Pharmacological Therapy for Fibrillations

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Human beings suffer from two different kinds of fibrillations: one is atrial fibrillation (AF) and the other is ventricular fibrillation (VF). AF is the most common sustained arrhythmia and VF is the most serious. Pharmacological cardioversion with conventional class I antiarrhythmic drugs is usually little help in terminating long-lasting AF. However, bepridil, a multi-channel blocker, alone or in combination with aprindine restored the sinus rhythm in about 70% of patients. The average time to conversion was one month, and cardioversion was associated with a significant increase in fibrillation cycle length. After cardioversion, atrial contraction recovered within one week, and sinus rhythm was maintained better than after conventional electrical cardioversion. Pharmacological cardioversion of long-lasting AF with bepridil could become a new therapeutic option targeting remodeled atria. Patients with idiopathic VF have a characteristic J wave and ST elevation along with a lower QT-RR slope and short QT interval at slower heart rates. Although an implantable cardioverter defibrillator (ICD) is the most reliable therapy for idiopathic VF, both bepridil and disopyramide normalized repolarization dynamics (slope of the QT-RR relationship) and reduced the frequency of spontaneous VF episodes and ICD shocks. Pharmacological therapy for cardioversion of persistent AF and prevention of idiopathic VF may play a key role in improving not only quantity but also quality of life.

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Key words: Antiarrhythmic drug, Atrial fibrillation, Ventricular fibrillation, Amiodarone, Bepridil

Introduction

Cardiac fibrillations can be divided into two types: one is atrial fibrillation (AF), and the other is ventricular fibrillation (VF). VF is the most serious arrhythmia and directly threatens survival, while AF is the most common sustained arrhythmia and mainly affects quality of life. Both electrical therapy and pharmacological therapy play important roles for the treatment of fibrillations. This review focuses on termination of long-lasting AF and prevention of idiopathic VF using antiarrhythmic drugs. Interestingly, bepridil hydrochloride, a multi-channel blocker, is effective for the treatment of both fibrillations.

Pharmacological Therapy for AF

Conversion of long-lasting AF to sinus rhythm with antiarrhythmic drugs
Pharmacological cardioversion is effective for termination of AF lasting only a few days, but is of little help for termination of long-lasting persistent AF. Amiodarone is the exception and has some efficacy for conversion of persistent AF to sinus rhythm. Long-lasting AF induces changes in ion...
channel properties, such as decreasing protein levels of the L-type Ca channel and several K channels (Kv4.3, Kv1.5, HERG, minK, and Kir3.1), that make pharmacological conversion more difficult in persistent AF than in paroxysmal AF. In a canine model of AF with atrial tachypacing, amiodarone was shown to prevent down-regulation of the L-type Ca channel and reversed pacing-induced shortening of atrial refractoriness. However, clinical use of amiodarone is limited because of its extracardiac side effects.

Bepridil is a multi-channel blocker like amiodarone, and has both anti-anginal and anti-arrhythmic effects. Several reports have demonstrated that bepridil inhibits both L- and T-type Ca currents as well as Na current in isolated cardiac myocytes. Bepridil also inhibits several K currents including slow, rapid, and ultra-rapid components of delayed rectifier K current, muscarinic acetylcholine receptor-operated K current, and ATP-sensitive K current. Bepridil prolongs atrial action potential duration and is expected to be effective for conversion of AF. The K channel blocking actions are, however, supposed to increase risks for prolongation of the QT interval and torsades de pointes.

Perelman et al. demonstrated that bepridil was more effective than amiodarone in terminating established AF (≥3 months) but was also associated with life-threatening ventricular arrhythmias. They concluded that arrhythmogenic actions of bepridil make it unsuitable for treatment of AF. However, they administered bepridil at dosages of 200 to 600 mg/day, which are extremely high compared with those employed in Japan (100–200 mg/day).

To minimize the adverse effects of bepridil without losing its efficacy, a combination therapy with bepridil and aprindine was chosen. Aprindine was selected because of its unique Na channel blocking properties. As a class Ib antiarrhythmic drug similar to lidocaine, aprindine may counterbalance excessive QT prolongation induced by bepridil. Aprindine blocks the Na channel mainly in the inactivated state; therefore prolongation of the action potential duration by bepridil would enhance the Na channel-blocking effect of aprindine on the atrial cells. In addition to its class I antiarrhythmic drug action, aprindine causes a moderate reduction of delayed rectifier K current and hyperpolarization-activated inward current.

Efficacy and safety of bepridil alone or in combination with aprindine for cardioversion of long-lasting AF

The study group consisted of 32 consecutive patients (23 men, mean age of 61 ± 8 years) with AF lasting ≥3 months without a history of sinus node dysfunction. Patients received bepridil (200 mg/day) for 4 weeks after anticoagulation therapy with warfarin. If sinus rhythm was not restored with bepridil and QT interval prolongation was not excessive (QTc <50 sec and %increase <25% of the baseline value), oral aprindine (40 or 60 mg/day) was added to bepridil (Figure 1). Fast Fourier transform analysis (20 consecutive 4096-msec epochs with 50% overlap) was performed using lead V1 before and after bepridil administration. The fibrillation cycle length (FCL) was calculated from the peak frequency of each epoch.

Representative electrocardiograms and spectral analyses from a patient with pharmacological conversion by a combination of bepridil with aprindine are shown in Figure 2. In 10 of 32 patients, oral bepridil converted AF to sinus rhythm an average of 19 days (7–28 days) after bepridil was started.
Sixteen of 22 patients who initially failed to respond to bepridil received oral aprindine in addition to bepridil. In 11 of the 16 patients, AF was terminated an average of 11 days (4–21 days) after aprindine was added to bepridil (phase II). Six patients who had failed to respond to bepridil were followed without administration of aprindine. Only one of them recovered sinus rhythm during phase II. The final rate of conversion with bepridil alone or in combination with aprindine was 69%, and the time to conversion after starting bepridil was 30 ± 12 days. The duration of AF was significantly shorter in responders than in non-responders. Responders had a greater increase in FCL due to bepridil than non-responders (Figure 2). The increase in the QTc interval with bepridil, left ventricular ejection fraction, and left atrial dimension did not differ between the two groups.

No adverse effects necessitating drug discontinuation occurred. However, bepridil dosage was reduced from 200 mg to 100 mg/day in 7 patients because of excessive QT prolongation and sinus bradycardia.

**Frequency analysis of fibrillation waves**

During AF, precise manual measurements of fibrillation intervals are practically difficult and inaccurate. Several investigators analyzed frequency characteristics of fibrillation waves from surface ECG using QRST subtraction methods and demonstrated that spectral analysis of surface ECG in AF is useful for quantification of fibrillation wave characteristics.\(^{16,17}\) In our previous study, the mean FCL obtained from intracardiac electrograms at the right atrial free wall was a good predictor of AF termination with class I antiarrhythmic drugs.\(^{18}\)
similar to termination of AF with bepridil alone or in combination with aprindine.  

Spectral analysis was performed not only to measure FCL but also to quantify AF organization. The ratio of the spectral zone with the maximum power to the total spectral area between 3 to 12 Hz was calculated from power spectral analysis of each epoch (Figure 3). The area ratio, which may represent the degree of AF organization, was termed the fibrillation organization index (FOI). FCL consists of a refractory period and a temporal excitable gap. On the other hand, the FOI is related to the size of the reentry circuit (pathway length), consisting of a wavelength and an spatial excitable gap. Power spectra showing multiple peaks and lower FOI may represent a greater number of circulating wavelets in the atria as compared with those with a single-peak pattern. Everett et al. quantified AF organization using spectral analysis in a canine AF model. They demonstrated that the defibrillation energy of AF was dependent on the degree of AF organization: higher defibrillation energy was required for termination of AF with less organized fibrillation waves. According to the multiple wavelets hypothesis, the number of wavelets varies as a result of variation in the rate of wavelet formation and extinction. Drugs decreasing the number of wavelets may increase the FOI and thereby increase the propensity for AF termination.

Serial changes of FCL and FOI were analyzed before and after bepridil administration. A critical increase in not only FCL but also FOI was required for termination of long-lasting persistent AF with bepridil alone or in combination with aprindine (Figure 4). The increase in FCL and FOI by bepridil alone may be attributable mainly to a class III action that increases atrial refractoriness, and a combination with aprindine may cause conduction delay at pivot points of functional reentry that increases FCL further. These effects may lead to prolongation of FCL with fewer organized wavelets and increase the possibility of eliminating all circulating wavelets simultaneously. In patients who are scheduled for termination of persistent AF, evaluation of FCL and FOI after drug administration is expected to be a useful predictor of success for pharmacological cardioversion.

**Figure 3** Power spectral analysis of fibrillation waves (from reference 19).

Fibrillation cycle length (FCL) was calculated from the peak frequency with the maximum magnitude from each epoch. The fibrillation organization index (FOI) was derived from the area ratio of the spectral zone with the maximum power to the total spectral area from 3 to 12 Hz from each epoch.

Recovery of atrial mechanical function after pharmacological restoration of sinus rhythm

The electrical remodeling is reversible within a few days after restoration of sinus rhythm. In contrast, recovery from mechanical stunning requires a longer time than recovery from electrical remodeling, depending on the duration of AF. Manning et al. reported that atrial mechanical recovery was achieved within one week in patients with AF of moderate duration (2–6 weeks) and within one month in patients with AF of longer duration (>6 weeks). Nishino et al. demonstrated that atrial mechanical function showed no change over the first week and improved between one and four weeks after conversion in patients with longer duration of AF (>6 months).
Compared with these reports, pharmacological cardioversion with bepridil or in combination with aprindine significantly enhanced the recovery of atrial mechanical function. As shown in Figure 5 (the same patient as in Figure 2), significant atrial contractile flow across the mitral valve was observed seven hours after pharmacological cardioversion with bepridil. After pharmacological cardioversion of long-lasting AF with bepridil, atrial contraction recovered faster, within one week, and did not change further from the first week in the first month. Pharmacological conversion with bepridil may be beneficial to prevent the occurrence of thromboembolic events, because left atrial mechanical dysfunction after cardioversion is implicated in the development of thromboembolic stroke.

Figure 4 Relationship between fibrillation cycle length (FCL) and fibrillation organization index (FOI) with respect to pharmacological cardioversion of atrial fibrillation (AF) (from reference 19).

Values of FCL and FOI included both before (●) and after (○) drug administration. Conversion of AF (●) occurred in 100% patients with both FCL ≥190 msec and FOI ≥45% and in 0% of those with both FCL <190 msec and FOI <45%. In patients with either a combination of FCL ≥190 msec and FOI <45% or a combination of FCL <190 msec and FOI ≥45%, 9 of 16 (56%) persistent AF converted pharmacologically.

Figure 5 Atrial mechanical function after pharmacological cardioversion evaluated by pulsed-Doppler echocardiography (the same patient as in Figure 2).

Left panel: The peak velocity of the A wave was 32 cm/sec seven hours after pharmacological conversion.

Right panel: The peak velocity of the A wave was 38 cm/sec two days after pharmacological conversion.
that not only a reduced systolic Ca transient but also impaired cellular Ca handling may contribute to atrial contractile dysfunction. Both bepridil and amiodarone have a T-type Ca channel blocking action similar to mibefradil, which attenuates atrial tachycardia-induced electrical remodeling. This T-type Ca channel blocking action may play a role in recovery of not only electrical remodeling but also post-cardioversion atrial stunning. In cultured rat ventricular myocytes, bepridil increased the Ca sensitivity of contractile proteins and offset the negative inotropic effect of the L-type Ca channel blocking action. This Ca-sensitizing effect may also contribute to the early recovery of atrial mechanical function after restoration of sinus rhythm.

Maintenance of sinus rhythm after pharmacological cardioversion of persistent AF

Human AF is associated with marked shortening of the action potential duration and FCL as the electrical remodeling progresses. A shortened FCL induced by persistent AF favors further perpetuation of AF. Pharmacological termination of long-lasting AF with bepridil alone or in combination with aprindine was preceded by an increase in FCL and FOI. The increase in FCL due to bepridil is in some part attributable to direct effects on several ion channels, but the time course of bepridil action (gradual increase in FCL and long pharmacological conversion interval) suggests the contribution of an additional effect on channel protein expression (anti remodeling action). Amiodarone is also effective for pharmacological cardioversion of persistent AF and increases the efficacy of electrical cardioversion because it may reverse already established atrial remodeling. The delay in pharmacological cardioversion due to amiodarone (≥one month) is attributed in part to this reversal of remodeling.

As shown in Figure 6, sinus rhythm was maintained better in patients with pharmacological cardioversion with bepridil (≥80% at 12 months) than in patients with electrical cardioversion (≤40% at 12 months). After successful pharmacological cardioversion, some patients may have recurrences of paroxysmal AF, but they could terminate spontaneously. On the other hand, electrical cardioversion terminates AF suddenly without affecting the remodeled AF substrate. Consequently, if AF recurs shortly after electrical cardioversion, it may not terminate spontaneously. These differences in the atrial substrate after sinus restoration may contribute to the lower recurrence rate of persistent AF in patients with pharmacological cardioversion with bepridil compared with electrical cardioversion.

Persistent AF with and without a history of drug refractory paroxysmal AF

AF usually starts as paroxysmal type and is transformed into persistent type. The mechanisms of paroxysmal AF consist mainly of initiating factors, and the role of maintaining factors is less important. The role of maintaining factors becomes more important in association with the progression of AF.

In our study, approximately one third of persistent AF had been preceded by drug-refractory paroxysmal AF. This type of persistent AF may have both initiating and maintaining factors. The remaining two thirds of patients with persistent AF did not have any history of paroxysmal AF as a prelude. This type of persistent AF depends mainly on maintaining factors caused by structural remodeling.

Although FCL after bepridil therapy was significantly shorter in patients with a history of paroxysmal AF than in those without, their conversion rates did not differ. Bepridil therapy for pharmacological conversion of persistent AF could become an additional therapeutic option irrespective of the history of drug-resistant paroxysmal AF.

Combination of inhibitors of renin-angiotensin system with bepridil

In the clinical setting, angiotensin-converting enzyme inhibitors can reduce the prevalence of AF in patients with congestive heart failure (CHF) or left ventricular dysfunction after myocardial infarction. In a canine CHF model of AF, enalapril
attenuated changes in tissue angiotensin II and atrial fibrosis and reduced AF duration.\textsuperscript{39} In our previous study, enalapril did not suppress shortening of the atrial refractoriness induced by long-term rapid atrial pacing but suppressed both atrial interstitial fibrosis and increased expression of connexin43 and perpetuation of AF without improving left ventricular function.\textsuperscript{40} Enalapril also prevented sinus node dysfunction induced by rapid atrial pacing, possibly through suppression of interstitial fibrosis and apoptosis in the sinus node.\textsuperscript{41} These observations suggest that combined administration of inhibitors of the renin-angiotensin system may be useful to preserve sinus node function after restoration of sinus rhythm with bepridil.

**Pharmacological Therapy for VF**

Repolarization dynamics in idiopathic VF patients

Idiopathic VF has been recognized as a cause of unexplained sudden nocturnal death in middle-aged men, especially in Asian countries.\textsuperscript{42,43} In some of these patients with idiopathic VF, a high-takeoff ST segment and prominent J wave in the right precordial leads have been reported as Brugada syndrome.\textsuperscript{44} Idiopathic VF patients without this specific ECG pattern have also been reported, and some of them have a prominent J wave in the inferior leads (Figure 7).\textsuperscript{45,46} In our previous study, we analyzed Holter ECGs recorded just after VF episodes and found that idiopathic VF patients had lower QT-RR slopes and impaired prolongation of the QT interval at longer RR intervals compared with control healthy subjects (Figure 8).\textsuperscript{40} These repolarization characteristics in idiopathic VF patients during sinus bradycardia may be related to the nocturnal occurrence of VF episodes.

**Mechanism of short QT interval at slower heart rates in idiopathic VF**

Several studies suggested that the presence of a prominent transient outward current (Ito) in the right ventricular epicardial layer and genetic abnormalities of the sodium channel gene (SCN5A) may play a key role in the characteristic ECG pattern in Brugada syndrome.\textsuperscript{47,48} Experiments using wedge preparations of canine heart revealed that a downsloping ST segment elevation may be caused by an earlier repolarization of the epicardial action potential due to a more intense Ito.\textsuperscript{47} Na channel blocking agents induced a coved type of ST elevation in the precordial leads\textsuperscript{49} because they accentuated the Ito-mediated notch and failed to develop the action potential plateau (loss of dome). In a canine in vivo model of Brugada syndrome, epicardial cooling at
the right ventricular outflow tract induced J point elevation and T wave inversion in the right precordial leads and enhanced ventricular vulnerability (Figure 9). Myocardial cooling increased Ito and slowed Ca channel activation, and vagal nerve stimulation increased these cooling-induced changes. In
patients with Brugada syndrome, vagal nerve activity evaluated by heart rate variability indices correlated with the degree of ST segment elevation.51)

We speculate that these abnormalities of ionic currents affect not only configuration of the ST segment pattern but also ventricular repolarization dynamics. Either reduction of inward currents or augmentation of outward currents causes early repolarization, resulting in shortening of the QT interval. At rest, an increase in Ito may limit the excessive prolongation of action potential duration, especially at slower heart rates, and also produce a J wave in surface ECG. During exercise, both faster heart rates and an increase in adrenergic tone may offset the excessive Ito current52) and make a difference in QT interval at higher heart rates insignificant compared with healthy subjects.

Pharmacological therapy for prevention of idiopathic VF

In idiopathic VF patients, the most reliable therapy for prevention of sudden death is implantation of implantable cardioverter defibrillator (ICD). However, frequent episodes of VF reduce the quality of life because of frequent shock therapy from the ICD. Belhassen et al. reported that quinidine is effective for prevention of spontaneous episodes of VF in Brugada syndrome, but it was associated with a 36% incidence of side effects.53)

Bepridil has unique electrophysiological abilities to inhibit outward currents, including most types of K current and Ito, along with weak inhibitory effect on inward Na current. Disopyramide possesses intermediate kinetics of the Na channel blocking effect and suppresses several types of K current (rapid component of delayed rectifier K current, muscarinic acetylcholine receptor-operated K current, and ATP-sensitive K current) and Ito.54) Both drugs prolong the QT interval significantly and seem to be effective for idiopathic VF patients.

Effects of bepridil and disopyramide on idiopathic VF

The study group consisted of 8 men (age 43.6 ±
9.1 years) with idiopathic VF (Brugada type 5 patients, prominent J wave in the inferior leads 3 patients) who had documented spontaneous episodes of VF, 7 of whom had ICD.55) The relationship between QT and RR intervals was analyzed by 24-hour Holter ECG using an automatic analyzing system before and after pharmacological therapy (bepridil 5 and disopyramide 3). From QT-RR linear regression lines, QT intervals were determined at RR intervals of 0.6 sec [QT(0.6)], 1.0 sec [QT(1.0)], and 1.2 sec [QT(1.2)].

Bepridil-prolonged QT interval, decreased J wave amplitude, and abolished T wave inversion in V2 of a representative patient are shown in Figure 10. QT-RR regression lines obtained from automatic analysis of 24-hour Holter ECG recordings revealed that bepridil increased the QT-RR slope from 0.10 to 0.16 (Figure 11). In 8 idiopathic VF patients, pharmacological therapy increased the slope of the QT-RR regression line from 0.11 ± 0.02 to 0.14 ± 0.04 (P < 0.05). Accordingly, QT(1.0) and QT(1.2) became longer after drug therapy [QT(1.0), 0.38 ± 0.02 sec vs. 0.41 ± 0.02 sec (P < 0.01); QT(1.2), 0.40 ± 0.02 sec vs. 0.44 ± 0.02 sec (P < 0.01)]. However, QT(0.6) did not change after drug administration.

Before drug therapy, the average number of episodes of VF was 5.5 ± 5.8 (range 1 to 17) during the observation period of 19.3 ± 17.6 months (range 6 to 60 months) (Table 1). After drug therapy, 6 patients had no episode of VF for 24 to 120 months (66.0 ± 38.5 months). Two patients had a single episode of VF in 12- and 96-month follow-ups. Pharmacological therapy decreased the frequency of VF episodes in association with prolongation of QT intervals at slower heart rates. Not only J wave and ST elevation but also shorter QT intervals at slower heart rates may represent an electrophysiological substrate for development of VF episodes in these specific idiopathic VF patients.

Safety of Antiarrhythmic Drugs

It is possible that adverse effects counterbalance the benefits of antiarrhythmic drugs in some patients. Hence, safe usage is essential for the treatment of arrhythmia using antiarrhythmic drugs. Physicians should pay more attention to identifying patients

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Figure 11 QT-RR relationship in a patient with Brugada syndrome before and after pharmacological therapy with bepridil (from reference 55). The slope of the QT-RR regression line before drug therapy (control) was lower than that after bepridil therapy. This is the same patient as shown in Figure 10.
who may suffer from adverse effects of antiarhythmic drugs.

Adequate evaluation of the QT interval is essential for safe use of K channel blockers including bepridil. However, correction of the QT interval by any heart rate adjustment method may have limitations. We made a nomogram of the normal QT interval at various heart rates based on automatic measurements of 24-hour Holter ECG recordings in 422 healthy subjects. Evaluation of the QT interval without the correction formula using this nomogram is useful for QT interval measurement after administration of K channel blockers. For safe use, the maximum dosage of bepridil should be limited to 200 mg/day, and serum K ≥ 4.0 mmol/L should be maintained by administration of renin-angiotensin-aldosterone system inhibitors.

Conclusion

Reversal of the remodeled atria in persistent AF and modification of the repolarization dynamics in idiopathic VF may become a new target for pharmacological antiarrhythmic therapy. Although the current trend in treatment for arrhythmia has shifted to non-pharmacological therapy, pharmacological therapy still plays a key role for treatment of fibrillations.

References

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Table 1 Effects of bepridil and disopyramide on episodes of ventricular fibrillation (VF) (from reference 55).

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ICD: implantable cardioverter defibrillator. # indicates Brugada syndrome. Bepridil was given to Cases 1–5, and disopyramide was given to Cases 6–8.


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