Does Sinus Rhythm Beget Sinus Rhythm? Effects of Prompt Cardioversion on the Frequency and Persistence of Recurrent Atrial Fibrillation

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Abstract. Recent clinical and experimental studies have demonstrated that atrial fibrillation (AF) alters the electrical and mechanical remodeling of the atrium, which subsequently promote the maintenance and recurrence of AF. If atrial remodeling can be prevented with prompt and repeated cardioversion, the likelihood of AF recurrence may be reduced. Recent clinical studies have demonstrated that the strategies of transesophageal echocardiography facilitated early cardioversion and early repeated cardioversion may be clinically valuable in some patients who have persistent AF and recurrence of arrhythmia after the initial cardioversion. Furthermore, the use an implantable atrial defibrillator (IAD) for early repeated device-based cardioversion to maintain sinus rhythm appears to be safe and clinically feasible. Early cardioversion by IAD reduces AF burden, reverses atrial remodeling and prevents subsequent AF recurrence in selected patients without structural heart disease implanted with this device, indicating possible “sinus rhythm begets sinus rhythm”. Despite encouraging initial observations, further long-term clinical studies in a larger patient population are needed to confirm this finding. Furthermore, whether the use of IAD in the fully automatic mode to provide immediate termination of AF episodes could intensify the potential beneficial effect and the clinical efficacy of this approach in patients with structural heart disease needs to be evaluated.

Key Words. atrial fibrillation, cardioversion

Background

Atrial fibrillation (AF) is the commonest sustained arrhythmia, and is associated with an increased mortality due to higher incidence of strokes and heart failure [1,2]. Together with heart failure, AF has been described as the two emerging epidemic of cardiovascular disease due to the aging of the population [3]. Furthermore, individuals with AF or heart failure who subsequently develop the other condition are associated with a poor prognosis [4]. Clinical management for patients with AF varies. The commonest strategy for management of AF is anticoagulation and either rate control or rhythm control with antiarrhythmic medications. Neither of these two strategies is ideal. Rate control alone does not eliminate symptoms in a significant proportion of AF patients, and antiarrhythmic drugs often do not maintain sinus rhythm and may provoke life-threatening ventricular arrhythmias [5,6]. In patients who remain symptomatic despite adequate rate control, chemical or electrical cardioversion is commonly performed to relieve symptoms and improve cardiac performance. Nevertheless, long-term maintenance of sinus rhythm remains a challenge. The purpose of this article is to discuss the potential role of early cardioversion to restore sinus rhythm for maintenance of sinus rhythm: “sinus rhythm begets sinus rhythm” for management of AF.

AF Begets AF

Prior clinical observations have suggested that AF is a progressive disease which has a tendency to become persistent over time. A significant proportion of patients with lone AF without any structural heart disease developed persistent AF during long-term follow-up [7]. Furthermore, the success rate of pharmacological and electrical cardioversion, and subsequent maintenance of sinus rhythm are reduced with increasing duration of AF [8–10]. In patients with structural heart diseases, the progression of AF can be related to the development of underlying atrial substrate such as fibrosis as a result of underlying heart diseases or aging. In turn, atrial fibrosis is associated with slowing and dispersion of conduction and an increase in heterogeneity of refractoriness to promote the development of AF [11,12]. These notions comply with the fact that the prevalence of AF increases with age, in particular persistent AF.

Recently, another important concept of “AF begets AF” emerged from an experimental model of AF [13–15]. These studies demonstrated that repetitive induction of AF by atrial burst pacing resulted in atrial remodeling by which atrial changes during AF promote the persistence and recurrence of AF. Understanding the mechanisms of atrial remodeling has provided important insights into AF and its management. Atrial remodeling is principally due to the
rapid atrial rate and is mediated by reduced L-type outward calcium current and changes in calcium handling and cellular ultra-structure changes that result in atrial myocyte calcium overload. Electrical remodeling with shortening of atrial refractoriness develops within the first days of AF and contributes to the increase in stability of the arrhythmia. However, the occurrence of sustained AF also depends on other mechanisms since the duration and persistence of AF continues to increase after electrical remodeling has been completed. Atrial mechanical remodeling also occurs at the same time course as electrical remodeling but progress over time. Atrial mechanical dysfunction not only enhances the risk of atrial thrombus formation, but also enhances atrial dilatation by increasing the compliance of the fibrillating atrium. Chronic atrial stretch induces activation of numerous signaling pathways leading to cellular hypertrophy, fibroblast proliferation and tissue fibrosis. The resulting electroanatomical substrate in dilated atria is characterized by increased non-uniform anisotropy and macroscopic slowing of conducting, promoting reentrant circuits in the atria. These electrical and mechanical changes during AF promote the persistence of the arrhythmia [15]. Clinical studies also confirmed these experimental findings and demonstrated the presence of atrial electrical and mechanical remodeling in patients with AF [16–18].

Sinus Rhythm Begets Sinus Rhythm?

Following conversion of AF, reverse remodeling of atrial electrical properties occurred in animal model of AF [19]. The recovery of atrial electrophysiological properties included a progressive recovery of shortening and maladaptation of atrial refractoriness, and decrease of duration and episodes of induced AF. Hobbs et al. [20] measured the atrial refractory period in patients underwent repeated internal cardioversion for persistent. After successful cardioversion, the changes in atrial electrophysiology associated with chronic AF in humans are reversible and that the extent of this reversal is dependent on the duration of sinus rhythm after cardioversion. However, the atrial mechanical function may require 1 week or more to recover, and is also dependent on the duration of AF before cardioversion [21]. These effects may well explain the high rate of early recurrence following conversion of AF. A corollary of the notion that ‘AF begets AF’ is the idea that ‘sinus rhythm begets sinus rhythm’. In this respect, prompt restoration of sinus rhythm once AF occurs should rapidly restore physiologic hemodynamics, avoid atrial remodeling that favor the maintenance of AF to reduce arrhythmia recurrence, and minimize the risk of stroke.

Early External Cardioversion

Previous clinical studies have demonstrated the duration of AF is an important predictor for AF recurrence [8–10]. Furthermore, when cardioversion is performed within 48 hours of the onset of AF, the risks of thromboembolism are lower than if cardioversion is delayed, and the undesirable complications of anticoagulation may be avoided [22]. Therefore, early cardioversion not only immediately relieves symptoms and improves exercise capacity, but also has theoretical advantage of avoiding the risk and inconvenience associated with anticoagulation prior to cardioversion, preventing atrial remodeling and may have a lower recurrence rate. The conventional strategy of anticoagulation for 3 weeks before cardioversion obligates a substantial delay and extends the duration of AF [23]. Recently, the use of transesophageal echocardiography (TEE) to detect the presence of thrombi in the left atrial appendage before cardioversion has facilitated early cardioversion for AF. Clinical studies [24,25] have demonstrated the TEE-facilitated cardioversion is a safe and convenient alternative to the conventional approach (Table 1).

Weigner et al. [24] studied the 1-year clinical outcome in 539 patients with AF who underwent TEE facilitated early cardioversion to restore sinus rhythm in patients with AF ≥2 days or of unknown duration before cardioversion. They demonstrated that patients with AF for less than 3 weeks were less likely to have recurrence of AF, and were more likely to have sinus rhythm 1 year after cardioversion. However, this study did not a randomize patients to the TEE strategy or conventional therapy. The ACUTE trial [25] was a multicenter, randomized, prospective trial to compare TEE facilitated early cardioversion versus conventional cardioversion in 1222 patients with AF ≥2 days. The median duration of AF in both arms was 13 days. In contrast, this trial showed no significant difference in short-term clinical outcomes between the two strategies. Despite a significant reduction in the time to cardioversion from 31 days to 3 days and a higher initial success rate of cardioversion with the use of TEE-facilitated early cardioversion, there was no significant difference between the two groups in the prevalence of sinus rhythm at 8 weeks. However, in both studies, the majority of patients had AF for >2 weeks before cardioversion. Therefore, it remains to be shown whether even earlier cardioversion of AF affect the initial and long-term success of cardioversion.

Repeated External Cardioversion on AF Recurrence

In addition to using TEE to facilitate early cardioversion, the other approach to avoid atrial remodeling