Atrial fibrillation threshold predicted long-term efficacy of pharmacological treatment of patients without structural heart disease

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Aims To ascertain if an electrophysiological study could predict long-term efficacy of anti-arrhythmic drugs in the treatment of lone atrial fibrillation.

Methods and results Forty-four patients (36 males, 8 females, age 55.5 ± 10.6) with paroxysmal atrial fibrillation were enrolled to undergo serial electrophysiological studies at the bedside. Two quadripolar catheters were inserted via the subclavian vein. Disopyramide (D: 2 mg/kg iv), cibenzoline (C: 1.4 mg/kg iv), aprindine (A: 2 mg/kg iv), pilscainide (P: 2 mg/kg po) and flecainide (F: 3 mg/kg po) were tested. Atrial fibrillation threshold (AFT) was measured as the lowest current amplitude of rapid pacing (50 Hz for 1 s) to induce atrial fibrillation lasting more than 30 s.

Before drug treatment, AFT was 3.9 ± 0.3 mA. Pharmacological treatment raised AFT as follows: D 5.9 ± 0.9 mA, C 7.6 ± 1.2 mA, A 8.1 ± 1.1 mA, P 6.0 ± 0.8 mA, F 7.3 ± 1.1 mA. Recurrence of atrial fibrillation was observed during 1-year follow-up in 12% of cases when they were treated with a drug that raised AFT by 5 mA or more. On the other hand, the recurrence rate was 87% when patients were treated with a drug that raised AFT by less than 5 mA (P = 0.001).

Conclusion AFT was a good predictor of long-term efficacy of pharmacological treatment against atrial fibrillation.

Introduction Atrial fibrillation is a common arrhythmia[1], which can cause severe symptoms such as palpitations as well as systemic thrombo-embolism to deteriorate the quality of life of patients. Although pharmacological treatment has been the most popular strategy against this arrhythmia[2], catheter ablation[3], surgical management[4], and implantable devices including defibrillators[5] are under intense investigation as therapeutic options. This research is motivated partly because the efficacy of available drugs is as low as 40% or even less to maintain sinus rhythm in the long term. The low efficacy, however, could be due to the diversity of aetiology of this arrhythmia. It might, therefore, be expected to experience difficulty in obtaining a single regimen that is effective against all cases of atrial fibrillation. Thus, we started to look at a method of customizing an individual regimen for each patient. Conventional approaches using Holter recordings are time-consuming for this purpose because of the sporadic nature of this arrhythmia.

Invasive electrophysiological tests have been used to evaluate drug efficacy against reentrant arrhythmia[6,7] in clinical electrophysiological laboratories. In the same way, inducibility of atrial fibrillation can be compared in the presence and the absence of a drug to predict its efficacy[8,9]. As it is often very difficult to induce atrial fibrillation reproducibly with an extra-stimulus method[8,10], rapid pacing at 50 Hz was introduced in our laboratory as a more reliable method[11–14]. We have proposed that atrial fibrillation threshold (AFT) can be used as a quantitative marker of atrial vulnerability[12]. Pharmacological treatment raised AFT in a guinea-pig model[13,14] and also in clinical cases[11]. AFT, therefore, could be a quantitative marker to predict long-term efficacy of pharmacological treatments of patients with atrial fibrillation. In this study, we compared the...
drug-induced increase of AFT in acute trial tests between responders and non-responders in long-term treatment.

Methods

Patient population

Forty-four patients (36 males and 8 females) who complained of frequent palpitation attacks due to paroxysmal atrial fibrillation were admitted to our institution. Atrial fibrillation was documented on ambulatory ECG monitoring, concurrent with symptoms. It occurred more than once a month (median: 1 week, interquartile range: 0·29–4·0 weeks) for at least 6 months (median: 19 months, interquartile range: 12–63 months). The duration of their attack was at least 1 h. Mean age of the patients was 55·5 ± 10·6 years. No patients had either structural heart disease or non-cardiac conditions (‘lone’ atrial fibrillation).

Electrophysiological protocol

Serial electrophysiological tests were performed after informed consent was obtained. The protocol was approved by Human Research Committee at Kyoto Prefectural University of Medicine. A 5Fr, quadripolar J-lead catheter (Sultzer Osypka, Germany) and a 6Fr, quadripolar Josephson catheter (Bard, MA, U.S.A.) with inter-electrode distance of 1 cm were introduced via the right subclavian vein into the right atrial appendage and the distal coronary sinus, respectively. Programmed stimulation was generated by Cardiac Stimulator SEC3102 (Nihon Koden, Tokyo) or Stimulator CE-6100 (NEC, Tokyo) with rectangular pulses of 2 ms duration at twice the diastolic threshold. Intra-cardiac electrograms were recorded with a high frequency filter at 500 Hz and a time constant of 0·003 s as a low-cut filter. Records were digitized at a sampling rate of 2 kHz by an NEC 1600 polygraph system (NEC, Tokyo). Before the stimulation procedure, heparin (3000 IU) was injected intravenously, followed by infusion at 1000 IU/h.

The pacing protocol was the same as previously reported from our laboratory.12 The following parameters were measured. (1) Inter-atrial conduction time: the duration between a pacing artifact and an initial deflection of the electrogram at the distal coronary sinus when the right atrial appendage was continuously paced at a rate of 120 min⁻¹. (2) Effective refractory period: the longest coupling interval between the last basic stimulus and the extra-stimulus that failed to evoke atrial excitation. Basic stimuli were delivered at the right atrial appendage with 500 ms intervals following an extra-stimulus. (3) Wavelength index: the ratio of effective refractory period/inter-atrial conduction time. (4) Atrial fibrillation threshold (AFT): the lowest current amplitude that could induce atrial fibrillation lasting for more than 30 s. Rapid pacing was delivered to the right atrial appendage at a rate of 50 Hz for 1 s after 8 basic stimuli at 500 ms intervals. Pacing pulses were delivered by an oesophageal constant current pacing unit (BC-02A and BC-02EP, Fukuda Denshi, Tokyo). Current increments were 1 mA. In all cases, irregular atrial activity was observed during rapid pacing with a current intensity of 1 mA or more. Generally, stronger currents could induce longer periods of atrial fibrillation. Figure 1 shows an example of the measurement. The time interval between consecutive attempts to measure atrial fibrillation threshold was 1 min.

Evaluation of drug efficacy

The intra-cardiac catheters were kept in situ for the entire hospitalization. Serial electrophysiological tests were performed to assess the drug efficacy at the bedside. All anti-arrhythmic drugs were discontinued prior to each drug trial for at least four half-lives. After the control measurements were obtained, in each test, the following agents were administered: disopyramide (2 mg/kg, intravenous), cibenzoline (1·4 mg/kg, intravenous), aprindine (2 mg/kg, intravenous), flecainide (3 mg/kg, orally), and pilsicainide (2 mg/kg, orally). The test was resumed 10 min after intravenous administration, or 60 min after oral administration. These intervals allowed us to maintain effective concentrations of the agent during the test. The drug was randomly assigned in the trials. Direct current shock was not used until all measurements were performed. A set of electrophysiological measurements was completed within 20 min. Thus it took 100 min for an oral, and 50 min for an intra-venous drug trial. The next drug trial was performed after four half-lives of the previous drug. In principle, the AFT measurement was continued until we found two drugs that increased AFT, or until all 5 drugs were tested.

The patients were discharged with the agent that increased AFT by 1 mA or more. If multiple drugs were available for long-term use, the drug that showed the largest increase AFT was the first used. The dosage was as follows: disopyramide 300 mg/day, cibenzoline 300 mg/day, aprindine 40 mg/day, flecainide 150 mg/day, and pilsicainide 150 mg/day. Patients visited the office every 2 weeks to report their symptoms and to have a 3 min ECG. Holter monitoring was also occasionally used. The drug was changed to another test drug when ECG or Holter monitoring revealed that recurrent palpitation attacks were due to atrial fibrillation. In the case that the patient had been free of symptoms due to atrial fibrillation for 1 year, the drug was considered effective.

Statistical analysis

Data were described as mean ± SEM Student t-test was used for the comparison of the paired data. To
determine the predictive accuracy of the agents, Fisher’s exact test was used. \( p < 0.05 \) was considered statistically significant.

**Results**

Forty-four patients were enrolled in this study, and 2.2 ± 1.2 agents were tested during a hospital stay for 9.9 ± 1.2 days. Eighteen patients (41%) were free of symptoms for 1 year with one of the anti-arrhythmic drugs tested (responders). Symptoms due to atrial fibrillation recurred in 17 patients (39%, non-responders). Among these patients, the frequency of their attacks was reduced with class I drugs in 12 patients, and heart rate was controlled during atrial fibrillation with verapamil in 15 patients. Nine patients (20%) dropped out without recurrence of symptoms from long-term follow-up. Two of them died of non-cardiac diseases, and the others (7 patients) could not be traced because of change of address.

The number of ineffective drugs that was used before enrolment in the study was 1.4 ± 0.3 for responders (n=18), and 1.5 ± 0.2 for non-responders (n=17).

(1) Acute effects of drugs on the electrophysiological parameters

Table 1 summarizes the acute effects of drugs on the electrophysiological parameters. In the absence of drugs, effective refractory period, conduction time and wavelength index were not statistically different in each group \( (p > 0.05) \). AFT of flecainide group, however, was lower than the other groups \( (p = 0.025) \).

Disopyramide and flecainide significantly increased effective refractory period \( (p < 0.001) \). All drugs increased inter-atrial conduction time \( (p < 0.001) \). Wavelength index became smaller in the presence of cibenzoline, pilsicainide or aprindine \( (p < 0.01) \). All drugs increased AFT \( (p < 0.001) \).

(2) Acute efficacy of drugs

The drugs that increased AFT by 1 mA or more in the acute tests were reserved for long-term treatment. An increase in AFT was obtained in 17/24 (71%) for disopyramide, 14/18 (78%) for cibenzoline, 11/15 (73%) for aprindine, 11/20 (55%) for pilsicainide, and 11/18 (61%) for flecainide, respectively.

(3) Long-term efficacy

Long-term follow-up for 1 year was possible in 12 patients on disopyramide, 10 patients on cibenzoline, 7 patients on aprindine, 10 patients on pilsicainide, and 8 patients on flecainide. When a drug failed during follow-up, it was changed to another drug that increased AFT in the acute trials. Thus multiple results could be obtained from a patient. The effectiveness of each drug in the long-term follow-up was 4/12 (33%) for disopyramide, 5/7 (71%) for cibenzoline, 3/7 (43%) for aprindine, 2/11 (18%) for pilsicainide and 4/8 (50%) for flecainide.

The results were divided into three categories. The first group consisted of the cases where no drug
increased AFT in an acute trial (failure). Drugs were not used for these patients in long-term follow-up. The second group consisted of the cases where a drug raised AFT in the acute trial, but the arrhythmia recurred during follow-up (recurrence). The third group comprised the cases where a drug raised AFT in the acute trial and no arrhythmia recurred for 1 year (success).

Figures 2 and 3 show the comparison of the electrophysiological parameters in the acute trials for these groups. The drug-induced increase in AFT was the largest in the successful cases without recurrence. The changes of wavelength index and conduction time were not different among the three groups. The effective refractory period was increased after medication in the cases that could proceed to long-term treatment, but it did not change when drugs failed in the acute trials.

Atrial fibrillation recurred in 12% (2/16) of the patients when AFT was increased by 5 mA or more in the acute trial, whereas the arrhythmia recurred in 87% (27/31) if AFT was not raised as much. To our knowledge, there has been no quantitative parameter that can predict long-term efficacy against this arrhythmia[8,9]. Although patients with this arrhythmia often have severe symptoms, nearly half of the patients do not have any apparent cardiac disease[17]. Cardiac function is preserved in this group of patients and class I antiarrhythmic drugs are the first choice in treatment[18].

Because of the sporadic nature of this arrhythmia, a conventional approach (trial and error with Holter) would take a long time to find an effective drug. The patients are often medicated for a long time without knowing whether it is truly effective. They often visit the emergency room simply because of vague feeling of palpitations. Moreover, the efficacy of any antiarrhythmic drugs against atrial fibrillation is as low as 40% if the drug is selected empirically[1,8,19,20]. Because there has been no criterion to select a drug against the arrhythmia individually, the result of treatment is often unsatisfactory. Thus, it would be useful to have a method by which we can select a drug in a relatively short time for the individual patient.

We have measured AFT in the human[11,12], and in a guinea-pig model[13,14], and found that this parameter can be safely and repeatedly measured. We have shown that this parameter was the best marker of atrial vulnerability[12]. It was also influenced by drug administration[11,13,14]. In this study, we have shown that AFT can predict long-term efficacy of an agent against

### Table 1  Electrophysiological parameters in acute treatment of each drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>ERP (ms)</th>
<th>CT (ms)</th>
<th>WLI</th>
<th>AFT (mA)</th>
<th>LAD (mm)</th>
<th>age (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disopyramide</td>
<td>220 ± 8**</td>
<td>115 ± 5*</td>
<td>1·93 ± 0·13</td>
<td>5·9 ± 0·9**</td>
<td>36·3 ± 1·1</td>
<td>56·5 ± 1·6</td>
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<tr>
<td>Control (n=24)</td>
<td>189 ± 6</td>
<td>100 ± 3</td>
<td>1·91 ± 0·10</td>
<td>3·3 ± 0·4</td>
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</tr>
<tr>
<td>Cibenzoline</td>
<td>195 ± 6</td>
<td>132 ± 5**</td>
<td>1·48 ± 0·05**</td>
<td>7·6 ± 1·2*</td>
<td>35·6 ± 1·2</td>
<td>57·7 ± 2·2</td>
</tr>
<tr>
<td>Control (n=18)</td>
<td>198 ± 6</td>
<td>111 ± 4</td>
<td>1·81 ± 0·06</td>
<td>4·8 ± 0·6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprindine</td>
<td>219 ± 8</td>
<td>137 ± 8**</td>
<td>1·60 ± 0·07#</td>
<td>8·1 ± 1·1*</td>
<td>36·3 ± 1·1</td>
<td>56·9 ± 3·0</td>
</tr>
<tr>
<td>Control (n=15)</td>
<td>204 ± 6</td>
<td>110 ± 4</td>
<td>1·80 ± 0·09</td>
<td>4·2 ± 0·8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>228 ± 8*</td>
<td>110 ± 3**</td>
<td>2·00 ± 0·14</td>
<td>7·3 ± 1·1*</td>
<td>35·7 ± 1·1</td>
<td>54·9 ± 2·4</td>
</tr>
<tr>
<td>Control (n=18)</td>
<td>210 ± 9</td>
<td>98 ± 3</td>
<td>2·05 ± 0·14</td>
<td>2·9 ± 0·4</td>
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<td></td>
</tr>
<tr>
<td>Pilsicainide</td>
<td>209 ± 7</td>
<td>153 ± 12*</td>
<td>1·46 ± 0·11#</td>
<td>6·0 ± 0·8</td>
<td>35·5 ± 1·1</td>
<td>58·5 ± 2·0</td>
</tr>
<tr>
<td>Control (n=20)</td>
<td>210 ± 8</td>
<td>121 ± 8</td>
<td>1·68 ± 0·11</td>
<td>4·8 ± 0·5</td>
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</tr>
</tbody>
</table>

ERP: effective refractory period.
CT: intra-atrial conduction time.
WLI: wavelength index (see text for definition).
AFT: atrial fibrillation threshold.
LAD: left atrial diameter on M-mode echocardiography.

#P<0·05, *P<0·01, **P<0·001 when compared to control.
Controls are not statistically different in each parameter except AFT of flecainide group (P=0·03). There was no complication during the electrophysiological tests, and no adverse effect of the drugs was observed during follow-up periods.

### Discussion

This study demonstrated that a drug could be effective against lone atrial fibrillation at least for 1 year if that drug increased AFT by 5 mA or more. To our knowledge, there has been no quantitative parameter that can predict long-term efficacy against this arrhythmia[8,9]. Although patients with this arrhythmia often have severe symptoms, nearly half of the patients do not have any apparent cardiac disease[17]. Cardiac function is preserved in this group of patients and class I antiarrhythmic drugs are the first choice in treatment[18].

Because of the sporadic nature of this arrhythmia, a conventional approach (trial and error with Holter) would take a long time to find an effective drug. The patients are often medicated for a long time without knowing whether it is truly effective. They often visit the emergency room simply because of vague feeling of palpitations. Moreover, the efficacy of any antiarrhythmic drugs against atrial fibrillation is as low as 40% if the drug is selected empirically[1,8,19,20]. Because there has been no criterion to select a drug against the arrhythmia individually, the result of treatment is often unsatisfactory. Thus, it would be useful to have a method by which we can select a drug in a relatively short time for the individual patient.

We have measured AFT in the human[11,12], and in a guinea-pig model[13,14], and found that this parameter can be safely and repeatedly measured. We have shown that this parameter was the best marker of atrial vulnerability[12]. It was also influenced by drug administration[11,13,14]. In this study, we have shown that AFT can predict long-term efficacy of an agent against
Atrial fibrillation. The drug-induced increase in the parameter was the largest in a group of patients who were free of arrhythmia for 1 year ('success'). The second largest increase in the parameter was observed in a group whose arrhythmia was suppressed in an acute trial, but recurred in long-term follow-up.

A measurement of fibrillation threshold was first introduced in the study of ventricular arrhythmia, and it reflects the electrical instability of the myocardium [21]. AFT, on the other hand, has been applied in animal experiments [13,14,22,23], but it has not been used clinically [11,12]. As was shown in the ventricular models [24,25], high frequency stimulation induced premature responses with short coupling intervals to facilitate greater dispersion of recovery from depolarization of the myocardium. This phenomenon often results in fibrillation. In a patient with atrial fibrillation, lower current amplitude could capture the atrium at short coupling intervals. This condition would facilitate electrical inhomogeneity to permit small reentry circuits in the atrium, which favour long-lasting atrial fibrillation [15,16].

Figure 2 Atrial fibrillation threshold and wavelength index. The electrophysiological parameters were compared according to the follow-up results. (A): Medication increased atrial fibrillation threshold by the largest margin in the cases that were successfully treated for 1 year ('success'). Panel (B): Wavelength index was decreased in all groups after medication, but the change was the smallest in the cases that were successfully treated. Control: control data before medication, drug: data after medication, success: no recurrence of atrial fibrillation for 1 year, recurrence in follow-up: increase in AFT in acute test (electrophysiological test at the bedside) but recurrence during long-term follow-up, failure in EPS: no increase in AFT in the acute test.

Figure 3 Effective refractory period and conduction time. The electrophysiological parameters were compared according to the follow-up results. (a): Effective refractory period was increased after medication when a drug raised AFT in the acute tests (groups of ‘success’ and ‘recurrence’). (B): Conduction time was increased after medication in all cases. Abbreviations are the same as in Fig. 2.
Other electrophysiological parameters

It has been demonstrated in human and animal models that local abnormality in conduction and/or refractoriness can be two major contributors to the occurrence of atrial fibrillation\cite{10,15,16}. Those abnormalities can be detected as dispersion of p wave duration in a standard 12 lead ECG\cite{26,27}. In the invasive electrophysiology laboratory, fragmented atrial activity\cite{28}, longer conduction delay from the extra-stimulus\cite{29}, shorter refractory period\cite{30} and abnormal rate adaptation of these parameters\cite{30,31} can be detected. Although these parameters reveal the abnormality that already exists in the myocardium (substrate), they did not predict the inducibility of the arrhythmia.

Wavelength\cite{15,16} is the product of refractory period and conduction velocity. This concept is associated with total area of refractoriness in the heart at a given time. When this parameter becomes larger, there is less left in the heart where the excitation can propagate. Class I drugs decrease conduction velocity preferentially rather than elongate refractory period at normal heart rates\cite{32}. Thus wavelength would be decreased after medication. This was also the case in our study, although we instead calculated wavelength index. Interestingly, however, wavelength index was less decreased or even increased in the patients whose arrhythmia was successfully treated when the current intensity was increased beyond the refractory period. As a definition, sustained atrial fibrillation was induced at least once during a control measurement. It was terminated spontaneously or by the test drug, and DC cardioversion was avoided. The maximum duration of atrial fibrillation was 30 min, and sinus rhythm was maintained for at least 20 min before the next measurement.

We determined long-term efficacy of the drug by symptoms and office visits including occasional Holter monitoring. Short periods of atrial fibrillation could not have been detected. Nevertheless, the drug was considered effective in terms of quality of life because all patients in this study had complained of frequent palpitation attacks before medication.

Our method was designed to individualize the regimen to treat atrial fibrillation in the most effective way. Initially, we expected to improve overall outcome of pharmacological therapy with this method. Although this expectation was not confirmed, our method can be used as a tool to find the effective drugs within a short period. This method can be also used as a criterion to move on to non-pharmacological therapy when no effective drug is found.

Recently, amiodarone and sotalol have been recognized as good choices for the treatment of atrial fibrillation\cite{36}. However, we did not use these agents for several reasons. Sotalol and intravenous amiodarone were not available for clinical use in our country (Japan) when we started this study. The pharmacological effects of bolus intake of amiodarone may be different from those of chronic treatment. Because our method can be readily applied to find the effectiveness of sotalol and intravenous amiodarone, such a study will be planned in the near future.

It would be possible that the measurement of AFT simply detects the patients who respond very well to any drug. This was not the case because there was no correlation between the increase of AFT induced by different drugs in the same patient, although the control measurement was reproducible within $\pm 1$ mA\cite{12}. Thus, this test could be useful to seek an effective drug against atrial fibrillation within a short time. Non-pharmacological therapy should be considered for the patient after effective drugs cannot be found with this method.

Study limitations

Focal atrial fibrillation has recently been reported\cite{33}. Spontaneous electrical discharges from pulmonary veins or other tissues can cause atrial fibrillation, or rather rapid excitations that could not be distinguished from atrial fibrillation. This type of atrial fibrillation is also induced by rapid pacing at the right atrial appendage which was used in our study. Some of our patients enrolled in this study may have had this type of arrhythmia, but we do not have any data to indicate how many because we did not employ extensive mapping in the atria.

One of the possible shortcomings of AFT measurement was that the duration of induced atrial fibrillation was highly variable. We must be careful in setting the definition of ‘sustained’ atrial fibrillation. Repeated trials under the same conditions, however, showed positive correlation of current intensity and the duration of the arrhythmia. When the current intensity was increased from 1 mA, the threshold was reproducible within $\pm 1$ mA\cite{12}.

Another potential drawback of this method was electrical atrial remodeling, which could affect the test results if atrial fibrillation was long lasting\cite{34}. Even DC shock could alter atrial electrophysiology\cite{35}. Our test protocol was designed to minimize the incidence of atrial fibrillation before measurement of the threshold. Continuous pacing at 120/min to measure conduction time never induced fibrillatory activity. Short runs of fibrillation were induced by an extra-stimulus, but they were never sustained when the coupling intervals were increased beyond the refractory period. As a definition, sustained atrial fibrillation was induced at least once during a control measurement. It was terminated spontaneously or by the test drug, and DC cardioversion was avoided. The maximum duration of atrial fibrillation was 30 min, and sinus rhythm was maintained for at least 20 min before the next measurement.

Conclusion

AFT was a good predictor of long-term efficacy of pharmacological treatment for the prevention of atrial
Atrial fibrillation. When a patient has severe symptoms due to atrial fibrillation, this method can be helpful to find an effective drug.

References