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# Endothelin-1 is associated with dilatation of the left atrium and can be an independent predictor of atrial fibrillation after mitral valve surgery

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## Abstract

**OBJECTIVES:** This study analysed the association between endothelin-1 (ET-1) and left atrial dimension (LAD) and evaluated whether ET-1 can be a predictor of postoperative atrial fibrillation (POAF) after mitral valve surgery.

**METHODS:** This is a prospective study that enrolled 80 patients who underwent isolated mitral valve surgery. Plasma concentrations of ET-1 from peripheral venous blood were tested. POAF was detected using a telemetry strip or 12-lead electrocardiogram until the time of discharge.

**RESULTS:** Patients undergoing mitral valve surgery with preoperative sinus rhythm ($n = 80$; average age 63.9 ± 7.9 years) were recruited to this study. POAF was documented in 31 (38.8%) patients. Preoperative plasma ET-1 levels were higher in patients with POAF compared to those without POAF (2.23 ± 0.67 vs 1.68 ± 0.59 pg/ml; $P < 0.001$). The plasma concentrations of ET-1 were positively correlated with LAD (Pearson's $r = 0.421$; $P < 0.001$). Multivariate logistic regression analysis revealed that LAD (odds ratio 1.170, 95% confidence interval 1.039–1.317; $P = 0.009$) and preoperative plasma ET-1 levels (upper versus lower 50th percentile: odds ratio 3.713, 95% confidence interval 1.085–12.701; $P = 0.037$) were predictors of POAF after mitral valve surgery.

**CONCLUSIONS:** Plasma levels of ET-1 were positively correlated with LAD in patients with mitral valve disease. An elevated preoperative plasma ET-1 level can be used as a predictor of POAF after mitral valve surgery.

**Keywords:** Endothelin 1 • Postoperative atrial fibrillation • Mitral valve surgery

## INTRODUCTION

Postoperative atrial fibrillation (POAF) is a frequent complication after cardiac surgery, occurring in approximately one-third of all patients within 5 days after the operation, with a peak incidence on the 2nd and 3rd postoperative day [1–3]. It is clinically evident that patients who develop POAF have increased risk of adverse events, such as thromboembolic events, haemodynamic instability, increased mortality and prolonged duration of hospital stay [4, 5]. Identification of patients who are at high risk of POAF may allow for preventive measures and intensive care during hospitalization.

The main pathophysiology of mitral valve disease was pressure and volume overload, and it is characterized by enlargement of the left atrium (LA) and ventricle. Endothelin-1 (ET-1), a vasoconstrictor peptide produced by endothelial cells, is a well-established biomarker of endothelial damage. Numerous studies have shown that elevated ET-1 was associated with elevated left atrial pressure and dilatation of the LA [6]. An elevated ET-1 level has been shown in some studies to be associated with atrial fibrillation (AF) due to the promotion of atrial fibrosis, hypertrophy and dilatation [7]. Both cell and animal experiments have suggested that ET-1 participates in the electrical and structural remodelling of AF [8, 9]. It has also been used to predict the recurrence of AF after catheter ablation [6, 10]. The aim of our study was to evaluate the potential use of ET-1 as a preoperative predictor of POAF.

## METHODS

### Study design

A total of 80 patients who underwent mitral valve surgery at the Department of Cardiothoracic Surgery at the Xinhua Hospital in Shanghai, China, between October 2015 and January 2017 were enrolled in this study. A previous history of atrial arrhythmia diagnosed by an electrocardiogram was the major exclusion

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criterion, whereas the other exclusion criteria were emergency cardiac surgery, concurrent congenital heart disease, usage of anti-arrhythmic or anticoagulant drugs within 1 week preoperation, end-stage renal failure and an implanted cardiac pacemaker. Preoperative detailed echocardiographic examination was routinely performed. Baseline demographic, clinical and laboratory parameters were carefully recorded. The study was approved by the local Ethics Committee, and written informed consent was obtained from all the patients.

## Blood sample collection and measurement of plasma endothelin 1 concentrations

Peripheral venous blood (2–5 ml) was obtained from an antecubital vein into ice-chilled tubes containing ethylenediaminetetraacetic acid before the induction of anaesthesia and was immediately centrifuged at 3000 rpm for 20 min at room temperature. The remaining supernatant was collected and preserved at -80°C prior to analysis. An enzyme-linked immunosorbent assay was performed to evaluate the plasma concentrations of ET-1 according to the kit instructions (BI-20082 H; Biomedica, Wien, Austria).

## Surgical procedure

A median full sternotomy or a right minithoracotomy was performed on all patients. Both anaesthesia and surgical procedures were performed by the same team in a standard fashion. All patients underwent cardiopulmonary bypass with mild hypothermia (32–34°C). During cardiopulmonary bypass, ascending aortic and bicaval drainage cannulations were performed using a median sternotomy approach, whereas a venous cannula was placed from the femoral vein into the right atrium and femoral artery cannulation was performed when using a right minithoracotomy approach. Local hypothermia and myocardial protection were performed using ice slash. The same cardioplegic solution was used in all the patients and was readministered every 30 min. The activated clotting time was maintained at more than 480 s. The mean arterial pressure was maintained at 50–70 mmHg. Mitral valvuloplasty or replacement was performed based on the function of valve. A mechanical or bioprosthetic valve was selected according to the patient's age and personal choice. Electrical defibrillation was performed if needed to terminate ventricular fibrillation. Patients were then transferred to the intensive care unit after surgery.

## Postoperative management and grouping

Patients were continuously monitored by a 5-lead telemetry strip in the intensive care unit. A standard 12-lead electrocardiogram was obtained each morning starting from the time of discharge from the intensive care unit until the time of discharge from the hospital. Additional 12-lead electrocardiogram recording was done to confirm the existence of POAF if the patient felt palpitations or if an irregular pulse was detected. POAF was defined as an absence of a P-wave before the QRS with irregular ventricular rhythm. Anti-arrhythmic drugs, including amiodarone and/or esmolol, were administered when POAF was confirmed. Electrical cardioversion was performed on patients with sustained AF that was unresponsive to pharmacological therapy or patients with haemodynamic instability. The end-point was the incidence of AF lasting more than 5 min during hospitalization. Based on whether they developed POAF, patients were divided into 2 groups: the POAF group and the non-POAF group.

## Statistical analysis

All continuous variables were presented as the mean ± standard deviation. The Levene's test was used to test the homogeneity of variance. Categorical data and proportions were analysed using the $\chi^2$ or the Fisher's exact test, whereas continuous variables were analysed using the Student's *t*-test (normally distributed) or the Mann–Whitney test (non-normally distributed). Correlation between left atrial dimension (LAD) and ET-1 was determined using Pearson's correlation analysis. The variables that attained a *P*-value of <0.10 by univariate logistic regression were entered into a multivariate logistic regression model. Multivariate logistic regression analysis was used to determine the predictors of POAF after adjusting for age, gender, hypertension, left ventricular ejection fraction (LVEF), LAD, type of surgery, type of mitral valve disease and surgical approach. The odds ratio and 95% confidence interval (CI) for each independent variable in the final regression model were presented. A *P*-value <0.05 (2-sided) was considered statistically significant for all the comparisons. Statistical analysis was performed with SPSS version 20 (SPSS Inc., Chicago, IL, USA).

# RESULTS

Baseline and operative characteristics of enrolled patients are summarized in Table 1. Of all the patients, 44 were men and 36 were women, and the mean age of the patients was 63.9 ± 7.9 years. Mitral valve replacement (mechanical valve 62 and biological valve 11) was performed in 73 patients, whereas mitral valvuloplasty was performed in 7 patients. Patients were subdivided into 2 groups: the POAF group ($n = 31$) and the non-POAF group ($n = 49$). Eleven patients had a single episode, 20 had multiple episodes and 2 had persistent AF lasting longer than 24 h. AF generally occurred within 5 days ($n = 28$) after the operation, and the distribution of the new-onset POAF showed a peak on Day 2 ($n = 11$) and Day 3 ($n = 10$). The POAF group was significantly older (65.5 ± 7.9 vs 62.9 ± 7.6 years; $P < 0.001$) with a lower LVEF (60.5 ± 7.0% vs 63.6 ± 5.9%; $P = 0.044$) and a larger LA (LAD 53.5 ± 5.6 vs 49.0 ± 4.4; $P < 0.001$). There were no statistically significant differences in gender distribution, hypertension, preoperative medication, type of mitral valve disease, surgery type and surgical approach between the 2 groups.

Plasma ET-1 levels were significantly higher in patients who developed POAF compared with those without POAF (2.23 ± 0.67 vs 1.68 ± 0.59 pg/ml; $P < 0.001$). To determine whether ET-1 was associated with the dilatation of the LA, we attempted to identify an association between LAD and plasma concentrations of ET-1. As demonstrated in Fig. 1, plasma concentrations of ET-1 were positively correlated with LAD (Pearson's $r = 0.421$; $P < 0.001$).

Characteristics of enrolled patients based on plasma ET-1 levels that were dichotomized into the upper and lower 50th percentiles are presented in Table 2. More AF occurred in patients with a plasma ET-1 level >the 50th percentile (52% vs 25%; $P = 0.012$). Patients with a plasma ET-1 level >the 50th percentile were older (65.9 ± 6.9 vs 61.9 ± 8.1 years; $P = 0.021$) and had a larger LA (LAD 52.3 ± 5.4 vs 49.1 ± 4.8 mm; $P = 0.006$). There were

**Table 1:** Preoperative clinical findings among patients with or without POAF

| Characteristics | POAF ($n = 31$) | No POAF ($n = 49$) | *P*-value |
|---|---|---|---|
| Age (years) | 65.5 ± 7.9 | 62.9 ± 7.6 | <0.001 |
| Male (%) | 61 | 51 | 0.368 |
| Smoking history (%) | 35 | 27 | 0.395 |
| Drinking history (%) | 26 | 22 | 0.731 |
| Hypertension (%) | 23 | 14 | 0.341 |
| Diabetes (%) | 35 | 29 | 0.516 |
| NYHA Class I–II (%) | 74 | 86 | 0.198 |
| LVEF (%) | 60.5 ± 7.0 | 63.6 ± 5.9 | 0.044 |
| LAD (mm) | 53.5 ± 5.6 | 49.0 ± 4.4 | <0.001 |
| Beta blockers (%) | 6 | 14 | 0.473 |
| Calcium channel blocker (%) | 13 | 4 | 0.306 |
| ACEI (%) | 19 | 16 | 0.964 |
| Statins (%) | 35 | 33 | 0.794 |
| ET-1 (pg/ml) | 2.23 ± 0.67 | 1.68 ± 0.59 | <0.001 |
| ET-1 >the 50th percentile (%) | 68 | 41 | 0.015 |
| Type of mitral valve disease (%) | | | 0.834 |
| MS (%) | 58 | 57 | |
| MR (%) | 26 | 31 | |
| MS + MR (%) | 16 | 12 | |
| Surgery type (%) | | | 0.864 |
| MVP (%) | 7 | 10 | |
| MVR (biological valve) (%) | 16 | 12 | |
| MVR (mechanical valve) (%) | 77 | 78 | |
| Surgical approach | | | 0.296 |
| Right minithoracotomy (%) | 14 | 28 | |
| Median sternotomy (%) | 17 | 21 | |
| CPB (min) | 71.4 ± 9.0 | 68.2 ± 8.9 | 0.118 |
| ACC (min) | 36.7 ± 7.6 | 34.8 ± 4.9 | 0.179 |

ACC: aortic cross-clamp time; ACEI: angiotensin-converting enzyme inhibitors; CPB: cardiopulmonary bypass time; ET-1: endothelin 1; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MS: mitral stenosis; MVP: mitral valvuloplasty; MVR: mitral valve replacement; NYHA: New York Heart Association; POAF: postoperative atrial fibrillation.

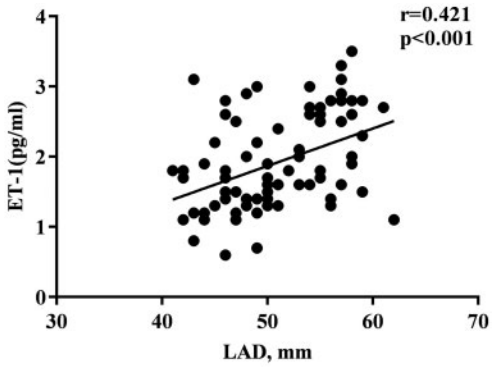


**Figure 1:** Correlation of plasma ET-1 levels with LAD in patients with mitral valve disease. *r* is Pearson's correlation coefficient. ET-1: endothelin 1; LAD: left atrial dimension.

no statistically significant differences in gender distribution, LVEF and hypertension between the 2 groups.

In the multivariate logistic regression analysis, after adjusting for age, gender, hypertension, LVEF, LAD, surgery type, type of mitral valve disease and surgical approach, the independent predictors of POAF were LAD (odds ratio 1.170, 95% CI 1.039–1.317; $P = 0.009$) and preoperative plasma ET-1 levels (upper versus lower 50th percentile: odds ratio 3.713, 95% CI 1.085–12.701; $P = 0.037$). The other variables that were studied were not predictors of POAF after mitral valve surgery (Table 3). The receiver operating characteristics curve of the model combining LAD and ET-1 is shown in Fig. 2, and the area under the receiver operating characteristics curve was 0.77 (95% CI 0.66–0.88).

All POAF patients underwent pharmacological cardioversion with intravenous amiodarone. Electrical cardioversion was performed in 11 patients with haemodynamic instability. An additional beta blocker was given for ventricular rate control and symptom relief in 6 patients who did not exhibit good control of their ventricular rate.

**Table 2:** Clinical characteristics by ET-1 percentile

| Characteristics | ET-1 >the 50th percentile ($n = 40$) | ET-1 <the 50th percentile ($n = 40$) | *P*-value |
|---|---|---|---|
| POAF (%) | 52 | 25 | 0.012 |
| Age (years) | 65.9 ± 6.9 | 61.9 ± 8.1 | 0.021 |
| Male (%) | 53 | 58 | 0.653 |
| LAD (mm) | 52.3 ± 5.4 | 49.1 ± 4.8 | 0.006 |
| LVEF (%) | 62.7 ± 6.6 | 62.1 ± 6.5 | 0.696 |
| Hypertension (%) | 20 | 15 | 0.556 |
| Smoking history (%) | 35 | 25 | 0.329 |
| Drinking history (%) | 25 | 23 | 0.793 |
| Diabetes (%) | 35 | 28 | 0.469 |
| Beta blockers (%) | 8 | 15 | 0.479 |
| Calcium channel blocker (%) | 10 | 5 | 0.671 |
| ACEI (%) | 20 | 15 | 0.556 |
| Statins (%) | 38 | 30 | 0.478 |

ACEI: angiotensin-converting enzyme inhibitors; ET-1: endothelin 1; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; POAF: postoperative atrial fibrillation.

**Table 3:** Multivariable logistic regression models for the prediction of POAF

| | OR | 95% CI | *P*-value |
|---|---|---|---|
| Age | 1.003 | 0.932–1.080 | 0.928 |
| Gender (men vs women) | 1.401 | 0.445–4.413 | 0.565 |
| LAD (mm) | 1.170 | 1.039–1.317 | 0.009 |
| LVEF (%) | 0.921 | 0.841–1.008 | 0.074 |
| Hypertension | 2.193 | 0.501–9.601 | 0.297 |
| Type of surgery | | | 0.813 |
| MVR (mechanical valve) | Ref. | | |
| MVR (biological valve) | 0.460 | 0.040–5.293 | 0.533 |
| MVP | 1.030 | 0.178–5.968 | 0.973 |
| Type of mitral valve disease | | | 0.596 |
| MS | Ref | | |
| MR | 0.743 | 0.167–3.305 | 0.697 |
| MS + MR | 1.966 | 0.370–10.450 | 0.428 |
| Right minithoracotomy vs median sternotomy | 0.447 | 0.137–1.458 | 0.182 |
| ET-1, upper vs lower 50th percentile | 3.713 | 1.085–12.701 | 0.037 |

CI: confidence interval; ET-1: endothelin 1; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MS: mitral stenosis; MVP: mitral valvuloplasty; MVR: mitral valve replacement; OR: odds ratio.

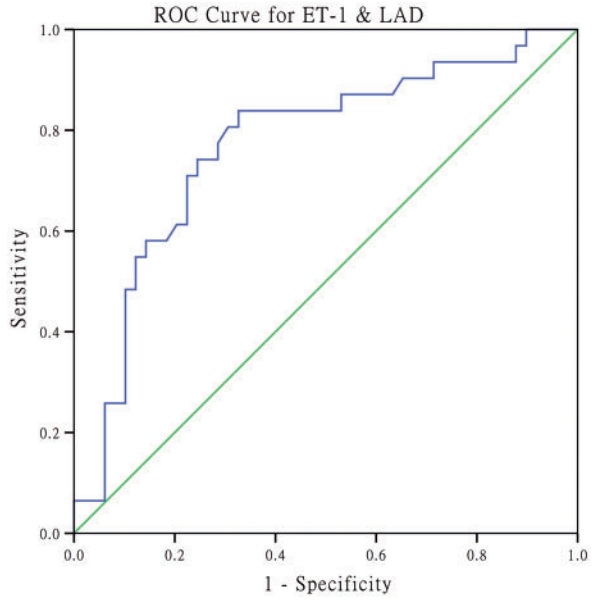


**Figure 2:** ROC curve for postoperative atrial fibrillation after mitral valve surgery, based on LAD and ET-1. Area under the curve: 0.77 (95% confidence interval: 0.66–0.88). ET-1: endothelin 1; LAD: left atrial dimension; ROC: receiver operating characteristics.

## DISCUSSION

Studies have been widely concerned about the mechanism and therapeutic strategies of POAF but have had limited results. Variables found to be independent predictors of POAF in previous studies mainly included age, LAD, postoperative low cardiac output, LVEF, systolic pulmonary artery pressure, and so on [1–3]. Furthermore, biomarkers such as B-type natriuretic peptide were also confirmed to be predictors of POAF [11]. In this study, after adjusting for age, gender, hypertension, LVEF, LAD, type of surgery, type of mitral valve disease and surgical approach, we had found that both LAD and elevated plasma ET-1 levels can be used as predictors of POAF after mitral valve surgery. To the best of our knowledge, this is the first time that ET-1 was to predict the occurrence of POAF.

ET-1, an important biomarker of endothelial damage, is secreted by endothelial cells; the secretion is promoted by stretching, pressure overload and increased wall shear stress [7, 12]. Plasma ET-1 levels were reported to be elevated in AF patients with heart failure and valvular heart disease [13]. ET-1 inhibited the L-type calcium current and muscarinic potassium current, leading to hyperpolarization of the membrane and shortening of the action potential duration in mammalian atrial myocytes [14]. *In vitro*, ET-1 has been confirmed to play an important role in fibroblast proliferation and extracellular matrix production [15]. Animal experiments have also suggested that ET-1 is proarrhythmic and induces arrhythmogenic $Ca^{2+}$ signalling [8]. By testing the expression of ET-1 in LAA, Mayyas *et al.* [16] found that elevated ET-1 was associated with atrial dilatation, fibrosis and hypertrophy and probably contributed to the maintenance of AF rhythm. In conclusion, ET-1 is associated with the structural and electrical remodelling of the atria and facilitates the occurrence of AF. We concluded that the elevated plasma ET-1 levels may participate in the pre-existing structural and electrical remodelling of LA and were associated with the occurrence of POAF. Mitral valve disease is characterized by left atrial overload and results in elevated left atrial pressure and dilatation of the LA; furthermore, left atrial dilatation is associated with a poor clinical prognosis [17]. Consistent with a previous study evaluating the association between ET-1 and structural heart disease [16], we also found that plasma ET-1 levels were positively correlated with LAD. Dilatation of the LA is one of the leading causes of AF [18], but the pathophysiological mechanisms connecting the dilatation of LA to AF development are not fully understood. Previous studies have shown that inflammation, fibrosis and increased infiltration of immune cells are associated with the dilatation of the LA and participate in the pathogenesis of AF [19]. According to our correlation analysis, we speculated that the dilatation of the LA may result in the elevated plasma concentrations of ET-1 and facilitate the development of AF.

Studies have been concerned about endothelial damage and thrombosis in patients with AF, but little is known about the pathogenic mechanism of endothelial damage in POAF. Spronk's latest research has shown that the hypercoagulable state during AF causes profibrotic and proinflammatory responses in adult atrial fibroblasts and promotes the formation of arrhythmia substrates in persistent AF. A positive correlation between plasma high-sensitivity C-reactive protein (CRP) and ET-1 level has been demonstrated, and ET-1 can also promote the production of proinflammatory cytokines in AF [20]. Because the hypercoagulable and inflammatory states are associated with AF, we speculate that because of the damaged integrity and increased permeability of the endothelium, the exposure of subendothelial tissue to the blood environment, which is rich in cytokines and coagulation agents, may facilitate the occurrence of POAF. Kaireviciute *et al.* [21] investigated the possible role of endothelial damage/dysfunction (as reflected by von Willebrand factor (VWF) changes) in the pathogenesis of POAF and proposed early interventions, which are often considered 'upstream therapies' that protect endothelial function. A randomized controlled study showed an advantage of the short-term use of atorvastatin in increasing circulating endothelial progenitor cells, which have been shown to play a key role in re-endothelialization and in preventing the occurrence of POAF [22].

## CONCLUSION

In summary, ET-1 may be an important factor connecting dilatation of the LA to AF development. ET-1 itself was associated with the pre-existing remodelling of the LA, and endothelial damage (marked by ET-1expression) may also participate in the pathogenesis of POAF. The preventive use of drugs that improve endothelial function may decrease the incidence of POAF. This study may help to determine the susceptibility of a patient to develop POAF after mitral valve surgery.

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**Conflict of interest:** none declared.

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