Is there a place for the late cardioversion of atrial fibrillation?

A long-term follow-up study of patients with post-thyrotoxic atrial fibrillation

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Aims As atrial fibrillation is associated with significant mortality and morbidity, restoration of sinus rhythm is desirable. However, previous data suggest that cardioversion should be restricted to patients in whom the fibrillation is of limited duration (<1–2 years) because of high relapse rates. It may be the frequent association with cardiac disease, rather than the duration of fibrillation itself, which determined the high relapse of earlier studies. The aim of this study was to investigate rates of cardioversion, maintenance of sinus rhythm and predictors of subsequent relapse in a homogeneous group of patients without evidence of any co-existent cardiac disease.

Methods and Results We report on a retrospective series of 106 patients with thyrotoxicosis-induced fibrillation but no other heart disease: 87% had been in atrial fibrillation for >12 months (median duration 28.5, interquartile range 15–47 months). Cardioversion was attempted using disopyramide and then electric shock. Ninety-eight patients were successfully cardioverted: at late follow-up, 80.6 ± 37 months (mean ± SD), 67% were in sinus rhythm.

Conclusion Although a relationship between the duration of fibrillation and maintenance of sinus rhythm was found, the high proportion remaining in sinus rhythm, compared with other series, suggests this influence may be less important than the presence or absence of structural heart disease.

Key Words: Longstanding atrial fibrillation, cardioversion, maintenance of sinus rhythm, disopyramide.

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Introduction

Atrial fibrillation is the commonest sustained arrhythmia with a reported prevalence rising to 9%[6] and above[2] in the over 70s. A significant associated morbidity and mortality argue against this arrhythmia being benign[3–7]. There may be much to be gained from a sustained return to sinus rhythm. Many patients develop atrial fibrillation as a result of underlying heart disease where changes in the atrium may pre-dispose to recurrent fibrillation following successful cardioversion.

Other patients with structurally normal hearts develop atrial fibrillation as a complication of some other acute event, such as anaesthesia, surgery, pneumonia, or thyrotoxicosis and then remain in atrial fibrillation. Clinical practice usually restricts cardioversion to patients with atrial fibrillation of less that 1 or 2 years duration, leaving others in chronic atrial fibrillation[8]. But these patients with apparently normal hearts and longstanding atrial fibrillation may not be resistant to cardioversion or subsequent maintenance of sinus rhythm and might benefit from an aggressive policy of cardioversion. The present study was designed to examine this possibility. We report a retrospective series of 106 patients who had developed atrial fibrillation as a complication of thyrotoxicosis but who were carefully selected from a larger group to exclude patients with evidence of any additional cardiac disease.


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Cardioversion was attempted in all patients provided they had been euthyroid for at least 3 months since spontaneous reversion to sinus rhythm is then unlikely. Follow-up of this group continues but at the time of reporting represents a median follow-up period of 79.7 (range 77–162.3) months.

**Patient selection**

Patients included in this study were selected from those referred for cardiological assessment at Ito Hospital, Tokyo, a large tertiary referral centre specialising in the management of thyroid disease. Patients with any evidence of additional cardiovascular disease including valvular heart disease, cardiomyopathy and coronary artery disease, were excluded from the study as were patients with atrial fibrillation clearly antedating the onset of thyrotoxicosis, i.e. where an ECG showing atrial fibrillation had been recorded a year or more before inclusion, and accompanied by normal thyroid function. Patients were assessed on the basis of history and clinical examination, chest radiograph, an electrocardiogram and transthoracic echocardiogram. Given the low prevalence of ischaemic heart disease in the Japanese population it was felt that a normal echocardiogram, in the absence of any history of angina or myocardial infarction or associated ECG changes, effectively excluded significant coronary heart disease. Patients with known hypertension were excluded and those who met electrocardiographic or echocardiographic criteria for left ventricular hypertrophy were also excluded. Patients who were found to have echocardiographic evidence of mitral valve prolapse with haemodynamically insignificant mitral regurgitation were not excluded from the study since an increased incidence of mitral valve prolapse is itself associated with thyrotoxicosis. In these patients there was either minimal or no regurgitation. Similarly, patients with modest increases in left atrial size were not excluded from the study on the basis that such changes might be the result of, rather than the cause of, the arrhythmia. If there was any uncertainty about the onset, subsequent duration or aetiology of atrial fibrillation those patients were not included in the study. Certain patients were referred for cardioversion many months or years after being rendered euthyroid: thus the prolonged duration of atrial fibrillation does not parallel the duration of hyperthyroidism. (Between 1979 and 1984 cardioversion was restricted to patients with atrial fibrillation which had been present for less than 5 years. Subsequently, because of the encouragingly high maintenance rate of sinus rhythm observed, this restriction was lifted.) From the outset a decision was made not to cardiovert patients if they relapsed whilst euthyroid and for consistency this policy was maintained throughout the study.

Earlier work, from the same institution, has shown that about 70% of patients with thyrotoxic atrial fibrillation, will spontaneously revert to sinus rhythm within the first 3 to 4 months following control of their thyrotoxicosis, but that if the atrial fibrillation persists beyond this period spontaneous cardioversion is highly unlikely. Attempted cardioversion was therefore deferred until the patients had been euthyroid for at least 3 months. This was assessed on the basis of serum tri-iodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone levels in the early phase of this study and subsequently using free T3, T4 and thyroid stimulating hormone. This euthyroid status was confirmed every 4 weeks and also re-measured on the day of cardioversion. Subsequently this was assessed every few months or as clinically indicated.

**Management of thyrotoxicosis**

Thyrotoxicosis was managed using a combination of antithyroid agents, radioactive-iodine (I131), and/or subtotal thyroidectomy. These treatments were adjusted to each individual using widely accepted guidelines.

**Protocol for cardioversion**

Cardioversion was undertaken once the patients had been euthyroid for at least 3 months and were fully anticoagulated. Chemical cardioversion was always attempted using disopyramide 600 mg per day for 3 days. The disopyramide was added to maintenance digoxin, on an outpatient basis. If disopyramide was ineffective digoxin was omitted and cardioversion then attempted using synchronized direct current shock under brief general anaesthesia. Cardioversion was deemed successful if sinus rhythm was established and maintained for at least 30 min. Following successful cardioversion the intention was to treat the patients with disopyramide for a minimum of 3 months (300 mg. day−1). The rationale for this approach was an earlier study which had shown that patients with post-thyrotoxic atrial fibrillation who were treated with disopyramide were more likely to maintain sinus rhythm than those not given any antiarrhythmic drugs in the early post-cardioversion period. Subsequently patients were treated for longer periods with disopyramide where it was well tolerated.

Attempts to cardiovert patients who had relapsed into atrial fibrillation were restricted to those patients in whom the atrial fibrillation could be attributed to a recurrence of their thyrotoxicosis. When they had again been rendered euthyroid the same approach as already described was employed: in principle there was no limit to the number of such episodes. Patients who developed recurrent atrial fibrillation, in the absence of thyrotoxicosis were not cardioverted (and their only follow-up for the purposes of this study was confirmation that they remained in atrial fibrillation).

**Analyses**

Differences in categorical variables between groups were analysed using the Chi-square test. Continuous data...
were analysed using unpaired two tailed t-tests for normally distributed variables and Mann–Whitney for data which were not normally distributed. Estimates of the proportion of patients remaining in sinus rhythm over time were constructed using the method of Kaplan and Meier[10]. Associations between age, sex, left atrial size, the duration of atrial fibrillation prior to cardioversion, initial outcome and subsequent relapse into atrial fibrillation were explored using a Cox proportional-hazards regression model[17].

Results

Patient profile

Between November 1979 and January 1993, 106 patients with post-thyrotoxic atrial fibrillation were managed as described above and followed-up over a mean period of 6.7 years (80.6 ± 37 months: range 7-7–162.3). The last patient enrolled in the study was recruited in June of 1992 and the data we present analysed with effect from 31 January 1993.

Two to three percent of patients referred to the hospital with thyrotoxicosis also had atrial fibrillation. At the beginning of the study about 30% remained in atrial fibrillation following a 3 month euthyroid period, whereas by the end of the study a higher rate of spontaneous reversion was seen and this figure had dropped to 10%. This is thought to reflect a tendency to earlier diagnosis, and so treatment, of the thyrotoxicosis. The majority (well over 95%) of these patients who remained in atrial fibrillation following a 3 month euthyroid period were eligible for and included in the study. This low rate of associated cardiac disease is thought to reflect the specialized practice of the hospital (exclusively thyroid disease).

The study population consisted of 65 men and 41 women aged between 19 and 70 (mean 47 ± 6 years). Recordings from which reliable measurements of left atrial size could be made were available for all but 12 patients. The mean left atrial size was 3.7 ± 0.6 cm (SD), with a range 2.1 to 5.7 cm. There was evidence of mitral valve prolapse in 20 patients. Mitral regurgitation was detectable (but not deemed haemodynamically significant) in 11 patients.

Initial outcome of cardioversion

Even though 87% of the patients had been in atrial fibrillation for more than 12 months and 55% for more than 24 months initial cardioversion rates were encouraging. Sinus rhythm was re-established in 98, or 92.5%, of the 106 patients. Seventeen of these patients with atrial fibrillation converted to sinus rhythm with disopyramide alone and 81 in response to direct current shock.

Subsequent outcome

On subsequent follow-up of the patients successfully cardioverted, recurrent thyrotoxicosis accounted for 30 episodes of atrial fibrillation in 25 patients: of these 30 episodes, 12 reverted to sinus rhythm with disopyramide alone and 17 with direct current cardioversion. Only one patient who relapsed into atrial fibrillation, as a function of recurrent thyrotoxicosis, could not be cardioverted. The 31 patients who relapsed whilst biochemically euthyroid were not subjected to further attempts at cardioversion and remained in atrial fibrillation.

At late follow-up (31 January 1993), 66 (62.3%) of the original cohort, or 67.3% of those initially cardioverted, were in sinus rhythm (see Figs. 1 and 2): the median duration of follow-up for these patients was 79.7 months (range 77–155.7). As a group, those patients who relapsed into atrial fibrillation whilst euthyroid were found to have had a significantly longer period of atrial fibrillation prior to initial cardioversion when compared with those who were in sinus rhythm at late follow-up (median 38.5, range 5–120 v 20, range 5–90 months, P=0.003) but within both groups there were many patients with very prolonged atrial fibrillation (see Fig. 2). Left atrial size did not distinguish between those who did and those who did not relapse into atrial fibrillation (mean left atrial size of 3.6 ± 0.6 cm for the patients relapsing into atrial fibrillation against 3.7 ± 0.6 cm for those who maintained sinus rhythm).

The only variable shown to independently influence late outcome by multiple regression was the duration of atrial fibrillation prior to cardioversion, although there was some evidence across the quartiles that increasing age, at the time of cardioversion, was associated with an increased tendency to relapse (see Table 1). Although the duration of atrial fibrillation prior to cardioversion emerges as predictive of subsequent relapse, even this influence appears to have limited impact on the patients studied. Hence, at 1 year post cardioversion Cox proportional hazard modelling suggests that 95% of patients who have been in atrial fibrillation for 5 to 14 months, and 82.5% of those whose atrial fibrillation has persisted for between 45 and 120 months would remain in sinus rhythm. With follow-up extending to 5 years these figures deteriorate only marginally, with persistent sinus rhythm being maintained in over 90% and 65% for the same groups (see Fig. 3).

Complications of treatment

There were no thromboembolic events related to cardioversion. Treatment with disopyramide, post-cardioversion, was maintained for a total of 1321 patient months without any fatal or symptomatic arrhythmias (other than the reported atrial fibrillation). The median duration of maintenance disopyramide was 5 months (range 0–92) and the 300 mg dose was well tolerated. Six patients were documented as not taking maintenance
disopyramide: 93.9% of the patients took disopyramide for at least 1 month and 71.4% for 3 months.

**Discussion**

This study shows that, in the absence of underlying heart disease, cardioversion of longstanding atrial fibrillation can be justified on the basis of initial cardioversion rates and the number of patients who remain in sinus rhythm, even at very late follow-up. These findings argue that although the duration of atrial fibrillation per se has an influence on long-term outcome it is probably a less important determinant than has previously been suggested.

The decision to attempt cardioversion in atrial fibrillation depends not so much on the ability to terminate the arrhythmia, initial success rates of over 70% being usual\[18–20\], but rather on the capacity to sustain sinus rhythm. The cardioversion of unselected atrial fibrillation patients results in consistently high rates of relapse into atrial fibrillation and at 1 year 40 to 80% or more patients successfully cardioverted will have reverted to atrial fibrillation\[18–25\]. A number of authors have tried to establish those characteristics which identify patients at high risk of relapse following cardioversion\[22,24,26\] and have suggested the duration of atrial fibrillation prior to cardioversion is a critical predictor of outcome. It is now common practice to limit cardioversion to patients with atrial fibrillation of less than 1 or 2 years’ duration. However, these conclusions have been based on series of unselected patients (many of whom are characterized by chronic cardiac disease) where assumptions are made about the ability to separate the influence of the duration of atrial fibrillation from that of underlying structural heart disease. These criticisms do not apply to the current study where a different approach was used: a homogeneous group of patients was studied whereby the trigger precipitating the atrial fibrillation (thyrotoxicosis) was recognized and had been specifically treated. The patients were also selected for an absence of concomitant cardiac disease rather than the duration of atrial fibrillation.

Despite a relatively long follow-up period, 67% of patients remained in sinus rhythm which compares favourably with any other published series and especially so given a duration of atrial fibrillation, prior to cardioversion, of more than 12 months in 92 (87%) of the 106 patients studied.

We recognize that the ‘normal’ values of ventricular function would not necessarily have excluded impaired left ventricular function, which may follow longstanding
atrial fibrillation since indices of cardiac function are themselves modified by interval variation during atrial fibrillation\textsuperscript{[27,28]}\textsuperscript{[27,28]}. The predominance of male patients is not unusual\textsuperscript{[29]}\textsuperscript{[29]} but raises the possibility that the men had some pre-disposition to developing atrial fibrillation: data were not available on alcohol consumption but a sex bias in the drinking habits of the patients studied cannot be excluded. There appears to be some evidence that relapse into atrial fibrillation was more likely with increasing age, a finding in keeping with earlier work and increasing prevalence of atrial fibrillation with increasing age\textsuperscript{[1,2]}\textsuperscript{[1,2]}.

Recent studies from a goat model of atrial fibrillation\textsuperscript{[30]}\textsuperscript{[30]} lend important insights into the relationship between the duration of atrial fibrillation at cardioversion and the likelihood of maintaining sinus rhythm. Rapid atrial pacing was used to induce atrial fibrillation in goats with normal healthy hearts and early episodes of atrial fibrillation were of short duration and self terminating, but with repeated precipitation of atrial fibrillation the episodes increased in length and eventually led to persistent atrial fibrillation, over a period of days or weeks\textsuperscript{[30]}\textsuperscript{[30]}. This was accompanied by electrophysiological changes in the atrium which tend to sustain atrial fibrillation\textsuperscript{[31,32]}\textsuperscript{[31,32]} or predispose to further episodes of atrial fibrillation. However, if sinus rhythm was then restored there was a gradual reversal of these electrophysiological changes.

If the same mechanisms apply in man there may be relatively short periods following the development of atrial fibrillation during which atrial fibrillation will either spontaneously revert or sinus rhythm can be easily restored. Our previous work in patients with thyrotoxicosis-induced atrial fibrillation, which shows that there is a high spontaneous rate of reversion to sinus rhythm within the first few weeks after the patients have become euthyroid, and virtually none beyond 3 months\textsuperscript{[12]}\textsuperscript{[12]}, is consistent with the goat studies. In the present study the majority of patients had been in atrial fibrillation for more than 12 months so all would be expected to have developed the electrophysiological changes that sustain chronic atrial fibrillation.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{The number of patients in sinus rhythm or atrial fibrillation at late follow-up relative to the duration of atrial fibrillation (AF) at the time of cardioversion.}
\end{figure}

\begin{table}[h]
\centering
\caption{Prediction of relapse into atrial fibrillation}
\begin{tabular}{llll}
\hline
Variables & Hazard ratio & 95\% CI & \(P\) value (likelihood ratio test) \\
\hline
Duration of atrial fibrillation pre-cardioversion* & 1.6 & 1.14–2.26 & 0.005 \\
Age* & 1.37 & 0.98–1.92 & 0.058 \\
Sex (male vs female) & 0.61 & 0.30–1.25 & 0.178 \\
Left atrial size* & 0.84 & 0.61–1.17 & 0.303 \\
\hline
\end{tabular}
\end{table}

Cox proportional multivariate analysis based on 98 patients of whom 32 relapsed.
*Variables entered as quartiles for distribution of:
\begin{itemize}
\item Duration of atrial fibrillation: 5–14, 15–28, 28–42, 45–120, months;
\item Age: 19–41, 41–48, 48–70, years;
\item Left atrial size: 2.1–3.3, 3.3–3.7, 3.7–4.2, 4.2–5.7, cm.
\end{itemize}
Paradoxically, this may explain why the duration of atrial fibrillation was less critical than in other studies. Certainly it is hard to explain why a cut-off period of 1 or 2 years should be clinically appropriate and our own data suggests that this is not so (see Fig. 3). Indeed the Cox proportional hazard model predicts that over 60% of the patients cardioverted even following 4–10 years of atrial fibrillation will remain in sinus rhythm. Patients in this study were given disopyramide for at least 3 months post cardioversion: this may explain, in part, the high rates of maintenance of sinus rhythm that we have described: this drug may offer protection against relapse into atrial fibrillation in the early post-cardioversion period when the atrial electrophysiology increases the vulnerability of the atrium to further episodes of atrial fibrillation[30]. The common clinical observation that a higher relapse rate is found in the early post-cardioversion period than subsequently is consistent with a gradual reversal of these electrophysiological changes, and might justify aggressive antiarrhythmic therapy for all patients with atrial fibrillation post cardioversion for a finite period. With growing awareness of the pro-arrhythmic risks of ‘antiarrhythmics’[33] the lack of any symptomatic arrhythmias in 1321 patient months of treatment with disopyramide in this study is encouraging. It is of note that this population was free of left ventricular dysfunction, which is a major risk factor for the development of serious arrhythmias with Class 1 antiarrhythmics. The study of patients with post-thyrotoxic atrial fibrillation has allowed us a unique opportunity to examine the influence of the duration of atrial fibrillation on long-term outcome of cardioversion without the influence of numerous confounding variables which so often complicate the analysis and interpretation of data from patients with atrial fibrillation. Notwithstanding the observed association between atrial fibrillation duration and late outcome our very encouraging results suggest that for patients who have already been in atrial fibrillation for 3 months or more, the duration of atrial fibrillation may be a much less important determinant of the long-term outcome of cardioversion than the presence or absence of structural heart disease. In earlier studies of unselected patients, associated cardiac disease and related pathoelectrophysiology may have contributed rather more to the poor outcome following cardioversion than has generally been recognized. Whilst we do not disagree with current clinical thinking that early cardioversion and where possible within the first few days of onset of atrial fibrillation is likely to result in the best long-term outcome, the findings of this paper suggest that even after this first early window of opportunity successful cardioversion and maintenance of sinus rhythm can be achieved despite longstanding atrial fibrillation. Thus factors other than the duration of atrial fibrillation alone should determine the decision of suitability for cardioversion, in particular the presence of absence of concomitant heart disease.

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References


