

Pericardial Reconstruction Using an Extracellular Matrix Implant Correlates with Reduced Risk of Postoperative Atrial Fibrillation in Coronary Artery Bypass Surgery Patients

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ABSTRACT

Background: Postoperative atrial fibrillation (AF) is a significant complication following open heart surgery, with potentially serious clinical and economic implications. To assess the effect of a novel procedure, pericardial reconstruction using a porcine-derived extracellular matrix (ECM) implant, on the risk of postoperative AF after primary isolated coronary artery bypass grafting (CABG), we performed a retrospective comparison of the incidence of postoperative AF in patients who underwent this procedure versus an untreated control group.

Methods: We performed a retrospective comparison of the incidence of postoperative AF in 111 patients who underwent a pericardial reconstruction procedure with the CorMatrix ECM for Pericardial Closure (CorMatrix Cardiovascular, Atlanta, GA, USA) following primary isolated CABG, versus a control group of 111 patients who did not undergo pericardial reconstruction.

Results: Postoperative AF occurred in 43 of 111 control patients (39%; lower control limit [LCL], 30%; upper control limit [UCL], 49%) but in only 20 of 111 treated patients (18%; LCL, 11%; UCL, 27%). This result represents a 54% reduction in relative risk in the treatment group ($P < .001$). There was a small but statistically insignificant decrease in the hospital length of stay for the treated patients. The 2 treatment groups exhibited similar postoperative complication profiles.

Conclusions: In this retrospective study, pericardial reconstruction with the ECM implant contributed directly to a statistically significant and clinically meaningful reduction in the rate of postoperative AF in patients undergoing primary isolated CABG. A prospective multicenter randomized trial has been planned to further test this approach.

INTRODUCTION

Postoperative atrial fibrillation (AF) is the most common arrhythmic complication following cardiac surgery, with

a reported incidence between 32% and 64% in patients undergoing various cardiac procedures [Creswell 1993; Auer 2005; Echahidi 2008]. Postoperative AF is usually well tolerated and self-limited, but refractory cases are occasionally associated with a significantly increased risk of hypotension, congestive heart failure, thromboembolic events such as cerebrovascular accident, and the need for postoperative implantation of a permanent pacemaker or implantable defibrillator [Creswell 1993].

The intensive management of postoperative AF and treatment of its comorbidities can be expensive, and postoperative AF has been associated with an increased length of stay (LOS) in the intensive care unit or on the postoperative telemetry floor [Aranki 1996; Mathew 2004]. A recent study from the Commonwealth of Virginia found that the mean added cost of isolated postoperative AF following isolated CABG was \$2574/patient [Speir 2009]. Annual costs to the US health care system due to postoperative AF and its sequelae are estimated to run in excess of \$2 billion [Echahidi 2008].

The etiology of postoperative AF remains unclear, although a number of risk factors have been implicated. The most definitively established clinical risk factor is age. The risk for postoperative AF increases by 75% for every decade of life after 30 years [Mathew 2004]. Potential structural risk factors include left atrial enlargement, diastolic dysfunction, systolic dysfunction, left ventricular hypertrophy, and heightened sympathetic tone [Steinberg 1993; Mattson 2000]. Intraoperative atrial injury, atrial ischemia and reperfusion injury [Maisel 2001], volume overload, increased stretch, and augmented volume changes [Kalus 2004] have also been implicated as contributing factors. A multitude of triggers, including enhanced atrial and ventricular ectopy, electrolyte imbalance, and autonomic nervous system imbalance [Jongnarangsin 2009], may also precipitate the process.

Currently, the best-studied and most common prophylactic intervention for postoperative AF is treatment with β -adrenergic blockers, but perioperative amiodarone, sotalol, non-dihydropyridine calcium channel blockers, magnesium sulfate, and biatrial pacing have also been associated with reduction in the risk of postoperative AF [Mayson 2007; Echahidi 2008]. These treatment choices are not without risk, however, and their efficacy can be variable. Accordingly, the search for additional prophylactic interventions continues.

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Recently, we began working with a novel implantable acellular xenograft derived from the extracellular matrix (ECM) of porcine small intestinal submucosa [Robinson 2005; Badylak 2006, 2008; Gerdisch 2009]. This material is cleared in the United States and Europe as an implant for pericardial closure and for cardiac tissue repair. Anecdotally, we noted a lower incidence of postoperative AF in patients who had undergone pericardial repair with this material following primary isolated coronary artery bypass grafting (CABG), compared with patients not so treated. As a preliminary evaluation of this approach's potential for reducing the risk of postoperative AF, we performed a 3-site retrospective chart review, the results of which are reported here.

MATERIALS AND METHODS

The institutional review boards at 3 institutions (Mobile Infirmary Medical Center [MIMC], Mobile, Alabama; Providence Hospital [PH], Mobile, Alabama; and Trinity Medical Center [TMC], Birmingham, Alabama, USA) approved the retrospective review study protocol. The study did not require informed consent.

Our hypothesis was that the group of patients who underwent pericardium reconstruction with the ECM implant (CorMatrix ECM for Pericardial Closure; CorMatrix Cardiovascular, Atlanta, GA, USA) following primary isolated CABG (repair group) experienced a lower rate of postoperative AF than the group of patients who underwent primary isolated CABG without pericardial reconstruction (control group). The institutions selected to test this hypothesis (MIMC, PH, and TMC) were chosen because of their demonstrated surgical expertise in the method for pericardial reconstruction with the ECM implant. The primary end point of this retrospective analysis was a comparison of the rates of postoperative AF among the patients in the repair group and the control group. The secondary end point of this retrospective analysis was a comparison of the hospital LOS for the 2 groups.

Patient Populations

The method of patient accrual to the repair and control groups is illustrated in Figure 1. For the repair group, we reviewed the charts of 111 consecutive patients who underwent primary isolated CABG with concurrent pericardial repair with the ECM implant. For the control group, we collected data from the charts of the 111 site-matched, consecutive patients who had undergone isolated CABG in the period immediately preceding the use of the ECM at each institution. For both groups, all patients who underwent first-time coronary revascularization in the appropriate time period were included. None of these control-group patients received the repair; otherwise, all institutional perioperative treatment and surgical techniques were standardized in the 2 groups during the time interval of the study. The numbers of patients from the 3 sites in each treatment group were balanced (ie, each group had 25 patients from MIMC, 36 from PH, and 50 from TMC). A single surgeon at each institution performed all of the operations (repair and control). The rates of postoperative AF in the 2 groups were compared. The same groups of patients were analyzed for hospital LOS and for the collection of adverse-event data.

Exclusion Criteria

Patients were excluded from the study if they had a history of preoperative AF, previous cardiac surgery, a planned concomitant cardiovascular procedure, or current treatment with a class III antiarrhythmic medication.

Surgical Technique

The operative procedure for the repair group was performed in the following manner. After sternotomy, the pericardium was incised in the midline with an inverted T inferiorly and was suspended laterally. CABG was performed with the aid of cardiopulmonary bypass. After the patient was separated from bypass, the entire perimeter of the pericardium was reconstructed with the CorMatrix Cardiovascular ECM implant (see Figures 2 and 3). The graft was placed by approximating the native pericardium to the perimeter of the ECM implant with a running 4-0 Prolene suture. Sutures were placed at approximately 1-cm intervals. The complete perimeter repair was concluded with the placement of one chest tube within the pericardial space and another anterior to the repair, with care taken to ensure minimal tension on the suture line. For the control group, the operative procedure was the same except that the pericardium was left open in the usual fashion.

Definition of AF

In both groups, postoperative AF was defined as any occurrence of postoperative AF documented by telemetry, regardless of duration and whether the AF was treated or not. The postoperative records, including notes, history, discharge summary, and in-hospital medications, were reviewed. The cardiology staff involved in each case then reviewed the telemetry tracings to determine the presence or absence of AF.

Statistical Analysis

After data collection was completed, a comparability analysis of baseline variables of the control and repair groups was performed with a 2-sided, 2-sample Student *t* test for quantitative variables and with a 2-sided Fisher exact test for qualitative variables. An initial statistical analysis of the primary effectiveness end point was carried out by means of a univariate Fisher exact test at a 1-sided α of .05. The initial analysis of the secondary effectiveness end point was carried out with a univariate 2-sample *t* test at a 1-sided α of .05. This

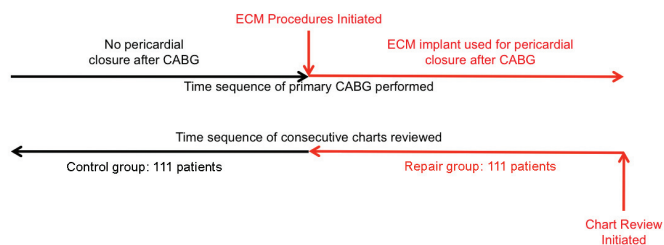


Figure 1. Accrual of patients in the groups for comparing the effects of pericardial reconstruction with the extracellular matrix (ECM) implant on postoperative atrial fibrillation. CABG indicates coronary artery bypass grafting.

Table 1. Preoperative Characteristics of the Patients Who Underwent Primary Isolated Coronary Artery Bypass Grafting with (Repair Group) and without (Control Group) Complete Pericardial Reconstruction with the Extracellular Matrix Implant*

Characteristic	Control Group (n = 111)	Repair Group (n = 111)	P
Age range, y	35-85	39-86	.13
Age, y	64.5 (11.2)	62.3 (10.7)	.13
Height, in	67.7 (3.9)	67.9 (3.9)	.69
Weight, lb	193.2 (40.9)	197.7 (38.4)	.46
Male sex	65%	68%	.78
White ethnicity†	85% (92/108)	82% (89/109)	.59
Medical history			
Left ventricular hypertrophy‡	5% (5/101)	7% (7/103)	.77
Left bundle branch block‡	2% (2/101)	3% (3/103)	>.99
Previous revascularization	12%	4%	.04
Congestive heart failure	9%	8%	>.99
COPD	15%	23%	.23
Hypertension	80%	84%	.60
Peripheral vascular disease	10%	18%	.12
Bleeding	0%	0%	—
Medications§			
β-Adrenergic blocker	47% (52/110)	50%	.79
Statin	61% (67/110)	54%	.34
Antiarrhythmic	4% (4/110)	4%	>.99
Calcium channel blocker	33% (36/110)	20%	.03
ACE inhibitor	28% (31/110)	29%	>.99
Angiotensin II receptor blocker	4% (4/110)	5%	.75
NSAID	38% (42/110)	33%	.49
Steroids	3% (3/110)	2%	.68
Magnesium	1% (1/110)	1%	>.99

*Data are presented as the mean (SD) where indicated. The total number of patients studied was 111 for the control group and 111 for the repair group. For data that were not recorded for all patients, the number of patients with the characteristic and the number of patients studied are indicated in parentheses. COPD indicates chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug.

†No data were recorded for 2 patients in the treatment group and 3 patients in the control group.

‡“Non-applicable” was reported for 8 patients in the treatment group and 9 patients in the control group; 1 control patient did not have a report.

§One patient in the control group did not have data reported for these items.

analysis was followed by a multivariate analysis using general linear models. The safety analysis was performed by defining the complication rates in the 2 groups and then comparing the rates to indicate that the rates and 95% exact confidence intervals for the proportion of patients experiencing a postoperative adverse event demonstrated overlapping intervals.

RESULTS

Table 1 summarizes routine demographic features, medical history, preoperative structural features, and pharmacologic treatments defining the 2 treatment populations.

Figure 4 shows the results of the primary end point analysis, a comparison of the rates of postoperative AF in the repair group

and the control group. Pericardial reconstruction with the ECM implant following primary isolated CABG reduced the relative risk of developing postoperative AF by 54%, compared with the control group (39% in the control group versus 18% in the repair group). Expressed in terms of the absolute risk reduction (ARR), the risk of postoperative AF was reduced by 21%.

The primary end point analysis was followed by a multivariate analysis using logistic regression. The eligible covariates were age, chronic obstructive pulmonary disease, peripheral vascular disease, hypertension, calcium channel blocker use, study site, medical history of “other condition,” previous revascularization, and pericardial reconstruction with the ECM implant. Table 2 presents the final model in the multivariate logistic regression analysis for the primary end point.

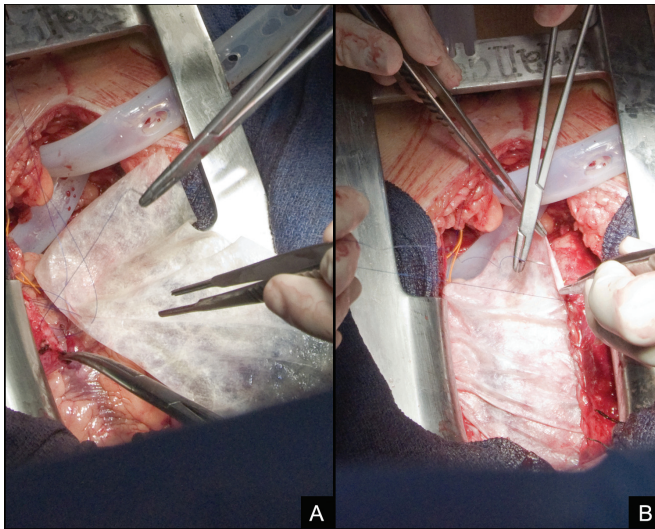


Figure 2. Intraoperative photographs of the complete pericardial reconstruction procedure. A, Initial placement of the extracellular matrix (ECM) implant. B, Approximation of the edges of the native pericardium to the entire perimeter of the ECM implant with a running 4-0 Prolene suture.

The secondary end point was a comparison of hospital LOS in the control and repair groups. Because the hospital LOS data were not normally distributed, both mean and median values are presented. For the control group, the mean (SD) hospital LOS was 7 (5) days, and the median (minimum, maximum) hospital LOS was 5 (3, 37) days. For the repair group, the mean (SD) LOS was 6 (4) days, and the median (minimum, maximum) LOS was 5 (2, 26) days. The *P* value determined in a 1-sided unequal-variance Student *t* test was .118 (not statistically significant).

Table 3 compares the postoperative adverse events in the 2 treatment groups.

DISCUSSION

Despite the availability of numerous therapeutic interventions for postoperative AF following CABG, this arrhythmia remains a significant problem with clinical and economic implications. Our anecdotal observation that pericardial reconstruction with the ECM implant (Figures 2 and 3) seemed to reduce the incidence of new-onset postoperative AF and its underlying difficulties was thus intriguing, and it formed the basis for this retrospective pilot study.

The primary end point of this study was to evaluate the efficacy of pericardial reconstruction using the ECM implant at the time of primary isolated CABG for reducing the risk of postoperative AF (Figure 4). The univariate analysis indicated a highly statistically significant reduction in postoperative AF, with a relative risk reduction of 54% (*P* < .001) and an ARR of 21%. Although these findings are preliminary, the data are highly suggestive that pericardial repair with the ECM implant may confer a substantial benefit in reducing the rates of postoperative AF among patients undergoing primary isolated CABG. Expressed in terms of the numbers needed to

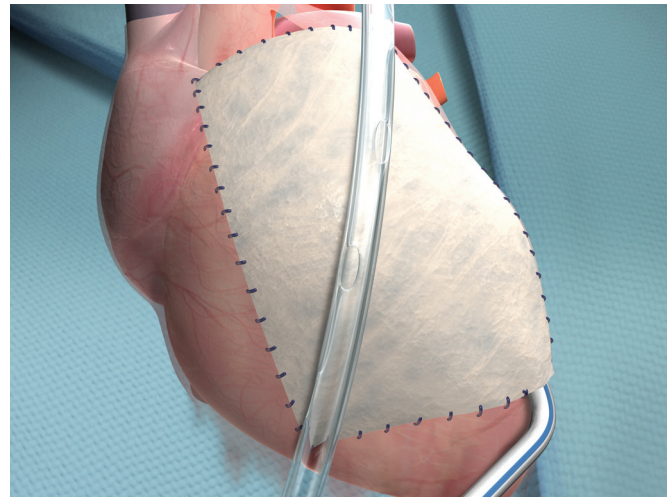


Figure 3. Conceptual illustration of pericardial reconstruction depicting the extracellular matrix implant sutured in place over the pericardial incision. Placement of the chest tubes is also shown.

treat, the results suggest that for every 5 patients treated with this procedure, 1 patient who would otherwise have developed postoperative AF will be spared this condition and its downstream clinical and economic consequences.

Subsequent multivariate analysis further confirmed that treatment with the acellular xenograft was, again, highly statistically significant in reducing postoperative AF in the post-CABG patient. The only other evaluated clinical factor that appeared to be associated with augmented risk was age, a finding that is consistent with previous studies [Mathew 2004]. Even after adjusting for age, the statistical benefit of pericardial repair with the ECM implant remained.

The secondary end point of this study was to determine whether there was a relationship between pericardial reconstruction with the ECM implant and hospital LOS. Although the mean LOS favored the ECM implant-treated patients by slightly greater than half a day, the statistical analysis did not support this finding. This study was not powered to address LOS, however, because it was a secondary end point. The data presented—particularly the narrower and more favorable range of LOS in the repair group—are suggestive, and additional studies with a larger patient population and a higher degree of power may reveal a more robust effect, given that LOS has been shown in prior studies to correlate with postoperative AF [Aranki 1996; Mathew 2004].

Table 2. Multivariable Logistic Regression Analysis of the Critical Factors Influencing the Primary End Point, the Development of Postoperative Atrial Fibrillation*

Factor	Odds Ratio	95% Confidence Interval	<i>P</i>
ECM treatment	0.37	0.19-0.70	.0024
Age	1.07	1.04-1.11	<.001

*Five patients were excluded from this analysis because no age was reported. ECM indicates extracellular matrix.

Of importance was the finding that the use of the ECM implant to achieve pericardial reconstruction did not increase the complication rate compared with the control group. The hypothetical complications that could ensue from the use of such a surgical intervention, such as allergy, bleeding, infection, migration of the ECM implant, myocardial infarction, pericarditis, tamponade, and death, were all <1% and were not different between the 2 groups.

The current study is unique in that it describes an intraoperative surgical intervention that significantly reduced the incidence of postoperative AF by restoring the normal pericardial anatomy. Few reports in the current literature describe operative procedures designed to reduce the incidence of postoperative AF. We were unable to locate any clinical or even preclinical reports that specifically evaluated the effect of pericardial repair on postoperative AF, whether with intrinsic pericardium or other patch materials. Previously reported operative strategies have included aortic fat pad removal with ventral cardiac denervation [Alex 2005] and the performance of a posterior pericardiectomy [Biancari 2010]. Posterior pericardiectomy has been shown to be somewhat effective in reducing postoperative AF after CABG. The success of this technique appears to be due to reducing the incidence of pericardial effusion [Biancari 2010].

Because the initial basis for the study was an empirical observation and given that the mechanisms of postoperative AF remain poorly understood, this preliminary study does not allow us to construct a definitive hypothesis explaining the observed effects. Further investigation is needed to understand whether the reduction in postoperative AF was due to the repair of the pericardium itself, the intrinsic properties of the ECM implant material, or some combination thereof. In the remainder of this discussion, we present a number of potential, albeit speculative, mechanisms by which postoperative AF may have been attenuated in this study.

Pericardial reconstruction employing closure of the intrinsic pericardium is usually precluded perioperatively, because

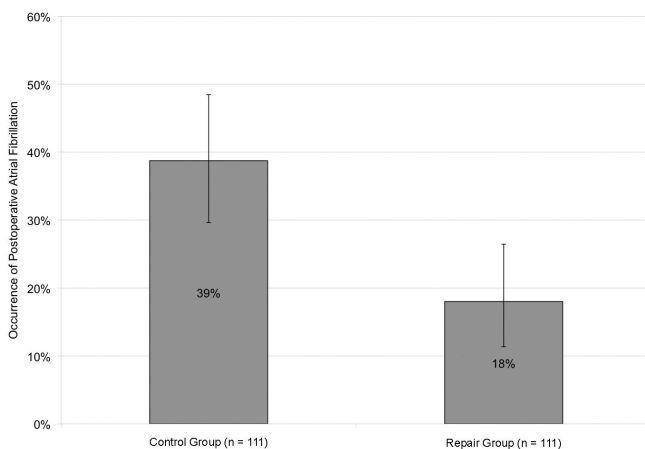


Figure 4. Occurrence of postoperative atrial fibrillation by treatment group ($P < .001$, 1-sided Fisher exact test). Error bars represent the upper and lower 95% confidence limits for the analysis.

of procedural and anatomic constraints. Repair of the pericardium following CABG, however, may limit volume shifts, atrial stretch, and secondary structural alterations due to postoperative inflammation [Hamilton 1994; Kroeker 2003; Ninio 2006].

Furthermore, when the pericardium is not closed after CABG, shed mediastinal blood containing proinflammatory cytokines is in direct contact with the epicardium, and it is likely that this contact causes epicardial inflammation. There is increasing evidence for a role of inflammation in the genesis of postoperative AF [Boos 2006]. It is possible that reconstitution of the normal pericardial anatomy with the ECM implant could have the dual beneficial effect of preventing shed mediastinal blood from coming in contact with the heart and attenuating inflammation by down-regulating helper T-cells [Palmer 2002]. Although we did not evaluate the issue directly in this study, it is also possible that the biological properties of the ECM implant used in this study may have contributed to decreasing inflammation and the subsequently observed reduced rate of postoperative AF [Badylak 2008].

We did not test the use of alternative prosthetic or bioprosthetic patch materials, such as bovine glutaraldehyde pericardium, pericardium homografts, or polytetrafluoroethylene, in

Table 3. Comparison of Postoperative Adverse Events in Patients Treated and Not Treated with Complete Pericardial Reconstruction with the Extracellular Matrix Implant*

Adverse Event	Control Group (n = 111), %	Repair Group (n = 111), %
Postoperative complications	26 (18, 35)	33 (25, 43)
Intraoperative complications	2 (0.2, 6)	5 (2, 11)
Acute inflammation	1 (0.02, 5)	0 (0, 3)
Acute respiratory distress syndrome	5 (2, 11)	3 (1, 8)
Allergic reaction	0 (0, 3)	1 (0, 5)
Angina	0 (0, 3)	0 (0, 3)
Anticoagulation complications	1 (0.02, 5)	1 (0, 5)
Bleeding	0 (0, 3)	0 (0, 3)
Chronic inflammation	0 (0, 3)	0 (0, 3)
Cognitive sequelae	1 (0.02, 5)	0 (0, 3)
Infection	0 (0, 3)	0 (0, 3)
ECM migration	0 (0, 3)	0 (0, 3)
Myocardial infarction	0 (0, 3)	0 (0, 3)
Noninfectious left pericarditis	0 (0, 3)	0 (0, 3)
Renal failure	2 (0.2, 6)	1 (0, 5)
Stroke	1 (0.02, 5)	1 (0, 5)
Tamponade	1 (0.02, 5)	1 (0, 5)
Death	1 (0.02, 5)	0 (0, 3)
Other†	20 (13, 29)	24 (17, 33)

*Data are presented with the 95% lower and upper confidence limits in parentheses.

†One control patient did not report either the presence or absence of an “other adverse event.”

this study. To our knowledge, these materials are not commonly used for pericardial repair, presumably because of their known proinflammatory properties and their predisposition to calcification. The potential mechanistic differences between the ECM implant and other available patch materials suggest direction for further clinical or preclinical investigation that might provide interesting insights into the development of postoperative AF.

In addition to the limitations noted above, it is important to note that this study also has the small sample size, the limited number of sites, and the lack of randomization typical of small retrospective series. The positive salutary effect suggested by these findings, however, does provide a starting point for additional studies.

In summary, the method of completely reconstructing the pericardium with the biomaterial patch used in this retrospective study appears to have contributed directly to a meaningful reduction in the rate of postoperative AF. Given these initial findings, we are currently executing a prospective, multicenter, randomized trial, the aim of which will be to further test the hypothesis that this innovative approach—repairing the pericardium—is beneficial for reducing postoperative AF in patients undergoing primary isolated CABG.

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Disclosures: W. Douglas Boyd is a consultant to CorMatrix Cardiovascular and owns stock in the company. Thomas F. Deering is a medical advisor to CorMatrix Cardiovascular and owns stock in the company. Robert G. Matheny is Chief Scientific Officer of CorMatrix Cardiovascular and owns stock in the company.

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