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Mitral Regurgitation and Atrial Fibrillation: The Contribution of Impaired Left Atrial Appendage Function to Atrial Thrombogenesis

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1. Introduction

1.1 Epidemiology of atrial fibrillation

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia which affects 1 to 2 % of the entire adult population [1]. Current studies indicate that the prevalence of AF will be doubled in a few decades [2]. As a major source of public health problem, atrial fibrillation increases the risk of stroke (up to 18 fold especially in patients with valvular AF), long term disability, hospitalizations, cardiovascular mortality and healthcare costs [3-4]. The prevalence of atrial fibrillation and its complications are more common among patients with rheumatic heart disease especially in patients with mitral stenosis and regurgitation. Stroke is one of the most common and disabling complication of atrial fibrillation. Recent studies indicated that age, presence of hypertension, diabetes, heart failure and/or previous stroke or transient ischemic attack (TIA) as pivotal contributor risk factors to generation of stroke in AF patients [5-8]. Although the presence of these factors increases the risk of stroke in non-valvular AF patients, the absolute risk of stroke is much higher in patients with valvular AF [9].

2. Mitral valve disease and atrial fibrillation

In patients with rheumatic mitral regurgitation (MR) major anatomic changes comprise annular dilatation and prolapse of the anterior mitral valve leaflet due to elongation of chordae tendineae [10]. However, retractile fibrosis of leaflets and chordae tendineae that leads loss of coaptation is the main pathologic finding in patients with chronic rheumatic MR [11]. In the early phases of rheumatic disease the most frequent echocardiographic finding is the enlargement of left atrium in patients on sinus rhythm. However, paroxysmal or permanent atrial fibrillation ultimately affects 50% of patients within 10 years of

diagnosis in sinus rhythm [12]. Left atrial enlargement causes impaired mitral apparatus function and loss of coaptation causes mitral regurgitation. On the other hand, left atrial enlargement contributes to the generation of atrial re-entry and atrial fibrillation. Progressive left atrial enlargement increases the risk of AF development. New onset AF occurs in 10 to 20% of patients with myocardial infarction due to ischemia of atria or sinus node [13]. Atrial fibrillation is more common among older and hypertensive patients with mitral regurgitation and enlarged left atria [13].

3. Left atrial appendage as a source of thrombi and stroke

The left atrial appendage (LAA), a blind-ended complex structure that is embryologically distinct from the body of the left atrium, is been identified as the major source of cardiac systemic embolic events in patients with AF [14]. The atrium and the LAA compensate for the age-induced changes in LV diastolic properties by increasing active atrial contraction (a-wave) [15]. An experimental study and a clinical study showed the presence of an inverse relationship between LA filling pressure and LAA emptying function (inverse correlation between capillary wedge pressure and LAA active emptying a-wave) [16, 17]. Due to its compliance, the LAA is acting as a modulator of LA pressure.

It has been demonstrated that more than 15% of strokes originate from the heart, and especially from the LAA [18]. A recent study showed the presence of thrombi in the left atrial cavity in 1.9% of the AF patients. In the same study, the incidence of LAA thrombi was reported 6.6-fold that of left atrial cavity thrombi. Of note, AF was also determined in most of the patients with LAA thrombi [19].

4. Left atrial appendage function in atrial fibrillation

LAA has hemodynamic roles and contributes to atrial function. Impaired LAA function is been shown to lead increased thrombosis in left atrium [19].

Another previous study evaluated LAA function in 60 patients with severe rheumatic MR on both sinus rhythm and atrial fibrillation. Impaired LAA functions were determined in patients with severe mitral regurgitation having AF, whereas LAA was preserved in patients with normal sinus rhythm compared to controls [20]. Another study which aimed to compare LAA functions before and after percutaneous balloon mitral valvuloplasty (PBMV) by tissue wave Doppler imaging enrolled 20 patients with symptomatic rheumatic mitral stenosis [21]. LAA functions were evaluated by the measurement of; LAA late filling (LAALF) velocity, LAA late emptying (LAALE) velocity, and percent area change of the LAA [21]. No significant difference was reported in LAALF velocity and area percent change of the LAA after PBMV [21] while LAALE velocity was found increased after PBMV compared to baseline values ($p=0.005$). In the same study increased late emptying, systolic, and diastolic wave values were determined by tissue Doppler imaging after PBMV when compared to basal measurements ($p=0.023$, $p=0.002$, and $p=0.002$, respectively). Of note, significant improvement was determined in left atrial spontaneous echo-contrast after PBMV and LAA functions [21].

The functions of LAA have been evaluated in patients with severe rheumatic mitral regurgitation both in AF or sinus rhythm [22]. Impairment of LAA functions is been shown

to contribute to thrombogenic processes and it is been often determined among AF patients when compared to those in sinus rhythm. Recent studies indicated that the LAA flows were strongly affected by the type of atrial arrhythmia. For example, the average emptying flow velocity was found weaker in AF than in sinus rhythm, and it was found greater in atrial flutter than in AF [23].

5. Markers of left atrial appendage function

The role of different markers that can be associated with LAA function has been evaluated in recent studies. One of these studies investigated the expression of proteins associated with the cytoskeleton, energetic metabolism, and cardiac cytoprotection between left atrial appendages (LAA) and right atrial appendages (RAA) obtained from patients with mitral valve disease both in sinus rhythm and in permanent atrial fibrillation. Similar levels of protein expression is been reported both in RAA and LAA samples. However, expression of cardiac alpha-actin isoforms 1 and 2, tropomyosin alpha- and beta-chains, and myosin light chain embryonic muscle/atrial isoform in LAA from AF patients was found increased when compared to those from SR patients [24]. Another potential contributor to atrial remodelling, cardiac endothelin-1 (ET-1), is expressed as a response to wall stress and can promote myocyte hypertrophy and interstitial fibrosis [25]. Elevated atrial ET-1 level is been found associated with increased LA size, AF prevalence, hypertension, and heart failure [25]. An association between ET-1 and atrial dilatation, fibrosis, and hypertrophy is been reported. Endothelin-1 is suggested as a contributing factor to AF persistence [25].

Although both mitral stenosis and MR are strongly associated with AF, the prevalence of AF in mitral stenosis patients is much higher than MR patients. Approximately 29% of the patients with isolated mitral stenosis develop AF while only 16% of the patents with isolated MR [26, 27].

6. Atrial remodelling in atrial fibrillation

A recent study aimed to assess the relationship between atrial structural remodelling in AF patients with different types of mitral valve diseases [28]. The study recruited 24 patients undergoing mitral valve surgery with different diagnoses. Left atrial appendage tissue samples were obtained from patients with mitral valve disease either in sinus rhythm or AF. Masson's trichrome staining and immunohistochemical staining were performed to assess the extent of the fibrosis. The authors reported significantly increased fibrosis in patients with AF when compared to patients in sinus rhythm ($p=0.023$) [28]. The collagen volume fraction of fibrosis was also significantly increased in patients with mitral stenosis and atrial fibrillation when compared to patients with mitral regurgitation and atrial fibrillation ($p=0.043$) [28]. Collagen Type I levels were also significantly increased in AF patients with mitral stenosis when compared to patients with mitral regurgitation and AF ($p=0.043$). Of note, different collagen volume fraction of Matrix MetalloProteinases-2 (MMP2) was determined between the patients with mitral stenosis and sinus rhythm and patients with mitral stenosis and AF ($p=0.001$). The authors concluded that heart rhythm status and type of underlying mitral valve disease influence

atrial structural remodelling and different atrial structural remodelling may contribute to the development of AF [28].

The remodelling processes involving atrial fibrosis and atrial dilatation in AF patients also recruit angiotensin II mediated pathways and MMPs. There are evidences showing that patients with mitral stenosis and AF have significantly larger atria than patients with mitral stenosis but sinus rhythm [29]. Fibrosis was found increased in mitral stenosis patients in AF and SR in the left atria, but only in mitral stenosis patients with AF in the right atria. Furthermore, MMP-1 was reported to be down-regulated in left atria of mitral stenosis patients ($p=0.02$) both in sinus rhythm or AF [29]. Although there is no evidence showing that AF contributes to altered fibrosis or MMP-expression in the left atria, atrial remodelling appears to recruit changes in MMP-expression in patients with mitral valve disease either in sinus rhythm or AF [29].

Interestingly, mitral regurgitation can provide protective effects against left atrial blood stasis. The relationship between the severity of MR and thromboembolic risk has been clarified in patients with AF. A recent study indicated a protective effect of MR against thromboembolic risk over reducing LA blood stasis but only limited to patients with severe MR [30].

7. Mitral valve disease, atrial fibrillation and thrombosis

The association between mitral valve disease and atrial fibrillation appears to constitute a vicious cycle. Different dynamics including changes in LAA functions affect the generation and persistence of atrial fibrillation. The severity of mitral valve regurgitation has pivotal influence on left atrial flow dynamics and LAA stasis which appears to be the major determinant of thrombus generation [31].

The mechanisms of thrombogenesis in patients with MR or aortic stenosis (AS) have been investigated in patients both in sinus rhythm and AF. Patients with MR or AS have been shown to have higher plasma fibrinogen levels when compared to healthy people and also lower plasma fibrin D-dimer levels suggesting decreased intravascular clotting has been reported [32]. Furthermore, the presence of immunoreactive von Willebrand factor (vWF) in the endocardial endothelium and its relationship to thrombogenesis in the human atrial appendage has been investigated [33]. Immunoreactive vWF in the endocardial endothelium was found increased in overloaded human atrial appendage, which was supposed to be a local predisposing factor for intraatrial thrombogenesis [33].

Another study investigated the contribution of plasma D-dimer levels to thrombogenesis in 89 patients with mitral valve disease and 21 subjects with AF but normal valves, and 15 healthy controls. Plasma D-dimer levels correlated with the embolic risk in mitral valve disease and non-valvular AF. The highest levels were found in patients with MS and AF and non-valvular AF. Severe MR decreased the D-dimer levels in MS and/or AF to control levels [34].

Transmitral pressure gradient is supposed to be another parameter that may influence the development of AF and thrombogenesis in patients with rheumatic heart disease [26]. However, patients' age and left atrial diameter has been shown to be the major parameters that predict the occurrence of AF in patients with rheumatic heart disease [26].

8. Conclusions

Atrial fibrillation is the most common sustained cardiac arrhythmia and a severe public health problem. The prevalence of AF increases while the population is ageing. Mitral valve diseases, including mitral stenosis and mitral regurgitation increase AF prevalence. There are strong associations between severe mitral valve disease and the development of atrial fibrillation. Once atrial fibrillation starts it causes impaired LAA function and leads to increased intraatrial thrombogenesis. Left atrial thrombi and especially LAA thrombi are shown to be the commonest causes of embolic stroke. Management of this complex situation should comprise several steps including restoration of impaired LAA function, prevention of thrombogenesis and maintenance of sinus rhythm whenever it is feasible.

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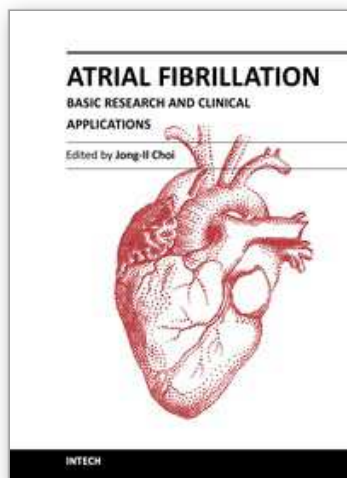
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