolic syndrome are independent risk factors for atrial fibrillation after coronary artery bypass graft surgery. Circulation 2007;116:I213–219. [PubMed: 17846306]
8. Patti G, Chello M, Candura D, Pasceri V, D'Ambrosio A, Covino E, Di Sciascio G. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. Circulation 2006;114:1455–1461. [PubMed: 17000910]
9. Amar D. Perioperative atrial tachyarrhythmias. Anesthesiology 2002;97:1618–1623. [PubMed: 12459693]
10. Argalious M, Motta P, Khandwala F, Samuel S, Koch CG, Gillinov AM, Yared JP, Starr NJ, Bashour CA. “Renal dose” dopamine is associated with the risk of new-onset atrial fibrillation after cardiac surgery. Crit Care Med 2005;33:1327–1332. [PubMed: 15942351]
11. Feneck RO, Sherry KM, Withington PS, Oduro-Dominah A. Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. J Cardiothorac Vasc Anesth 2001;15:306–315. [PubMed: 11426360]
12. Cuffe MS, Califf RM, Adams KF Jr. Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. Jama 2002;287:1541–1547. [PubMed: 11911756]
13. Mangano DT, Miao Y, Vuylsteke A, Tudor IC, Juneja R, Filipescu D, Hoeft A, Fontes ML, Hillel Z, Ott E, Titov T, Dietzel C, Levin J. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. Jama 2007;297:471–479. [PubMed: 17284697]

14. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373–1379. [PubMed: 8970487]
15. Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF, Gutteridge G, Tonkin AM. Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. Ann Thorac Surg 1995;60:1709–1715. [PubMed: 8787468]
16. Hogue CW Jr. Domitrovich PP, Stein PK, Despotis GD, Re L, Schuessler RB, Kleiger RE, Rottman JN. RR interval dynamics before atrial fibrillation in patients after coronary artery bypass graft surgery. Circulation 1998;98:429–434. [PubMed: 9714093]
17. Crystal E, Garfinkle MS, Connolly SS, Ginger TT, Sleik K, Yusuf SS. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev. 2004CD003611
18. Sampson KJ, Terrenoire C, Cervantes DO, Kaba RA, Peters NS, Kass RS. Adrenergic regulation of a key cardiac potassium channel can contribute to atrial fibrillation: evidence from an I Ks transgenic mouse. J Physiol 2008;586:627–637. [PubMed: 18006587]
19. El-Armouche A, Boknik P, Eschenhagen T, Carrier L, Knaut M, Ravens U, Dobrev D. Molecular determinants of altered Ca2+ handling in human chronic atrial fibrillation. Circulation 2006;114:670–680. [PubMed: 16894034]
20. Patterson E, Yu X, Huang S, Garrett M, Kem DC. Suppression of autonomic-mediated triggered firing in pulmonary vein preparations, 24 hours postcoronary artery ligation in dogs. J Cardiovasc Electrophysiol 2006;17:763–770. [PubMed: 16836675]
21. Vinogradova TM, Sirenko S, Lyashkov AE, Younes A, Li Y, Zhu W, Yang D, Ruknudin AM, Spurgeon H, Lakatta EG. Constitutive phosphodiesterase activity restricts spontaneous beating rate of cardiac pacemaker cells by suppressing local Ca2+ releases. Circ Res 2008;102:761–769. [PubMed: 18276917]
22. Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. Ann Thorac Surg 2000;69:823–828. [PubMed: 10750767]
23. Tuman KJ, McCarthy RJ, March RJ, Najafi H, Ivankovich AD. Morbidity and duration of ICU stay after cardiac surgery. A model for preoperative risk assessment. Chest 1992;102:36–44. [PubMed: 1623792]
24. Vogt PR, Brunner-LaRocca HP, Rist M, Zund G, Genoni M, Lachat M, Niederhauser U, Turina MI. Preoperative predictors of recurrent atrial fibrillation late after successful mitral valve reconstruction. Eur J Cardiothorac Surg 1998;13:619–624. [PubMed: 9686790]
25. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. N Engl J Med 1999;340:839–846. [PubMed: 10080846]
26. Marin F, Pascual DA, Roldan V, Arribas JM, Ahumada M, Tornel PL, Oliver C, Gomez-Plana J, Lip GY, Valdes M. Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. Am J Cardiol 2006;97:55–60. [PubMed: 16377284]
27. Welke KF, Peterson ED, Vaughan-Sarrazin MS, O'Brien SM, Rosenthal GE, Shook GJ, Dokholyan RS, Haan CK, Ferguson TB Jr. Comparison of cardiac surgery volumes and mortality rates between the Society of Thoracic Surgeons and Medicare databases from 1993 through 2001. Ann Thorac Surg 2007;84:1538–1546. [PubMed: 17954059]
28. Denault AY, Lamarche Y, Couture P, Haddad F, Lambert J, Tardif JC, Perrault LP. Inhaled milrinone: a new alternative in cardiac surgery? Semin Cardiothorac Vasc Anesth 2006;10:346–360. [PubMed: 17200091]

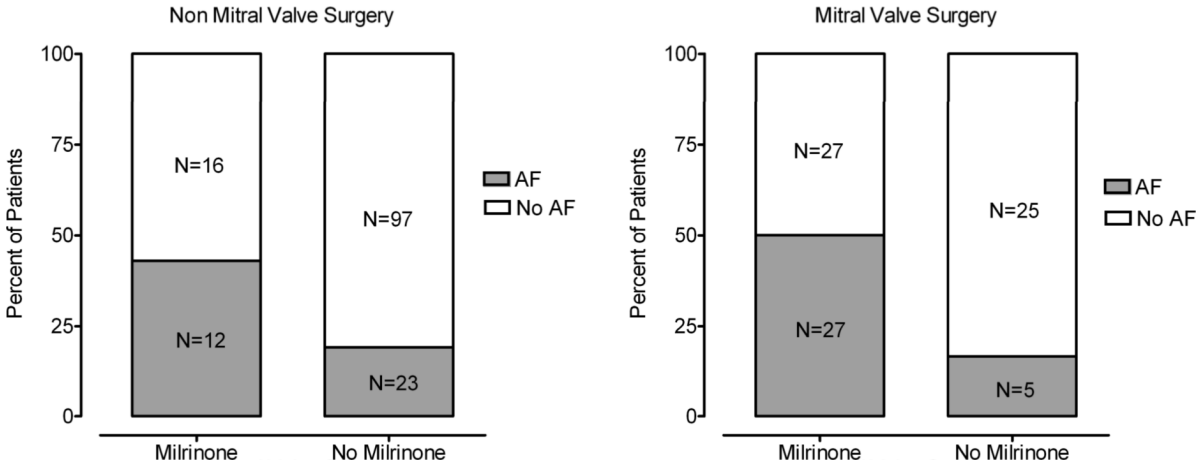

Figure 1.
Rates of postoperative atrial fibrillation (AF) according to milrinone exposure, stratified by mitral valve surgery

Table 1

Preoperative Subject Characteristics

Characteristic	No Milrinone (N=150)	Milrinone (N=82)	P-value
Age	59.5±12.0	57.1±12.5	0.15
Gender, women N (%)	47(31.3)	37(42.7)	0.08
Race, Caucasian N (%)	140(93.3)	71(86.6)	0.09
Body Mass Index (kg/m^2)	29.3±5.9	29.5±7.2	0.96
Mean arterial pressure (mmHg)	92.8±11.2	91.9±10.6	0.57
Heart rate (bpm)	64.3±12.7	67.9±14.6	0.10
Medical History, N(%)			
Current Smoker	35(23.3)	17(20.7)	0.65
Hypertension	102(68)	48(58.5)	0.15
Diabetes	42(28)	13(15.9)	**0.04**
Preoperative medication pre-randomization, N (%)			
β-Blockers	78(52.3)	39(47.6)	0.49
ACE inhibitors	57(38)	23(28)	0.13
Aldosterone receptor blocker	0(0)	2(2.4)	0.06
Angiotensin receptor blocker	32(21.3)	12(14.6)	0.21
Statins	88(58.7)	35(42.7)	**0.02**
Preoperative			
Hematocrit, %	42.1±4.0	41.2±5.2	0.37
Creatinine, mg/dl	1.02±0.4	0.97±0.2	0.44
Potassium, mmol/l	4.2±0.5	4.2±0.5	0.73
Ejection fraction, %	56.3±9.4	56.4±10.4	0.56

ACE indicates angiotensin-converting enzyme.

Table 2

Intraoperative Subject Characteristics

Characteristic	No Milrinone (N=150)	Milrinone (N=82)	P-value
On-pump surgery, N (%)	125 (83.3)	80 (97.6)	**0.001**
CABG surgery, N (%)	77 (51.3)	20 (24.4)	<**0.001**
Number of grafts	2.5±1.0	2.8±1.1	0.35
Valvular surgery, N (%)			
Mitral valve surgery	30 (20.0)	54 (65.9)	<**0.001**
Aortic valve surgery	44 (29.3)	26 (31.7)	0.71
Cardiopulmonary bypass time, min	114.9±50.7	131.9±58.6	**0.005**
Cross-clamp time, min	86.3±39.8	105.6±50.0	**0.008**
Inotropes, N (%)			
Dopamine	9 (6.1)	1 (1.2)	0.08
Dobutamine	24 (16.2)	5 (6.1)	**0.03**
Epinephrine	6 (4.1)	12 (14.6)	**0.004**
Norepinephrine	100 (67.6)	69 (84.1)	**0.006**
Blood product transfusion in OR, Units			
PRBC	1.3±2.1	1.5±1.7	0.08
FFP	0.6±1.9	0.5±1.2	0.97
Random donor platelets	0.7±1.9	0.4±1.6	0.11
Pheresed platelets	0.12±0.4	0.13±0.3	0.53
Cryoprecipitate	0.11±0.9	0	0.29
Mean PAP at end of surgery (mmHg)	21.8±7.6	25.9±8.9	**0.001**
Right ventricular dysfunction*, N (%)	8 (6.5)	17 (25)	<**0.001**
Left ventricular dysfunction*, N (%)	2 (1.7)	6 (9.1)	**0.03**

CABG indicates coronary artery bypass graft, OR indicates operating room, PRBC indicates packed red blood cells, FFP indicates fresh frozen plasma, and PAP indicates pulmonary artery pressure.

*Data from intraoperative transesophageal echocardiography were available for 192 subjects.

Table 3

Preoperative Subject Characteristics

Characteristic	No Atrial Fibrillation (N=165)	Atrial Fibrillation (N=67)	P-value
Age	56.7±12.3	63.4±10.7	<**0.001**
Gender, women N (%)	52 (31.5)	30 (44.8)	0.06
Race, Caucasian N (%)	151 (91.0)	62 (91.2)	0.96
Body Mass Index (kg/m^2)	29.6±6.6	28.9±5.7	0.51
Mean arterial pressure (mmHg)	92.8±11.0	91.7±11.1	0.51
Heart rate (bpm)	65.5±12.9	65.8±14.9	0.89
Medical History, N (%)			
Current Smoker	42 (25.5)	10 (14.9)	0.08
Hypertension	100 (60.6)	50 (74.6)	**0.04**
Diabetes	37 (22.4)	18 (26.9)	0.47
Preoperative medication pre-randomization, N (%)			
β-Blockers	77 (47.0)	40 (59.7)	0.08
ACE inhibitors	56 (33.9)	24 (35.8)	0.79
Aldosterone receptor blocker	1 (0.6)	1 (1.5)	0.50
Angiotensin receptor blocker	34 (20.6)	10 (14.9)	0.32
Statins	88 (53.3)	35 (52.2)	0.88
Preoperative			
Hematocrit, %	42.1±4.4	41.1±4.7	0.10
Creatinine, mg/dL	1.0±0.2	1.1±0.6	0.44
Potassium, mmol/L	4.2±0.4	4.2±0.6	0.56
Ejection fraction, %	57.2±9.6	54.3±9.8	**0.03**

ACE indicates angiotensin-converting enzyme.

Table 4

Intraoperative Subject Characteristics

Characteristic	No Atrial Fibrillation (N=165)	Atrial Fibrillation (N=67)	P-value
On-pump surgery, N (%)	143 (86.7)	62 (92.5)	0.21
CABG surgery, N (%)	72 (43.6)	25 (37.3)	0.38
Number of grafts	2.6±1.0	2.5±1.2	0.43
Valvular surgery, N (%)			
Mitral valve surgery	52 (31.5)	32 (47.8)	**0.02**
Aortic valve surgery	48 (29.1)	22 (32.8)	0.57
Cardiopulmonary bypass time, min	119.5±49.5	126.0±64.7	0.43
Cross-clamp time, min	91.7±40.7	92.6±51.4	0.77
Inotropes, N (%)			
Dopamine	13 (8.0)	3 (4.5)	0.41
Dobutamine	15 (9.2)	9 (13.4)	0.34
Milrinone	43 (26.1)	39 (58.2)	<**0.001**
Epinephrine	16 (9.9)	7 (10.6)	0.87
Norepinephrine	128 (78.0)	59 (88.1)	0.08
Blood product transfusion in OR, Units			
PRBC	1.2±1.9	1.7±2.3	0.13
Fresh frozen plasma	0.5±1.7	0.7±1.7	0.10
Random donor platelets	0.6±1.8	0.6±1.9	0.99
Pheresed platelets	0.1±0.4	0.2±0.4	0.18
Cryoprecipitate	0.1±0.8	0.1±0.7	0.54
Mean PAP at end of surgery (mmHg)	21.8±7.5	27.1±9.3	<**0.001**
Right ventricular dysfunction*, N (%)	13 (9.6)	12 (21.4)	**0.03**
Left ventricular dysfunction*, N (%)	5 (3.8)	3 (5.6)	0.69

CABG indicates coronary artery bypass graft, OR indicates operating room, PRBC indicates packed red blood cells, and PAP indicates pulmonary artery pressure.

*Data from intraoperative transesophageal echocardiography were available for 192 subjects.

Table 5

Multivariate Logistic Regression Model for Postoperative Atrial Fibrillation

Variables	Odds Ratio	P value	95% CI
Milrinone use	4.86	<0.001	2.31-10.25
Age, years	1.06	<0.001	1.03-1.10
Baseline ejection fraction, %	0.96	0.02	0.93-0.99
Hypertension	1.63	0.23	0.74-3.58
Gender, male versus female	0.63	0.19	0.31-1.26
Mitral valve surgery	1.34	0.40	0.64-2.99
Preoperative β-Blocker use	1.33	0.42	0.66-2.67

CI indicates confidence interval. Including mean pulmonary artery pressure, right ventricular dysfunction, perioperative dobutamine, perioperative norepinephrine, or preoperative statin use in the multivariate model did not change the association between milrinone and postoperative atrial fibrillation.