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Circulating Biomarkers Predictive of Postoperative Atrial Fibrillation

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Abstract

Postoperative atrial fibrillation (PoAF), a common complication of cardiac surgery, contributes significantly to morbidity, mortality, and increasing health care costs. Despite advances in surgical and medical management, the overall incidence of PoAF has not changed significantly, partly due to the limited understanding of mechanisms underlying acute surgery-related factors, such as myocardial injury, inflammation, sympathetic activation, and oxidative stress, which play an important role in the initiation of PoAF, while a preexisting atrial substrate appears to be more important in the maintenance of this dysrhythmia. Thus, in a majority of patients, PoAF becomes a manifestation of an underlying arrhythmogenic substrate that is unmasked following acute surgical stress. As such, the ability to identify which patients have this proarrhythmic substrate and are, therefore, at high risk for developing AF postoperatively, is important for the improved selection for prophylactic interventions, closer monitoring for complications, and establishing the probability of AF in the long term. This review highlights the role of the underlying substrate in promoting PoAF, proposed mechanisms, and the potential role of serum biomarkers to identify patients at risk for PoAF.

Keywords

postoperative atrial fibrillation; atrial remodeling; atrial fibrosis; biomarkers; cardiac surgery; collagen; BNP; micro-RNA

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Postoperative atrial fibrillation (PoAF) is a common complication of surgery, with an incidence varying from 10–63% for cardiac^{1,2} (38–63% for valve, 10–33% for coronary artery bypass graft surgery) and 0.3–30% for noncardiac surgeries.^{1–9} Despite advances in surgical management, the overall incidence of PoAF has not changed significantly,⁷ contributing to prolonged intensive care and hospital stays,⁷ increases in health care costs, and the risk of stroke, heart failure, rehospitalization and short- and long-term mortality.^{4,10–13} In most cases, PoAF occurs on day 2 and declines with each passing day,^{1,4} self-limiting in the majority, with >95% of patients with de novo AF back in normal sinus rhythm (SR) within two months of surgery.^{1,4,7} The exact mechanisms and signaling pathways involved in the development of PoAF remain incompletely understood, therefore, preventive strategies are only partially effective, with little impact on reducing the overall incidence of AF over the last two decades (Figure 1).^{7,14–17} In 10,390 patients without preexisting atrial arrhythmias undergoing various cardiac surgical procedures (79% elective; 7,284 coronary artery bypass grafting [CABG] only, 1,399 valve only, 887 both CABG and valve, and 820 other cardiac procedures), the average incidence of PoAF was reported to be 30%, with an age-dependent increase (Figure 1A) but without any significant change in the incidence over the last 20 years (Figure 1B).

Both acute (trauma, inflammation, sympathetic activation, oxidative stress)^{13,15,18–21} and chronic factors (abnormal atrial substrate, fibrosis)^{5,9,22–26} play a role in the initiation and maintenance of PoAF. A preexisting, otherwise stable atrial substrate that becomes unstable by acute surgery-related factors appears to be important as the majority of PoAF cases are seen in patients with underlying atrial disease.^{5, 27–30} Patients with a history of AF are, therefore, at increased risk for developing AF postoperatively, and those who develop new-onset PoAF are at higher (up to eightfold) risk for developing future AF.¹² The ability to identify which patients have a preexisting substrate and are, therefore, at high risk for developing PoAF, is important for improved selection of prophylactic interventions, closer monitoring for postoperative complications, and establishing the risk of long-term AF.^{1,7,31–34} The latter is particularly important because the number of patients who are at risk for cardiac arrhythmias³⁵ is expected to increase⁷ with the rapid growth in the elderly population^{4,31} and the increase in the prevalence of cardiovascular diseases. Biochemical, electrocardiogram, and imaging biomarkers have been used to stratify patients at risk for AF and its complications and have been recently reviewed.^{36–39} This article focuses on the role of circulatory biomarkers in predicting PoAF in patients undergoing cardiac surgery, and highlights the underlying substrate in promoting PoAF, proposed mechanisms, and the potential role of serum biomarkers in identifying patients at risk for PoAF.

ROLE OF ABNORMAL ATRIAL SUBSTRATE IN POAF

The precise cause of PoAF is not known and varies depending on the underlying structural heart disease, comorbidities, age, body mass index, race, family history, type of surgery performed, and acute postoperative factors, such as excessive catecholamine, use of inotropes, pericardial inflammation and alterations in neurohumoral and other metabolic influences.^{5,7,18,40–44} Advanced age and the presence of mitral valve disease, diastolic dysfunction, atrial enlargement, or fibrosis independently predict the risk of PoAF.^{3,4,7} In particular, the strong relationship of age and PoAF,⁷ with an almost 24% increase in the odds

of developing AF for every 5 years in age,⁴ suggests a direct impact of aging on atrial substrate for the development of PoAF. In addition, the observations that one-fourth of patients with PoAF develop subsequent AF and that PoAF is one of the strongest independent predictors for the development of late AF,⁴⁵ suggest the presence of a preexisting atrial substrate for AF that is unmasked by surgical stress and other acute factors, promoting arrhythmogenesis during the postoperative period and eventually leading to recurrences of AF as the underlying substrate progresses.^{12,42,46} The existence of a pre-existing abnormal atrial substrate is supported by studies demonstrating prolonged P-wave duration on pre-operative ECG, abnormal epicardial mapping,⁴⁷ increased intra-atrial conduction times, lower voltages, and the inducibility of AF by electrical stimulation during surgery in those who develop PoAF.^{3,28,30} The association between PoAF, a self-limited and reversible arrhythmia, to long-term mortality¹⁰ also suggests that PoAF is a surrogate for an underlying cardiac substrate that is unmasked during acute perioperative stress.

Various types of electrical, mechanical, and structural remodeling predisposing to and resulting from AF have been described.^{5,9,24,25,46,48} The role of electrical remodeling in PoAF has been investigated by several researchers.^{5,9} Autonomic sympathetic activation^{18,49} and sympathomimetic inotropic agents⁵⁰ facilitate the induction of PoAF by their impact on repolarizing K⁺ currents and Ca²⁺ homeostasis,⁵¹ promoting early or delayed afterdepolarization and triggered activity. However, preoperative changes in cellular Ca²⁺ and K⁺ channels do not appear to play an immediate role in the occurrence of de novo PoAF.^{52,53} In patients with pre-existing AF, a reduction in the L-type Ca²⁺ channels and key K⁺ channel proteins (Kv4.3, Kv1.5, KCNH2, KCNE1, Kir3.1) has been documented,⁵⁴ with upregulation of IK₁ and downregulation of IK_{ACh} in those with chronic AF, but the current through IK₁, IK_{ACh} and IK_{ur} was not significantly different in those who had PoAF or maintained SR.^{52,53} However, the gap junction protein Connexin40 expression was increased heterogeneously in patients susceptible to PoAF.⁵⁵ Ultrastructural changes in the atria of patients who developed AF after cardiac surgery have been documented.^{24,25,56} In patients without a history of AF, the severity of preoperative myolysis correlated well with the occurrence of PoAF.²⁴ A relationship of the incidence of PoAF and the amount of fibrosis in the right³⁵ and left⁵² atrial appendages of patients undergoing cardiac surgery highlights the pathogenic role of atrial fibrosis in arrhythmogenesis (Figure 2).⁵⁷ The collagen volume fractions, i.e., fibrosis in the atrium, independently predicted PoAF. In patients with no prior history of AF and no documented abnormality on echocardiogram, the patients who had PoAF had a higher percentage of collagen deposition in the right atrial appendage segment compared to those free of PoAF (Figure 2A). In patients who developed PoAF, the ratio of collagen to myocardium was significantly higher than in those who remained in normal SR (Figure 2B).⁵⁷

MECHANISM UNDERLYING ATRIAL FIBRILLATION AND CIRCULATORY BIOMARKERS PREDICTIVE OF ATRIAL FIBRILLATION

Atrial structural remodeling is connected to disturbances in extracellular matrix (ECM) turnover and subsequent atrial fibrosis.^{27,58} The exact mechanism and signaling pathways involved in the development of atrial fibrosis remain unclear; however, they involve complex

interactions between various cellular and neurohumoral mediators, which have been recently reviewed.^{5,17,27,46,59} Various circulatory biomarkers, including cytokines, markers of collagen turnover and ECM remodeling, inflammation, and myocardial stretch have been associated with AF or PoAF and are summarized below.

Transforming Growth Factor- β 1

Transforming growth factor beta 1 (TGF- β 1) is a multifunctional cytokine secreted by both fibroblasts and cardiomyocytes that acts as a primary downstream mediator of angiotensin II effects via activation of specific serine/threonine kinase receptors (T β RI and T β RRII), modulating tissue response to injury, activating fibroblasts to myofibroblasts, promoting ECM synthesis, and suppressing receptor degradation.⁶⁰ TGF- β 1 synthesis is induced by angiotensin II, which in turn stimulates fibroblast activity and creates a positive feedback by reciprocally stimulating the production of angiotensin II and other profibrotic factors.⁶¹ In a recent report, tissue levels of TGF- β 1 and angiotensin II, as well as collagen I and III, were elevated in atrial biopsies of patients with no prior history of AF but who developed PoAF.⁶² In a transgenic mouse model overexpressing TGF- β 1, the susceptibility to fibrosis was higher in the atria compared to ventricles⁶³ and atrial fibrosis alone was a sufficient substrate for AF, thus substantiating the role of TGF- β 1 in the development of atrial fibrosis.^{59,63} This was further confirmed in a canine model of experimental heart failure (HF), where enhanced TGF- β 1 expression was associated with an increase in atrial fibrosis.⁶⁴ The reduction in TGF- β 1 expression with the use of pirfenidone⁶³ or tranilast⁶⁴ mitigated arrhythmogenic remodeling with a reduction in the left atrial fibrosis, associated conduction abnormalities, and AF burden.^{63,65} In rapid atrial pacing-induced AF, downregulation of Smad7, an antagonist of TGF- β 1 receptor signaling and increased phosphorylation of Smad2/3, profibrotic signal transducers and transcriptional modulators activated by TGF- β 1 also highlight this pathway's critical contribution in promoting fibrosis and AF.^{59,66} These changes were reversed by losartan, angiotensin II type 1 (AT1) receptor antagonism with upregulation of Smad7 and reduction in levels of phosphorylation of Smad2/3, Smad4 and collagen I. Thus, blockade of the AT1 receptor is proposed as a strategy to limit AF progression.⁶⁶ However, despite initial promising results from retrospective observational studies, large-scale randomized clinical trials failed to demonstrate a beneficial effect in using angiotensin receptor antagonists to prevent recurrences of AF,^{67,68} and these agents currently are not recommended solely for the prevention of AF recurrence in patients without underlying heart disease.^{69,70} This suggests that blocking the effect of angiotensin II alone may not effectively prevent AF substrate progression in patients without underlying heart disease. The decrease in TGF- β 1 or inhibition of extracellular signal-regulated kinases (ERK) upregulated Smad7, a key endogenous antagonist of TGF- β 1/Smads-mediated fibrosis,⁶¹ could be alternative strategies to limit progression of the substrate promoting AF progression. This is substantiated by studies that show pirfenidone⁶³ or tranilast⁶⁴ reduced expression of TGF- β 1 and diminished left atrial fibrosis and AF burden.^{63,65} In patients with AF, atrial fibrosis appears to have a biphasic response, an early increase and a later loss of responsiveness, to TGF- β 1.⁷¹ With the progression of AF, collagen content of the atria along with the expression of TGF- β 1, its receptor T β RRII and profibrotic phospho-Smad2 and 4 proteins increased. With the increasing duration of AF, however, the TGF- β 1 effect declined with a reduction in T β RI, increase in TGF- β -inhibiting Smad7 protein, and a reduction of p-

Smad2.⁷¹ These results suggest that during the evolution of the atrial substrate a time window may exist during which strategies targeting profibrotic signaling through the AT1 or TGF- β 1 receptor may be most effective.

Elevated preoperative serum levels of TGF- β 1 correlated with the recurrence of AF after MAZE surgery and has been proposed as a marker to predict the failure of the surgical MAZE procedure and persistence of AF at 1-year follow-up in patients who underwent valvular and MAZE surgery.⁷² This is reflective of more advanced atrial substrate that was also demonstrated in other studies where elevated TGF- β 1 level was associated with failure to cardiovert patients with persistent AF⁷³ or correlated with advanced electroanatomical remodeling of the left atrium with reduced mean left atrial voltage and greater left atrial volumes in patients undergoing catheter ablation of AF.⁷⁴ Elevated TGF- β 1 levels, however, are not universally associated with AF recurrence after catheter ablation,⁷⁴ or associated with AF.⁷⁵ Large prospective studies assessing preoperative TGF- β 1 levels in identifying patients at risk of PoAF are therefore required to clarify its role as a predictor of PoAF.

Markers of Collagen Turnover

The ECM predominantly consists of structural proteins (such as collagen, fibrillin, fibronectin, and laminin), matricellular proteins, and glycosaminoglycans^{76,77} that are differentially affected by HF and AF.^{58,60,62,78–81} In animal models of HF, a greater than tenfold upregulation of ECM genes has been documented in the myocardium, with chamber-specific alterations in myocardial collagen content and proteins involved in ECM remodeling seen in patients with AF and end-stage HF.⁷⁸ The history of AF was associated with a higher collagen content within the atrial myocardium, compared to ventricular myocardium, of explanted hearts, with a differential upregulation of matrix metalloproteinases (MMP) and tissue inhibitor of matrix metalloproteinases (TIMP) in a chamber-specific manner.⁷⁸ Various peptides and proteins released during collagen synthesis, maturation, and remodeling have been used to characterize the substrate and risk for AF.^{62,79,80} Collagen I and III are secreted as procollagen precursors containing amino-(CINP, CIIINP) and carboxyl-terminal (PICP, PIICP) propeptides^{58,81} that are released into the circulation by proteases, and their levels correlate with the rate of collagen synthesis (Figure 3). Collagen degradation results in the release of a carboxyl-terminal telopeptide of collagen I (CITP) and collagen III (CIIITP).^{58,81–83} Serum levels of CITP, PICP and amino-terminal peptide from procollagen type III (PIIINP) were previously examined to assess for cardiac fibrosis during hypertension or HF and after acute myocardial infarction.^{58,81,83} A summary of markers of ECM turnover associated with AF and/or PoAF in humans is provided in Tables 1 and 2.^{62,72,74,78–80,84–100} Kallergis et al⁷⁹ reported that serum markers of collagen type 1 turnover PICP and CITP were significantly higher in persistent AF patients compared to healthy control subjects, and the levels of PICP, but not CITP, were higher in persistent AF patients than paroxysmal. Persistent AF patients also had a lower level of MMP-1 and increased levels of TIMP-1, suggesting that overall collagen type 1 synthesis was increased and the observed increase in collagen-1 degradation was insufficient to compensate for increased synthesis resulting in progression of fibrosis in patients with persistent AF. The serum concentrations of CITP, reflective of collagen type I degradation but not PINP (collagen synthesis marker), was reported in another study to be elevated in

patients with AF compared to a control population.⁸⁵ Serum CITP levels tended to be higher in those with permanent AF compared to persistent or paroxysmal AF. This study suffers from several limitations including inclusion of older patients in permanent AF, more patients with AF on digoxin, diuretics, and amiodarone, and fewer patients on angiotensin-converting enzyme inhibitors, beta-blockers and statins, drugs which may influence cardiac remodeling. Also, patients with AF had greater left atrial dimension, reflecting an advanced substrate that could influence the reported results.⁸⁵

In 54 patients with no prior history of AF who underwent cardiac surgery, Swartz et al⁶² reported elevated serum PICP and PIIINP levels in the preoperative blood samples to correlate with PoAF compared to those who remained in SR, and to the extent of left atrial fibrosis and elevated transcripts for collagen I, III, TGF- β 1, and angiotensin. Of the various markers of collagen remodeling studied, only PICP was independently predictive of the PoAF that developed in 18 patients. The findings are of interest but limited by the small number of patients and baseline differences in comorbidities that can explain the higher level of biomarkers and atrial fibrosis in patients who developed AF, who were older with larger left atria, increased left ventricular mass, more diastolic dysfunction, and a higher prevalence of mitral valve disease. The enthusiasm for these biomarkers as predictive of atrial fibrosis as a substrate for PoAF is also decreased by other studies that did not confirm these findings.⁸⁰ Neuberger et al⁸⁰ prospectively studied 28 patients in SR undergoing cardiac surgery, and PICP, PIIINP and CITP levels were not correlated to left or right atrial collagen content or to the spatial heterogeneity of atrial fibrosis despite the observation that spatial heterogeneity of fibrosis had a direct correlation to interstitial collagen content. Furthermore, a negative correlation between the serum PINP concentration and the degree of fibrosis in the atria was observed.⁸⁰ The reason behind these discrepant findings is not clear, but could potentially be related to variable pathologies, age groups, small number of patients enrolled (Table 1), chronicity of AF and degree of fibrosis. It is therefore essential that these biomarkers are validated in large prospective multicenter studies to assess their incremental value in predicting AF or PoAF before they can be accepted as markers of high risk for AF.

Connective Tissue Growth Factor

Connective tissue growth factor (CTGF), or CCN2, is a member of the CCN (CYR61, CTGF, NOV) family of matricellular proteins involved in cellular signaling and regulation of cellular function, including fibroblast proliferation, ECM remodeling, inflammation, cellular adhesion, and angiogenesis.^{77,101} CCN2 previously has been shown to play a role in the development of cardiac remodeling and fibrosis.^{77,102,103} The expression of CCN2 is induced by angiotensin II^{91,101,103} and TGF- β 1 in cardiac fibroblasts and cardiomyocytes.¹⁰⁴ CCN2 acts as a mediator of TGF- β 1 effect¹⁰² through the Smad pathway⁹⁰ and angiotensin II effect through small G-protein Rac-1 and nicotinamide adenine dinucleotide phosphate oxidase.⁹¹ TGF- β 1 appears to be involved in the initial acute phase of inflammation and repair after myocardial necrosis, whereas CCN2 is found in the ongoing fibrosis after myocardial injury¹⁰⁵ and has been suggested to facilitate fibrosis promoted by hemodynamic stress.¹⁰⁶ CCN2 expression is elevated in cardiac hypertrophy and failing hearts^{77,102} and in patients with permanent and non-paroxysmal AF.^{90,92} Elevated CCN2 levels were predictive of AF recurrence after catheter ablation of non-

paroxysmal AF, independent of other risk factors.⁹² In experimental models using isolated cardiomyocytes, CCN2 increased cell size through AKT signaling^{101,107} and induced fibrosis with upregulation of collagen I and III in a pacing-induced HF model through TGF- β 1-independent, but angiotensin II-dependent manner.¹⁰³ In patients with AF, a marked upregulation of CCN2 expression was observed in the left atrial myocardium compared to those who remained in SR and was associated with increased fibrosis, angiotensin II tissue concentration, NADPH oxidase, Rac1 and RhoA activity, as well as upregulation of N-cadherin and connexin 43 expression.⁹¹ The role of CCN2, however, in identifying those at risk of PoAF has not been evaluated.

Matrix Metalloproteinase/Tissue Inhibitor of Metalloproteinase

MMPs are a family of nine or more zinc-dependent endopeptidases that are responsible for the cleavage and degradation of most constituents of the ECM.^{58,60} An increase in MMP activity enhances cleavage of ECM proteins, resulting in remodeling of the scar within the myocardium^{60,108} that contributes to the heterogeneity of electrical conduction and refractoriness of the atria, an essential substrate for AF.^{58,60,109} TIMP, on the other hand, inhibits the proteolytic activity of activated MMPs by forming tight-binding, noncovalent, 1:1 stoichiometric complexes between them. The activity of MMPs is regulated by myeloperoxidase, a leukocyte-derived heme enzyme expressed by neutrophils that generate reactive oxygen species that in turn create a positive feedback for further activation of MMPs.⁹³ Experimental evidence about the role of myeloperoxidase in AF comes from animal models and a few clinical studies.^{86,87,93,110} When myeloperoxidase-deficient mice were treated with angiotensin II to promote leukocyte activation, there was reduced activity of MMPs, blunted atrial fibrosis, and protection from AF, which was reversed when myeloperoxidase was restored.⁹³ Similar findings were reported in humans with AF who were found to have higher plasma concentrations of and a larger myeloperoxidase burden in right atrial tissue as compared to people without AF.⁹³

Altered atrial MMP and TIMP expressions were reported in patients with atrial fibrosis and AF; however, the number of studies are limited (Table 1). Boixel et al.¹¹⁰ reported that atrial fibrosis was associated with an increased expression and activity of MMP-2 and -7 but no change in the expression or activity of TIMP-1, -2 and -4 in a myocardial infarction model. In hypertensive patients with AF when compared to those in SR, higher serum levels of MMP-2, MMP-3 and MMP-9 and lower TIMP-1 levels were reported.⁸⁹ Paroxysmal AF was associated with higher MMP-2 levels compared to permanent AF, while MMP-9 was higher in permanent AF patients. Lower TIMP-1 was the only independent factor associated with AF in this study. AF patients, however, were older and had significantly lower left ventricular ejection fraction with greater left atrial volume index than patients with SR, and a strong inverse correlation between left atrial volume index and TIMP-1 levels was reported for AF patients, whereas a positive correlation was noticed between left atrial volume index and MMP-9, suggesting that the imbalance of TIMP-1 and MMP-9 could enhance atrial remodeling and promote maintenance of AF. A selective downregulation of tissue levels of TIMP-2 and upregulation of MMP-2 level and activity was also reported in patients with permanent and persistent AF and increase in MMP-9 level and activity in permanent AF with advanced HF compared to non-AF patients with HF or those in SR with normal heart

function.⁸⁸ These changes in gelatinases (MMP-2 and -9 levels and activity) correlated with an increase in atrial type I collagen volume fraction, collagen type I/III ratio, left atrial dimension and the maintenance and recurrence of AF, indicating the importance of gelatinases in the ECM remodeling of the failing heart and in the development of sustained AF.⁸⁸ This was also demonstrated in another study from patients with dilated cardiomyopathy and end-stage HF, in which gelatinase activity and atrial expression of MMP-9 (both messenger ribonucleic acid and protein) were significantly elevated in atria of patients with AF compared to non-AF patients.⁸⁶ In patients without a previous history of AF, a relationship between the circulating levels of MMP-9 to new onset-AF was also demonstrated in a sub-analysis of the prospective community-based Atherosclerosis Risk in Communities (ARIC) study,⁸⁴ in which the elevated level of circulating MMP-9 was independently associated with an increased risk of AF, whereas MMP 1 and 2, TIMP 1 and 2, and collagen synthesis biomarker PICP were not associated with AF over a mean follow-up of 11.1 years. A chamber-specific increase in collagen content in the atria of explanted hearts from patients with end-stage HF and AF compared to non-AF patients was associated with a differential increase in the levels of MMP-1 in the right atrium, MMP-9 and TIMP-3 in the left atrium, and TIMP-3 in right and left ventricles in the AF patients.⁷⁸ In patients undergoing mitral valve surgery, a downregulation in MMP-1 and MMP-9 was reported compared to patients without severe mitral valve disease undergoing CABG, with little impact of AF on the level of metalloproteinases in the atria that were massively enlarged with a higher degree of fibrosis due to greater hemodynamic loading.⁸⁷ The discrepancy in the level of MMPs and other markers of collagen turnover reported in various studies could be partly explained by chamber-specific alterations in enzymes regulating ECM turnover and the underlying disease process on the expression of ECM modulating proteins.⁸⁶⁻⁸⁹

Markers of Myocardial Stretch

B-type natriuretic peptide (BNP) is an important marker for increased myocardial wall stress observed in patients with ventricular overload with HF or acute myocardial infarction.¹¹¹ Synthesized as an inactive prohormone, BNP is cleaved in equimolar amounts into the active BNP, and the inactive N-terminal fragment (NT-proBNP).¹¹² The circulating half-life of NT-proBNP is longer than BNP, in particular, in patients with HF.^{39,95} In the community-based Cardiovascular Health Study, NT-proBNP levels were elevated in the elderly patients with AF and was a predictor of new-onset AF independent of other risk factors during a median follow-up of 10 years.¹¹³ Similar results were reported in other populations.⁹⁶ Left atrial volume index, left atrial dimension, left ventricular ejection fraction, left ventricular mass index, and AF duration have been shown to be independent predictors of plasma BNP or NT-pro-BNP levels in patients with long-lasting AF and even with preserved left ventricular systolic function.^{94,112} In a prospective analysis of the Framingham Offspring Study, patients without HF had both elevated NT-proBNP and NT-pro atrial natriuretic peptide levels in their plasma, and these factors were associated with an increased risk of death, HF or new-onset AF during a mean follow-up of 5.1 years.¹¹⁴

The role of BNP and other biomarkers in the prediction of PoAF was recently evaluated in patients with SR undergoing CABG.¹¹⁵ Elevated preoperative NT-proBNP levels were independently predictive of PoAF, but transcatheter lactate gradient and C-reactive protein

(CRP) were not different between those who remained in SR and those who developed PoAF.¹¹⁵ In a systematic review and meta-analysis of 10 studies enrolling 1,844 patients, the use of perioperative BNP and NT-proBNP levels for predicting PoAF were further confirmed with a pooled sensitivity and specificity of 75% and 80%, respectively.¹¹⁶ NT-proBNP had a better predictive power than BNP. Not all studies, however, have identified an association between elevated preoperative NT-proBNP levels and PoAF or AF.¹¹⁷ A lower preoperative ANP level was reported with a longer duration of AF and higher left atrial collagen volume and was associated with lower success in restoring SR after MAZE surgery.¹¹⁸ The messenger RNA expressions of ANP, collagen type I, and collagen type III were lower in patients with AF than those who maintained SR, suggestive of reduced atrial natriuretic peptide levels as a potential marker for atrial degenerative changes and AF recurrence.¹¹⁸ Overall, the role of preoperative levels of atrial natriuretic peptide in predicting PoAF is not clear due to the scarcity of data and the limitations imposed by the inclusion of older, more symptomatic patients with advanced functional class, a higher risk profile, and longer duration on the cardiopulmonary bypass. NT-proBNP appears to be a useful biomarker for identifying patients at risk for PoAF. However, differences in age, gender, left ventricular dysfunction, renal clearance, and other comorbidities should be taken into consideration when using natriuretic peptides as a predictor for PoAF, as previous studies in normal populations have demonstrated a strong age and gender effect on the circulating levels of natriuretic peptides.¹¹⁹

Markers of Inflammation

There is growing evidence that inflammation is associated with AF;^{5,13,19,20,100} however, the causative role of inflammation in AF remains controversial.³⁹ In PoAF, inflammation appears to play a contributory role as anti-inflammatory agents reduce the incidence of AF after CABG and/or valve surgery.^{15,100,120–124} The timing of peak incidence of PoAF temporally correlates with transient sterile pericarditis that accompanies surgical trauma and repair.¹²⁵ Inflammation in the postoperative period results from multiple acute factors, including surgery-related processes such as local incision or manipulation of the heart, acute systemic reaction from complement activation, and release of proinflammatory cytokines associated with CABG surgery, superimposed on chronic proinflammatory processes related to the aging process, underlying structural heart disease, or comorbidities such as diabetes, hyperlipidemia or metabolic syndrome.^{13,15} Oxidative injury and release of reactive oxygen species as a result of surgical stress contribute to electrostructural remodeling of the atria, **which in turn????** and contributes to PoAF.⁴² Therefore, elevated peroxynitrite and superoxide, markers of oxidative stress, are indicative of a higher risk for PoAF.¹²⁶ A systemic inflammatory response with elevated serum levels of inflammatory markers, such as CRP and interleukin-6 (IL-6), correlates well with the degree of surgical stress, and a strong inflammatory response with increase in postoperative inflammatory markers independently predicts PoAF.^{13,19} Elevated preoperative CRP levels indicative of ongoing inflammation were associated with PoAF after CABG in some,⁹⁸ but not all studies,^{99,115} suggesting that local stress and inflammation induced by surgery is more important than preexisting inflammation in precipitating PoAF.^{5,127} In the elderly and high-risk patients, cardiopulmonary bypass and cardioplegic arrest were the main predictors of PoAF.¹²⁸ In patients with metabolic syndrome, mitochondrial dysfunction with reduced preoperative

mitochondrial respiration and increased sensitivity to calcium-induced mitochondrial permeability transition pore opening that is sensitized by oxidative stress, were significantly associated with PoAF.⁴²

Pericarditis stimulates the proliferation and activation of atrial epicardial fibroblasts and alters distribution of connexins 40 and 43 and gap junction proteins,¹²⁹ increasing anisotropy and heterogeneity of conduction slowing that increases a predisposition to arrhythmogenesis. The role of various ILs (IL-2, 6, and 8) in PoAF has been reported, but all have limitations.^{100,130} Osteoprotegerin, a member of the tumor necrosis factor receptor superfamily, functions as a decoy receptor by binding to a receptor activator of nuclear factor kappa B (RANK) and RANK ligand (RANKL), and competitively inhibits the interaction between RANKL and RANK.⁹⁷ Researchers studying the Framingham Offspring cohort¹³⁰ recently reported an association between serum osteoprotegerin concentration and incident AF. Another study⁹⁷ demonstrated that elevated preoperative serum soluble RANKL level and soluble RANKL/osteoprotegerin ratio are independent predictors of PoAF in patients undergoing cardiac valve surgery. Although these novel biomarkers appear to be promising for the prediction of PoAF, further research is needed.

Markers of Cell Death: Serum Fas Concentration

The role of increased atrial apoptosis in the fibrosis pathway has been described in atrial tissue of animals using the tachypacing model of AF as well as in patients with AF.^{5,131} Muller et al¹³² reported that preoperative serum apoptosis-stimulating fragment ligand (Fas) concentration that binds with the death receptor mediating the extrinsic pathway of apoptosis was significantly higher in patients with PoAF compared to patients maintaining SR, and correlated with the degree of atrial apoptosis and fibrosis. Although promising, the results are from a small number of patients and the contribution to Fas levels by left ventricular dysfunction cannot be excluded. These results need to be confirmed in larger studies before acceptance into clinical practice for prediction of PoAF.

Gene Expression Markers: MicroRNA

Genetic factors predispose to AF initiation and maintenance and contribute to electrical and structural atrial remodeling.^{36,41,133,-135}

Recent studies have demonstrated that altered expression of noncoding RNA transcripts known as microRNAs (miR), a class of 19–25-nucleotide noncoding RNA, also play a role in the etiology of AF and its progression.^{17,36,136–138} Various miRs have been associated with AF, including miR-1, miR-21, miR-29, miR-30, miR-328, miR-499, and miR-133, possibly contributing to AF by modulating the expression of ion channels or proteins involved in inflammation and fibrosis.^{136–145} Lu et al¹³⁶ reported that miR-328 levels increased more than threefold in dogs with AF as well as in patients with AF, and contributed to the adverse atrial electric remodeling in AF through targeting L-type Ca²⁺ channel genes. AntagomiR reversed the increased miR-328 levels, and genetic knockdown of endogenous miR-328 reduced AF inducibility.¹³⁶ In another study, miR-499 was found to be upregulated in the atria of patients with AF, whereas the expression of protein for the small-conductance calcium-activated potassium channel 3 (SK3) was downregulated,

possibly contributing to the electrical remodeling in AF.¹⁴³ Reduced levels of miR-1 in humans with AF have been suggested to contribute to upregulation of Kir2.1 subunits, leading to increased IK₁ expression,¹⁴⁶ but others have not confirmed changes in miR-1 in AF.¹³⁷ The impact of miRs regulating atrial fibrosis was reported by several investigators. MiR-21 is important for regulation of fibrosis, and elevated atrial tissue expression has been correlated with atrial fibrosis.¹⁴⁰ Increased expression of miR-21 in human left atria^{140,145} was associated with a reduced expression of Sprouty-1 and increased expression of CTGF lysyl oxidase and Rac1-GTPase in patients with AF,¹⁴⁵ which correlated with atrial collagen content. This was further confirmed in neonatal cardiac fibroblasts challenged with angiotensin II or CTGF that increased miR-21 expression with reduction in expression of Sprouty-1 protein mediated through Rac1 GTPase and lysyl oxidase, whose inhibition attenuated angiotensin II- and CTGF-induced upregulation of miR-21.¹⁴⁵ MiR-21 appears to be important in the regulation of atrial substrate promoting arrhythmogenesis and is a potential target for prevention of AF and its progression. This was demonstrated¹⁴¹ in a rat model of post-myocardial infarction AF with upregulation of miR-21, along with dysregulation of the target genes Sprouty-1, collagen-1, and collagen-3. Treatment with anti-miR-21 reduced atrial miR-21 expression levels and decreased atrial fibrosis and AF duration when compared to animals treated with scrambled miR-21. The plasma levels of miR-21 could also potentially identify patients at risk for AF; however, contradictory results have been reported with decreased levels in AF patients in one study¹⁴⁰ and no significant difference between the AF and non-AF groups in another study.¹⁴⁴ Specific signatures of other miRs expressions in the circulation have also been demonstrated in patients with AF.¹⁴⁴ Twenty-two specific miRs were dysregulated in AF patients compared to the non-AF group. Of these, four miRs were different between the AF and non-AF group, with a more than fivefold increase in the level of miR-146 and miR-19a and reduced levels of miR-150 and miR-375 in AF patients. When validated prospectively, only the reduced plasma level of miR-150 was independently associated with the presence of AF.¹⁴⁴ This is of significance because miR-150 target genes include IL-6, IL-18, TNF- α , and TGF- β , known modulators of inflammation and fibrosis.¹⁴⁴ Studies with circulating miRs as biomarkers for AF are limited and suffer from several limitations, including small sample size, contradictory results due to differences in age, atrial dimensions and volumes, underlying pathophysiology, and use of medications that can impact expression of these non-coding RNA. To our knowledge, no systemic study assessing circulatory miR as a biomarker for PoAF is available. Prospective trials on larger patient cohorts may provide information to establish the roles of miRs in predicting AF.

CONCLUSIONS

The overall incidence of PoAF has not changed significantly despite advances in medical and surgical management.⁷ Due to the impact of PoAF on intensive care and hospital stays,⁷ health care costs, and patient morbidity and mortality,^{4,10–13} it is critical that we improve our ability to identify patients at high risk for developing PoAF for improved selection of prophylactic interventions, closer monitoring for postoperative complications, and establishing the risk of long-term AF.^{1,7,31,32,34} Although several circulatory biomarkers have been proposed to stratify patients with a history of AF or at risk of AF and its

complications, the existing data are conflicting (Table 1). Markers of active collagen synthesis (elevated PICP and PIIINP), ECM remodeling (elevated MMP-9), myocardial stretch (BNP, NTpro-BNP), inflammation (RANKL, IL-6) and profibrotic mediators (TGF- β 1) appear to be promising in identifying those at risk for the development of PoAF (Table 2). However, alterations in these markers should be interpreted with caution, as differences in methodology of how the biomarkers were collected and stored,^{147,148} the patient population included, the type of AF (paroxysmal, persistent or permanent),^{85,88,89} the presence of atrial or ventricular dysfunction, differences in age, gender,¹¹⁴ renal clearance, presence of hypertension,¹⁴⁹ diabetes or use of remodeling altering medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins), and the lack of specificity of markers to myocardial ECM remodeling to differentiate atrial from more generalized fibrosis, complicates the picture. Carefully conducted studies involving a larger number of patients, excluding those with confounding effects of extra cardiac fibrosis, to confirm whether the markers reflect the impact of atrial fibrosis or more generalized fibrosis on risk of incident AF, are warranted.

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FIGURE 1.

Incidence of postoperative atrial fibrillation (PoAF) with age and over time. (A) Estimated probability of developing PoAF by age rises slowly in younger patient (<55 years age), but more steeply beyond age 55 years. (B) The overall incidence of new-onset PoAF in 10,390 patients without preexisting atrial arrhythmias undergoing cardiac surgeries (7,284 coronary artery bypass grafting [CABG] only, 887 CABG and valve, 1,399 valve only, 820 other cardiac surgeries), has not changed significantly over the last 20 years. CI indicates confidence interval. (With permission from Shen J, Lall S, Zheng V, et al. The persistent problem of new-onset postoperative atrial fibrillation: a single-institution experience over two decades. *J Thorac Cardiovasc Surg.* 2011;141:559–570.) ref 7

FIGURE 2.

The underlying substrate increases the risk of postoperative atrial fibrillation (PoAF). (A) Histological differences in interstitial collagen deposition demonstrated by increase in mason trichrome positive areas (blue) within the myocardium (magenta) in a patient who was free of PoAF (sinus rhythm) versus a patient who developed PoAF. Both patients had no prior history of AF and no significant cardiac abnormality by echocardiogram. (B) In patients with no prior history of AF, the percentage of collagen content within the myocardium was significantly higher in those who developed PoAF than those who remained in sinus rhythm. With permission from Mirza M, Strunets A, Holmuhamedov E, et al: A novel histology based classification system to identify patients at risk of postoperative atrial fibrillation. *Circ Res* 2013;113:A038. Ref 57

FIGURE 3.

Schematic representation of collagen protein secreted as a procollagen molecule and its breakdown peptides that can be measured in circulating blood. (A) Collagen I and III are secreted as a procollagen precursor containing an amino and carboxy terminal propeptide and telopeptides that are released during collagen synthesis and degradation. (B) During injury the released cytokines and profibrotic mediators activate fibroblasts (vimentin positive) to myofibroblasts that express alpha-smooth muscle actin (α -SMA). Myofibroblasts increase production of collagen I and III in the myocardium and trigger a cascade of events that take place during the synthesis and degradation of collagen type I and III molecules. PICP indicates carboxy terminal propeptide of collagen I; PINP, amino terminal propeptide of collagen I; PIIINP, amino terminal propeptide of collagen III; PIIICP, carboxy terminal propeptide of collagen III; CITP, carboxy terminal telopeptide of collagen I; MMP, matrix metalloproteinases; and TIMP, tissue inhibitor of matrix metalloproteinases. In the boxed inset, several micro-RNA (miR) that have been shown to regulate expression of genes involved in extracellular matrix remodeling are summarized. (The fibroblast and myofibroblast figures were isolated from right atrial appendage of a patient undergoing coronary artery bypass grafting).

Table 1

Markers of extracellular matrix turnover associated with atrial fibrillation and or post-operative atrial fibrillation in humans

Marker	Patient Group	Mean Age (Years)	Collagen Turnover			Reference
			Tissue	Levels	Serum	
Collagen Turnover						
PICP	Persistent AF (n=32) vs. no AF (n=20)	65 vs. 56		↑	Kallergis (2008) ⁷⁹	
	New onset postoperative AF (n=18) vs. no AF (n=36)	73 vs. 64		↑	Swartz (2012) ⁶²	
	Correlation with atrial fibrosis in non-AF patients (n=28) undergoing surgery	65		↔	Neuberger (2012) ⁸⁰	
	Incident AF (n=580) over 11 years vs. no AF (n=500)	60 vs. 59		↔	Huxley (2013) ⁸⁴	
PINP	Persistent AF (n=80) vs. non-AF (180) or paroxysmal AF (n=98)	70 vs. 66		↔	Tziakas (2007) ⁸⁵	
	Correlation with atrial fibrosis in non-AF patients (n=28) undergoing surgery	65		↓	Neuberger (2012) ⁸⁰	
PIIINP	New onset postoperative AF (n=18) vs. no AF (n=36)	73 vs. 64		↑	Swartz (2012) ⁶²	
	Correlation with atrial fibrosis in non-AF patients (n=28) undergoing surgery	65		↔	Neuberger (2012) ⁸⁰	
CITP	Persistent AF (n=32) vs. no AF (n=20)	65 vs. 56		↑	Kallergis (2008) ⁷⁹	
	Persistent AF (n=80) vs. non-AF (180) or paroxysmal AF (n=98)	70 vs. 66		↑	Tziakas (2007) ⁸⁵	
	New onset postop AF (n=18) vs. no AF (n=36)	73 vs. 64		↔	Swartz (2012) ⁶²	
	Correlation with atrial fibrosis in non-AF patients (n=28) undergoing surgery	65		↔	Neuberger (2012) ⁸⁰	
Matrix Metalloproteinases						
MMP-1	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↑ (RA)		Mukherjee (2006) ⁷⁸	
	Persistent AF (n=32) vs. no AF (n=20)	65 vs. 56		↓	Kallergis (2008) ⁷⁹	
	AF (n=13) vs. SR (n=25)	68 vs. 65	↔ (RA)		Nakano (2004) ⁸⁶	
	Permanent AF (n=9) vs. SR (n=10) mitral valve surgery	70 vs. 66	↔ (LA)		Anne (2005) ⁸⁷	
	Incident AF (n=580) over 11 years vs. no AF (n=500)	60 vs. 59		↔	Huxley (2013) ⁸⁴	
	End-stage HF permanent and persistent AF vs. non-AF	52 and 57 vs. 52	↔		Xu (2004) ⁸⁸	
	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↔		Mukherjee (2006) ⁷⁸	
MMP-2	AF (n=13) vs. SR (n=25)	68 vs. 65	↔ (RA)		Nakano (2004) ⁸⁶	
	Permanent AF (n=9) vs. SR (n=10) mitral valve surgery	70 vs. 66	↔ (LA)		Anne (2005) ⁸⁷	

Marker	Patient Group	Mean Age (Years)	Levels		Reference
			Tissue	Serum	
	Incident AF (n=580) over 11 years vs. no AF (n=500)	60 vs. 59		↔	Huxley (2013) ⁸⁴
	Paroxysmal AF (n=33) vs. SR (n=27) and permanent AF (n=26)	69.5 vs. 62.7 vs. 68.3		↑	Kalogeropoulos (2011) ⁸⁹
	End-stage HF permanent and persistent AF vs. non-AF	52 and 57 vs. 52	↑		Xu (2004) ⁸⁸
MMP-3	Paroxysmal AF (n=33) and permanent AF (n=26) vs. SR (n=27)	69.5 and 68.3 vs. 62.7		↑	Kalogeropoulos (2011) ⁸⁹
	End-stage HF permanent and persistent AF vs. non-AF	52 and 57 vs. 52	↔ (RA, LA)		Xu (2004) ⁸⁸
MMP-8	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↓ (RA)		Mukherjee (2006) ⁷⁸
MMP-9	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↑ (LA)		Mukherjee (2006) ⁷⁸
	End-stage HF AF (n=13) vs. SR (n=25)	68 vs. 65	↑ (RA)		Nakano (2004) ⁸⁶
	Incident AF (n=580) over 11 years vs. no AF (n=500)	60 vs. 59		↑	Huxley (2013) ⁸⁴
	Permanent AF (n=26) vs. SR (n=27) and paroxysmal AF (n=33)	68.3 vs. 62.7 and 69.5		↑	Kalogeropoulos (2011) ⁸⁹
	Permanent AF (n=9) vs. SR (n=10) with severe mitral valve disease	70 vs. 66	↔ (LA)		Anne (2005) ⁸⁷
	End-stage HF permanent vs. persistent AF or non-AF	52 and 57 vs. 52	↑ (RA, LA)		Xu (2004) ⁸⁸
MMP-13	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↔		Mukherjee (2006) ⁷⁸
MMP-14	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↑ (RA)		Mukherjee (2006) ⁷⁸
Tissue Inhibitor of Metalloproteinases					
TIMP-1	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↑ (RV)		Mukherjee (2006) ⁷⁸
	Persistent AF vs. no AF	65 vs. 56		↑	Kallergis (2008) ⁷⁹
	Permanent AF (n=9) vs. SR (n=10) mitral valve surgery	70 vs. 66	↔ (LA)		Anne (2005) ⁸⁷
	Incident AF (n=580) over 11 years vs. no AF (n=500)	60 vs. 59		↑	Huxley (2013) ⁸⁴
	Paroxysmal AF (n=33) and permanent AF (n=26) vs. SR (n=27)	69.5 and 68.3 vs 62.7		↓	Kalogeropoulos (2011) ⁸⁹
TIMP-2	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↑ (LV)		Mukherjee (2006) ⁷⁸
	Permanent AF (n=9) vs. SR (n=10) mitral valve surgery	70 vs. 66	↔ (LA)		Anne (2005) ⁸⁷
	Incident AF (n=580) over 11 years vs. no AF (n=500)	60 vs. 59		↔	Huxley (2013) ⁸⁴
	End-stage HF permanent and persistent AF vs. non-AF	52 and 57 vs. 52	↓		Xu (2004) ⁸⁸
TIMP-3	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↑ (LA, RV, LV)		Mukherjee (2006) ⁷⁸
TIMP-4	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↔		Mukherjee (2006) ⁷⁸
Collagen					

Marker	Patient Group	Mean Age (Years)	Levels		Reference
			Tissue	Serum	
Soluble collagen I	End-stage HF AF (n=23) vs. no AF (n=20)	54 vs. 56	↑ (RA, LA) ↓ (RV, LV)		Mukherjee (2006) ⁷⁸
Profibrotic Signaling					
TGF-β1	Permanent AF (n=28) vs. SR (n=12) undergoing mitral valve surgery		↑ (RA)		Li (2013) ⁹⁰
	Post-valvular plus MAZE surgery AF (n=10) vs. SR (n=76)	58 vs. 55		↑ (failed MAZE)	On (2009) ⁷²
	Persistent AF and electroanatomical remodeling			↑ (remodeling but effect on recurrence)	Kim (2011) ⁷⁴
	Persistent AF with failed cardioversion (n=7) vs. no recurrence (n=74)	64 vs. 59		↑ (failed cardioversion)	Kim (2009) ⁷³
	Acute decompensated heart failure with AF (n=107) vs. non-AF (n=294)	75 vs. not reported		↓ (AF)	Behnes (2011) ⁷⁵
Angiotensin II	Permanent AF (n=5) vs. SR (n=5) undergoing mitral valve surgery	63 vs. 67	↑ (LA)		Adam (2010) ⁹¹
Connective Tissue Growth Factor (CCN2)	Permanent AF (n=5) vs. SR (n=5) undergoing mitral valve surgery	63 vs. 67	↑ (LA)		Adam (2010) ⁹¹
	Permanent AF (n=28) vs. SR (n=12) undergoing mitral valve surgery		↑ (RA)		Li (2013) ⁹⁰
	Recurrence of AF (n=61) after catheter ablation of persistent AF vs. no recurrence group (n=31)	56 vs. 54		↑	Song (2014) ⁹²

AF = atrial fibrillation; CCN2 = connective tissue growth factor; CTFP = carboxy terminal telopeptide of collagen I; HF = heart failure; LA = left atrium; LV = left ventricle; MMP = matrix metalloproteinase; PICP = carboxy terminal propeptide of collagen I; PINP = amino terminal propeptide of collagen I; PIINP = amino terminal propeptide of collagen III; RA = right atrium; RV = right ventricle; SR = sinus rhythm; TGF-β1 = transforming growth factor beta 1; TIMP = tissue inhibitor of matrix metalloproteinases

Table 2

Markers of extracellular matrix turnover associated with new onset postoperative atrial fibrillation in humans

Circulating Serum Biomarkers	New-Onset PoAF vs. No AF	Reference
Markers of Collagen Turnover		
PICP	↑, ↔	Swartz (2012), ⁶³ Kallergis (2008), ⁷⁹ Neuberger (2012) ⁸⁰
PINP	↓, ↔	Neuberger (2012), ⁸⁰ Tziakas (2007) ⁸⁵
PIIINP	↑, ↔	Swartz (2012), ⁶² Neuberger (2012) ⁸⁰
CITP	↔	Swartz (2012), ⁶³ Kallergis (2008), ⁷⁹ Tziakas (2007) ⁸⁵
Markers of ECM remodeling		
MPO	?	Rudolph (2010) ⁹³
MMP-1	↔	Mukherjee (2006), ⁷⁸ Kallergis (2008), ⁷⁹ Huxley (2013), ⁸⁴ Nakano (2004), ⁸⁶ Anne (2005) ⁸⁷
MMP-2	↔	Mukherjee (2006), ⁷⁸ Huxley (2013), ⁸⁴ Nakano (2004), ⁸⁶ Anne (2005) ⁸⁷
MMP-9	↑	Mukherjee (2006), ⁷⁸ Huxley (2013), ⁸⁴ Nakano (2004), ⁸⁶ Anne (2005) ⁸⁷
TIMP-1	↑	Mukherjee (2006), ⁷⁸ Kallergis (2008), ⁷⁹ Huxley (2013), ⁸⁴ Anne (2005) ⁸⁷
TIMP-2	↔	Mukherjee (2006), ⁷⁸ Huxley (2013), ⁸⁴ Anne (2005) ⁸⁷
TGFβ1	↔	On (2009), ⁷² Kim (2009), ⁷³ Kim (2011), ⁷⁴ Behnes (2011), ⁷⁵ Li (2013) ⁹⁰
Markers of Myocardial Stretch		
BNP	↑	Letsas (2009), ⁹⁴ Pfister (2004) ⁹⁵
NT-Pro-BNP	↑	Letsas (2009), ⁹⁴ Pfister (2004), ⁹⁵ Patton (2013) ⁹⁶
Markers of Inflammation		
RANKL/osteoprotegerin	↑	Cao (2013) ⁹⁷
CRP	↑	Bruins (1997), ¹³ Kaireviciute (2010), ⁹⁸ Marott (2010) ⁹⁹
IL-6	↑	Gaudino (2003), ¹⁹ Issac (2007) ¹⁰⁰

AF = atrial fibrillation; BNP = B-type natriuretic peptide; CITP = carboxy terminal telopeptide of collagen I; CRP = C-reactive protein; IL-6 = interleukin-6; MMP= matrix metalloproteinase; MPO = myeloperoxidase; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PICP = carboxy terminal propeptide of collagen I; PINP = amino terminal propeptide of collagen I; PIIINP = amino terminal propeptide of collagen III; PoAF = postoperative atrial fibrillation; RANKL = receptor activator of nuclear factor kappa B ligand; TGF-β1 = transforming growth factor beta 1; TIMP = tissue inhibitor of matrix metalloproteinases