Is There a Role for Repeated Cardioversion in Patients with Recurrent Atrial Fibrillation?

HUNG-FAT TSE, CHU-PAK LAU

From Cardiology Division, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

TSE and LAU: ***Is There a Role for Repeated Cardioversion in Patients with Recurrent Atrial Fibrillation?*** *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 this encouraging initial observation, 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 remains to be evaluated. (J HK Coll Cardiol 2003;11:90-96)*

Atrial fibrillation, Cardioversion

摘要

最近的臨床和實驗研究證實房顫將改變心房電和機械的重構，由此將促進房顫的維持和復發。如果用即時反復的心臟複律能夠防止心房的重構，那麼房顫復發的發生比例可能會減少。最近的臨床研究經食管超聲心動圖這一策略，對於一些持續性房顫和初次複律後心律失常復發病人，在幫助其早期心臟複律和早期心臟反復複律中可能具有臨床價值。此外，對於早期反復的設備依賴的心臟複律治療，運用可植入式心房除顫器能夠保持竇性心律，顯示出安全和臨床的可行性。通過可植入式心房除顫器進行早期心臟複律可以減少房顫的負擔，逆轉心房的重構，在一些沒有心臟結構性疾病的病人中植入這一裝置可以防止以後房顫的復發，提示可能“竇性心律產生竇性心律”。除了這些令人振奮的初步觀察，還需要大量病人進一步的長時間的臨床研究來證實這一發現。此外，是否在可植入式心房除顫器的運用中完全採用自動模式，當房顫發作提供迅速終止能夠強化可能的益處，以及對有心臟結構性疾病的病人採用這一方法的臨床效果，這些問題還有待評估。

關鍵詞：房顫　心臟複律

Address for reprints: Dr. Hung-Fat Tse
Division of Cardiology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong

Tel: (852) 2855 4244, Fax: (852) 2855 1143

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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 lead to 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 repeated cardioversion to restore sinus rhythm for maintenance of sinus rhythm in patients with persistent AF.

Electrical and Mechanical Remodeling in 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" is emerging from the 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 ultrastructure 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 conduction, 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]

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 reinduced 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

Prior 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 anti-coagulation for 3 weeks before cardioversion always lead to a much longer delayed in elective cardioversion.[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).

Table 1. Comparison of characteristics of patients undergoing TEE facilitated early cardioversion in the studies of Weigner et al[24] and Klein et al[25]

	Weigner et al[24]	Klein et al[25]
Number of patients	533	619
Age, years±SD	72±13	65±16
Female sex, %	46	33
Etiology of AF, %		
Hypertension	54	51
Ischemic heart disease	31	NA
Valvular heart disease	7	NA
Cardiomyopathy	6	NA
Lone	15	NA
First episode of AF, %	60	NA
Estimated duration of AF	Mean: 4±9 weeks (range: 0.3-102 weeks)	Median: 13 days (range: 4-48 days)
Antiarrhythmic therapy, %	52	82.2
History of thromboembolism, %	8.3	7.9
Left atrial thrombi on TEE, n (%)	70/533 (13.1)	76/549 (13.8)
Success electrical cardioversion, n (%)	413/463 (89.2)	344/425 (80.9)
Thromboembolic events, n (%)	1 (0.2)	10 (1.6)
AF recurrence, %	1 year: 57	8 weeks: 47.3

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 was not a randomized study comparing the TEE strategy with conventional therapy. The ACUTE study[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 study 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 rate of maintenance of sinus rhythm after 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 is by repeated electrical cardioversion (Table 2). This strategy aims to maintaining patients in sinus rhythm to promote reverse remodeling of the atrium, which may subsequently lead to a reduction in the subsequent likelihood of AF recurrence. Van Gelder et al[9] performed the clinical trial to evaluate the role serial cardioversion in 236 patients with persistent AF. In this study, patients initially underwent external cardioversion without the use of antiarrhythmic agent, and then serial testing of different antiarrhythmic agents (sotalol→flecainide→amiodarone) and up to a maximum of four cardioversions were performed in those who had AF recurrence. The serial cardioversion

Table 2. Comparison of characteristics of patients undergoing repeat cardioversion in the studies of Van Gelder et al,[9] Fynn et al[26] and Bertaglia et al[27]

	Van Gelder et al[9]	Fynn et al[26]	Bertaglia et al[27]
Number of patients	236	59	45
Age, years	63±12	60±10	68±8
Female sex, %	44	29	36
Etiology of AF, %			
Hypertension	17	20	42
Ischemic heart disease	28	15	9
Valvular heart disease	33	10	11
Other	21	16	9
Lone	22	39	29
Mean duration of AF, months	NA	30±46	2.5±2.1
Antiarrhythmic therapy, %			
Class III	NA	8	68
Class IC	NA	0	31
Beta-blockers	NA	15	7
Calcium antagonists	NA	0	22
Digoxin	NA	0	60
Left atrial size, cm	4.6±8	4.04±0.5	4.76±5.8
AF recurrence, %	1 year: 58 4 years: 73	1 month: 76	12 months: 47

approach was effective to increase the duration of sinus rhythm in a subgroup of patients with shorter duration of AF. In a recent study, Bertaglia et al[27] randomized 90 patients with persistent AF treated with either class IC or III antiarrhythmic agents to either a single cardioversion or a maximum of three repeated cardioversions. In this study, the mean duration of AF before cardioversion was 10 weeks, and the mean duration in AF prior to the repeat cardioversion was 1 month. After 1 year follow-up, 53% of patients who underwent repeated cardioversion were in sinus rhythm compared to only 29% in patients with only single cardioversion. Therefore, both studies demonstrated that serial cardioversion is useful in maintaining sinus rhythm in patients with persistent AF. However, in order to maximize the benefit of this approach, serial cardioversion should be performed early after the occurrence of persistent or recurrent AF.

Fynn et al[26] assessed the atrial electrophysiological properties and clinical outcome in patients with persistent AF who underwent repeated internal cardioversion. In this study, 59 patients with persistent AF were monitored on a daily basis for 1 month after the initial cardioversion of AF, and were readmitted for repeated cardioversion (up to a maximum of three times) as soon as AF recurrence was detected. Successful cardioversion was achieved in 55 patients (93%) and 29 of them subsequently had AF recurrence during monitoring. In those patients who underwent repeated internal cardioversion, their atrial effective periods increased after serial cardioversion, suggesting reversal of atrial electrical remodeling during this period. However, there was no significant increase in the duration of sinus rhythm after serial cardioversion, and only 14 patients maintained sinus rhythm for 1 month. The authors concluded that a policy of early repeated cardioversion for recurrence of AF has a very limited role, despite evidence of reversal of electrical remodeling. The difference in the clinical outcome between this study and those discussed above is likely due to the difference in their patient selection and study design (Table 2). Fynn et al[27] included patients with unfavorable arrhythmia profile with long duration of AF (median 13 months), failed prior cardioversion (13%), a higher prevalence of structural heart diseases (61%) and only a minority were taking antiarrhythmic medications. In patients with prolonged duration of AF and underlying structural heart diseases, other additional factors, such as structural remodeling and fibrosis might be irreversible,[11,12] and render the atria vulnerable to recurrent AF despite reversal of electrical remodeling. Furthermore, only 27 of 59 patients (48%) finally completed the protocol as intended which limited the sample size and thus conclusion of this study.

Effect of Prompt Cardioversion by Implantable Device

The success of the implantable ventricular defibrillator and internal atrial cardioversion using low energy led to the concept of the development of implantable devices for atrial defibrillation.[28] The implantable atrial defibrillator (IAD) is designed to provide an effective method for early detection and cardioversion in patients with AF, with the hope that it might provide immediate benefits of sinus rhythm and positively alters the progressive natural history of AF.[29-31] Timmermans et al[32] evaluated the effect of repeated device-based atrial shock using an IAD on the clinical course of the arrhythmia in patients with AF. In this study, 51 patients with drug-refractory AF underwent implantation of a stand-alone IAD for treatment of AF. The majority of these patients had no structural heart disease and normal left ventricular function. The IAD performed periodic monitoring of AF and atrial shocks were delivered under physician supervision during spontaneous AF. The majority of treated AF episodes in this study were >8 hours with a median duration of ~18 hours. After a mean of 260 days follow-up, all patients remained in sinus rhythm, the time interval between episodes requiring device therapy increased, and the risk of having an episode requiring treatment decreased. These findings suggest that repeated device-based cardioversion for AF was effective in maintaining sinus rhythm and progressively decreased the need for cardioversion over time.

Tse et al[33] investigated the effects of the IAD on

the total duration of AF, number of AF recurrences and left atrial size in 16 patients with AF. In this study, 8 patients had paroxysmal AF and 8 patients had persistent AF with a mean AF duration of 72±91 months. Except for 1 patient who received digoxin, all patients received the same class I or III antiarrhythmic agent throughout the study. The IAD successfully converted 93% of spontaneous episodes of AF in 12 patients. After 6 month of follow-up, maintaining sinus rhythm by repeated device-based cardioversion using IAD in patients with persistent AF reduced the total burden of AF and the left atrial size. These favorable effects were not observed in patients with paroxysmal AF. The results of this study suggest that repeated cardioversion with an IAD might reverse the process of mechanical atrial remodeling and modify the natural history of AF in patients with persistent AF. It is likely that in patients with paroxysmal AF, a significant proportion of their AF episodes were short lasting and were not treated by the device, therefore, IAD had a lesser impact on the natural history of their AF.

Furthermore, the occurrence and time course of recovery of atrial mechanical dysfunction after cardioversion of AF appear to be related to the duration of arrhythmia. A recent study[34] in patients with IAD have demonstrated that prompt termination of AF episodes using device-based cardioversion may further enhance the recovery of left atrial mechanical dysfunction as assessed by Doppler echocardiography. At 1 minute after cardioversion, the transmitral flow Doppler parameters were significantly smaller during episodes of AF treated at >48 hours than at <48 hours. At 4 hours and 1 week after cardioversion, the mean peak A-wave velocity and the mean deceleration of the A wave increased during episodes of AF at <48 hours, and became significantly greater than those during AF episodes at <48 hours. In addition, early cardioversion of AF using the IAD prevented AF induced left and right ventricular dysfunction.[35] These findings provide further evidence to support a prompter cardioversion of AF using an IAD to enhance the recovery of the atrial and ventricular function from the mechanical remodeling changes.

Conclusions

Based on the available data as discusses above, TEE facilitated cardioversion and early repeated cardioversion may be clinically valuable in some patients who have short duration of persistent AF and recurrence of arrhythmia after the initial cardioversion. Both studies from Fynn et al[26] and Bertaglia et al[27] suggested that in patients who have a recurrence of AF after a second cardioversion, there is little to be gained from a third cardioversion. A strategy of early repeated external cardioversion for AF poses major practical problems in both early detection and external cardioversion for obvious logistic reasons. In the Fynn's study,[26] the mean duration in AF prior to the repeat cardioversion was 13-20 hours, which is a rather long period to allow the occurrence of atrial remodeling. Therefore, serial cardioversion using this method may not have been performed early enough to prevent AF recurrence.

Clinical studies[29-34] using an IAD for early repeated device-based cardioversion to maintain sinus rhythm have shown to be safe and clinical feasible. Furthermore, this approach allows prompter cardioversion of AF and has shown to reduce AF burden, reverse atrial remodeling and prevent subsequent AF recurrence, indicating "sinus rhythm beget sinus rhythm" in a subgroup of selected patients without structural heart disease implanted with this device. Despite this encouraging initial observation, further long-term clinical studies in a large patients population are needed to confirm this finding. It is not known whether the use of an IAD in patients with structural heart diseases, in whom irreversible atrial structural changes have been developed, might observe similar clinical benefit. Furthermore, in these initial clinical studies of IAD,[32-36] device-based cardioversion was performed under physician supervision or patient- activated due to safety and patient's tolerance issues. As a result, the duration between the onset of AF and device-based cardioversion remained long (~18 hours). Whether the use of IAD in the fully automatic mode to provide prompter termination of AF episodes may intensify the potential benefit effect remains unclear.

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