Usefulness of Preoperative Transforming Growth Factor-Beta to Predict New Onset Atrial Fibrillation After Surgical Ventricular Septal Myectomy in Patients With Obstructive Hypertrophic Cardiomyopathy

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Postoperative atrial fibrillation (AF) occurs frequently after cardiac surgery and contributes significantly to mortality. Transforming growth factor-beta (TGF-β) is associated with postoperative AF after coronary artery bypass grafting and valve surgery. We performed a prospective study to evaluate the role of TGF-β as a predictor of AF after myectomy. A total of 109 consecutive obstructive hypertrophic cardiomyopathy patients without previous AF who underwent myectomy were identified. We measured plasma TGF-β levels before surgery, monitored heart rhythm until discharge, and followed patients for a mean of 36 ± 10 months. AF was documented in 19 patients (17%). AF patients were older (50 ± 10 vs 43 ± 15 years, p = 0.037). Patients who developed AF had higher plasma TGF-β levels (1,695 ± 2,011 vs 1,099 ± 2,494 pg/ml, p = 0.011), more major adverse cardiac events (32% vs 7%, p = 0.006), and more strokes (16% vs 0%, p = 0.005) than patients who did not. TGF-β level ≥358 pg/ml predicted AF with sensitivity and specificity of 58% and 77% (p = 0.011), respectively. Higher TGF-β levels were associated with pulmonary hypertension (25% vs 8%, p = 0.033). In multivariable regression analysis, age (odds ratio 1.05, 95% confidence interval 1.00 to 1.11, p = 0.041) and TGF-β levels (odds ratio 2.42, 95% confidence interval 1.30 to 4.50, p = 0.005) predicted AF independently. In conclusion, elevated preoperative TGF-β value is an independent predictor of postoperative AF in hypertrophic cardiomyopathy patients after surgical ventricular septal myectomy. (Am J Cardiol 2017;■:■−■)

Postoperative atrial fibrillation (AF), a common complication after cardiac surgery, contributes significantly to increased complications, mortality, length of stay in hospital, and costs.[1,2] It has been reported that obstructive hypertrophic cardiomyopathy (HC) patients performing surgical myectomy have increased risk of postoperative AF (20% to 30%) and more postoperative problems.[3−5] However, these reports have included patients with a history of AF and patients receiving antiarrhythmic drugs. Transforming growth factor-beta (TGF-β) is a profibrotic cytokine involved in cardiac fibrosis.[6] TGF-β expression is enhanced in atrial biopsies of patients with AF and patients who developed AF after coronary artery bypass grafting (CABG) and valve surgery.[7,8] Elevated TGF-β level is associated with poor prognosis in HC patients and recurrent AF which occurs after catheter, electrical cardioversion, and maze procedures.[9−12] Nevertheless, none of these studies have investigated the role of plasma TGF-β level in predicting AF after myectomy. The present study is designed to prospectively assess possible predictors, especially TGF-β, of postoperative AF for HC patients performing surgical myectomy.

Methods

We prospectively evaluated 133 consecutive obstructive HC patients performing surgical septal myectomy with cardiopulmonary bypass, between November 2012 and March 2015 in Fuwai Hospital, Beijing, People's Republic of China. The diagnosis of HC was based on the presence of a hypertrophied and nondilated left ventricle in the absence of another cardiac or systemic disease that would lead to hypertrophy.[13] This diagnosis was confirmed by postoperative pathologic examination. For this research, we excluded patients with (1) previous AF (paroxysmal or permanent) and AF surgery, a history of emergency operation, previous history of pacemakers (n = 9); (2) liver or kidney failure, chronic inflammatory, hematological, and

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Table 1
Baseline characteristics of patients

Characteristic	Postoperative Atrial Fibrillation		*P* value
	No (n = 90)	Yes (n = 19)	
Preoperative data			
Age (years)	43 ± 15	50 ± 10	0.037
Men	31 (34%)	7 (37%)	0.842
Hypertension	19 (21%)	4 (21%)	1.000
Hyperlipidemia	16 (18%)	6 (32%)	0.295
Diabetes mellitus	3 (3%)	1 (5%)	0.541
NYHA functional class III/IV	45 (50%)	13 (68%)	0.144
Body mass index (kg/m^2)	24.5 ± 4.0	25.5 ± 3.1	0.233
Transforming growth factor-beta (pg/ml)	1099 ± 2494	1695 ± 2011	0.011
Drug therapy			
Beta-blockers	53 (59%)	14 (74%)	0.229
Calcium channel blockers	21 (23%)	4 (21%)	1.000
Procedural data			
Isolated myectomy	54 (60%)	14 (74%)	0.263
Myectomy + valve surgery	22 (24%)	2 (11%)	0.305
Myectomy + coronary artery bypass grafting	10 (11%)	2 (11%)	1.000
Myectomy + valve surgery + coronary artery bypass grafting	4 (4%)	1 (5%)	0.624
Cardiopulmonary bypass pump time (min)	129.3 ± 41.8	130.0 ± 61.3	0.485
Aortic cross clamp time (min)	85.0 ± 26.5	83.0 ± 31.7	0.778
Postoperative data			
Mechanical ventilation time (h)	21.6 ± 12.6	30.0 ± 24.4	0.110
Postoperative length of stay (d)	9.4 ± 4.3	12.7 ± 6.9	0.026
Major adverse cardiac events	6 (7%)	6 (32%)	0.006
Strokes	0	3 (16%)	0.005

Data are expressed as mean ± SD for continuous data or number (percent) for categorical data.

neoplastic diseases (n = 2); and (3) use of angiotensin-converting aldosterone system inhibitors or antiarrhythmic drugs (except for beta blockers or calcium channel blockers for reasons other than antiarrhythmia) (n = 13). Ultimately, 109 patients were identified in our work. This study was approved by the local ethics committee and conducted according to the Declaration of Helsinki. All patients provided written informed consent.

All patients underwent preoperative, postoperative, and follow-up echocardiograms including 2-dimensional and Doppler type. Measurements of septum thickness, wall thickness, cardiac chambers, and left ventricular outflow tract gradient were performed according to standard recommendations.[14,15] All surgical procedures were performed by a single professional team according to institutional protocols. Types of surgeries were as follows: (1) isolated septal myectomy, (2) septal myectomy plus valve surgery, (3) septal myectomy plus CABG, and (4) septal myectomy plus valve surgery plus CABG. Procedural data, including cardiopulmonary bypass pump and aortic cross-clamp time, were recorded.

AF was defined as an episode of AF lasting for >5 minutes or requiring intervention of antiarrhythmic therapy. During postoperative hospital stay, AF was documented through continuous cardiac monitoring by 5-lead telemetry. Twelve-lead electrocardiograms and electrocardiographic Holter monitoring were performed when necessary to confirm the diagnosis. Preoperative electrocardiograms were performed on all patients. Electrocardiograms were routinely obtained and checked daily during hospitalization after operation.

Medical data (including demographic, clinical evaluation, medication use, and treatment information) were collected prospectively at admission and discharge. Follow-up information was obtained from clinic or telephone contact with patients by investigator blinded to TGF-β levels and presence of AF. Death documentation was obtained from hospital medical records and phone conversations with family members. The study end point was the occurrence of first documented AF. Major adverse cardiac events were defined as myocardial infarction, revascularization, congestive heart failure requiring hospitalization, stroke, and death.

Venous blood samples were obtained on first admission before operation. Plasma was isolated after centrifugation and frozen immediately at −20°C until analyzed. Plasma TGF-β1 levels were determined by enzyme-linked immunosorbent assay technique using a specific TGF-β1 kit (eBioscience, San Diego, CA), after the manufacturer's instructions. All samples were assayed in duplicate, and mean values were calculated respectively. We considered TGF-β1 results valid when intra-assay and interassay coefficients of variation was <20%. A run was regarded as valid when >85% of the samples were within these ranges. The standard curve range of the assay was 8 to 1,000 pg/ml.

Statistical analyses were performed with SPSS version 21.0 (IBM Corp, Armonk, NY). Comparison of normally distributed variables between groups was performed by an independent-sample and paired *t* test, as appropriate. Non-normally distributed variables were compared by Mann-Whitney *U* test. The chi-square or Fisher's exact tests were used for categorical data. Correlation analyses were