Tricuspid Regurgitation, the last challenge left.

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Abstract

Atrial fibrillation (AF) provides extremel rapid excitation frequency in both atria, and induces several pathophysiological mechanisms by influencing each other to promote AF. This auto-enhancing feature is often described by the well-known concept "AF begets AF". The cure of AF by creating pulmonary vein (PV) isolation may be able to reverse the spiral and be able to achieve reverse remodeling. Because of the initial focus on PV in the pathogenesis of AF, the effects of reverse remodeling after catheter ablation (CA) have been investigated on improvement of the left-sided cardiac system. On the other hand, tricuspid regurgitation (TR), the most neglected of all valvular diseases, is increasingly recognized as an important prognostic condition in heart failure patients. Previous reports, which tested the role of CA for AF patients with TR, have demonstrated that maintenance of SR provides reverse remodeling of the right-sided cardiac system, but have yet to prove whether this leads to improvement in patient prognosis. What is new and noteworthy about the report by Ukita et al. in this issue is that they found that TR improvement itself improves major event-free survival rate (incidence of heart failure hospitalization and all-cause mortality). However, several issues remain unresolved in their report. They observed a low AF recurrence rate in the TR-improved group, but did not address the possibility that AF suppression itself contributed to improve event-free survival rate. Further investigation is required to clarify whether TR improvement or maintenance of SR is the greater contributor to improved prognosis in AF.

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Since the discovery that atrial fibrillation (AF) is mostly caused by the transition area between the left atrium (LA) and the pulmonary vein (PV), catheter ablation (CA) of AF based on PV isolation (PVI) has achieved remarkable success in its cure and is now established as the principal technique for AF treatment [1)]. Because of the initial focus on LA in the pathogenesis of AF, the effects of reverse remodeling after CA have been investigated on improvement of the left-sided cardiac system, mitral regurgitation (MR), and left ventricular systolic function [2)]. The most extreme of these is the concept of functional atrial MR. This final aspect of AF indicates that this is not necessarily a benign disease, and is a useful concept to explain the pathogenesis of AF-induced heart failure death and sudden cardiac death [3)].

On the other hand, tricuspid regurgitation (TR), which has been the most neglected pathophysiology among all valvular diseases in adults, is increasingly recognized as an important prognostic condition in heart failure patients.

Several clinical conditions such as ischemic heart disease, cardiomyopathy, pacemaker leads, COPD, and AF are well known as causes of functional TR [4)]. The severity of TR is graded as none/trivial, mild, moderate,

and sever, and its severity is associated with the patient's life expectancy, with the 5-year survival rate for severe TR being reduced to 20% [5]. It is also known that patients with TR progression have a worse prognosis than those without. Among the etiologies of TR, AF is extremely important as a particular condition that cardiologists can directly intervene and resolve.

AF provides extremely rapid excitation frequency in both atria, and induces following four pathophysiological mechanisms: electrical remodeling, structural remodeling, autonomic nervous system changes, and abnormal Ca^{++} handling, which influence each other to promote AF [6]. This auto-enhancing feature is often described by the famous concept "AF begets AF" [7]. In particular, structural remodeling caused by AF leads to enlargement of both atria and atrioventricular (AV) annulus and AV valve regurgitation (atrial functional MR, TR), which in turn lead to ventricular enlargement and further worsen AV valve regurgitation, a negative spiral. [6] (Figure).

Radical therapy of AF may be able to reverse the negative spiral or prevent the patient from falling into it. And many reports have shown its remarkable efficacy, and the therapeutic concept of reverse remodeling has been established [8-9].

To the best of the author's knowledge, the first report to demonstrate that restoration of SR from AF with CA improves TR was by Itakura et al. in January 2020 [8]. They conducted a retrospective cohort study of 86 patients with persistent AF and found that 71 patients who were maintained in SR by CA had reductions in right atrial (RA) area, RA diameter, tricuspid annular diameter, and resulting in improvements of functional TR. The same effect was not observed in the 15 patients in whom SR could not be maintained, and the authors concluded that right atrial remodeling was achieved by SR maintenance in persistent AF patients.

Subsequently, several clinical trials have confirmed that maintenance of SR produces similar results [9,10]. In particular, Soulat-Dufour et al. studied 117 patients hospitalized for AF and divided them into two groups: non-spontaneous restoration (n=86) and spontaneous restoration of SR (n=31), with subsequent follow-up by UCG[9]. In this study, non-spontaneous restoration group (n=39) had worsening TR and MR, while those who underwent active restoration by electroshock or ablation (n=47) showed significant improvement. In this study, the spontaneous restoration group had fewer comorbidities and significantly smaller both atria, and left ventricular diameters, suggesting that the progression of cardiac structural remodeling had been less pronounced in spontaneous restoration group. In other words, once caught in the spiral of structural remodeling, CA plays a pivotal role to reverse it.

Previous reports have demonstrated that maintenance of SR in patients with AF provides reverse remodeling of the right-sided cardiac system, but have yet to prove whether this leads to improvement in patient prognosis. What is new and noteworthy about the report by Ukita et al. in this issue is that they found that TR improvement is more likely to be obtained in patients whose remodeling is not so significant, and that TR improvement itself improves patient prognosis [11]. By defining improvement in TR as an improvement of at least one-grade, they found that patients in the TR-improved group were significantly younger than those in the non-improved group in their baseline data, with 71 years old being the best cutoff value. Although no significant difference was observed, the duration of AF in the TR-improved group tended to be shorter, suggesting that early detection of AF was less likely in elderly AF patients, and that structural remodeling may have had progressed. One of the most important implications in this study is that the major event-free survival rate (incidence of heart failure hospitalization and all-cause mortality) was significantly better in the TR-improved group, but no difference in prognosis was observed between the groups when the subjects were divided by MR or LVEF improvement. This suggests that TR improvement may be an independent factor that determines the prognosis of post-CA patients with AF.

However, several issues remain unresolved even by the report of Ukita et al [11]. They observed a low AF recurrence rate in the TR-improved group, but did not address the possibility that AF suppression itself contributed to improve event-free survival rate. Further investigation is required to clarify whether TR improvement or maintenance of SR is the greater contributor to improved prognosis in AF patients. Also, the conclusion that improvement in left-sided cardiac parameters was not associated with prognosis should

be interpreted with caution, since it is clear that most AF substrates are located in the LA, and theoretically, a reduction in over load on the LA due to MR reduction and restoration of left ventricular function should have a more direct favorable effect [12)]. Future studies are needed to examine the mechanisms of how the improvement of TR contributes to the improvement of the "substrate" present in LA and how the occurrence of TR results in a worse prognosis for patients with AF.

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Figure legend Title: Pathophysiology of atrial fibrillation and the remodeling of the heart. ANS: Autonomic nervous system APD: Action potential duration CM: Cardiomyopathy MR: Mitral regurgitation RAA: Renin-Angiotensin-Aldosterone TR: Tricuspid regurgitation

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