Patients with Persistent Atrial Fibrillation Taking Oral Verapamil Exhibit a Lower Atrial Frequency on the ECG

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Background: While there is agreement that verapamil attenuates the AF-induced refractory period shortening when given before AF induction, controversy exists regarding its effects when given after the onset of persistent AF. This study aimed to compare atrial fibrillatory frequency obtained from the surface ECG in patients with persistent atrial fibrillation (AF) with oral verapamil treatment to those without this treatment.

Methods and Results: Surface ECG recordings were performed in 57 patients (34 male, 23 female, mean age 59 ± 11 years) with persistent AF (> 7 days). The frequency content of the fibrillatory baseline was quantified using digital signal processing (filtering, QRST complex averaging and subtraction, Fourier transformation). In 27 patients with verapamil treatment (120 or 240 mg/day for at least 7 days) mean fibrillatory frequency measured 6.4 ± 0.2 Hz, compared to 7.0 ± 0.4 Hz ($P = 0.012$) in 30 patients without verapamil. In a subset of 20 randomly selected patients (10 with, 10 without verapamil treatment) a 24-hour Holter ECG recording was performed and fibrillatory frequency determined at 4 PM, 10 PM, 4 AM, and 10 AM. While there was a significant frequency reduction in the verapamil treated patients at night ($P = 0.011$), it remained constant over time in the other patients.

Conclusion: In patients with persistent AF, fibrillatory frequency assessed by spectral analysis of the surface ECG is lower in patients taking verapamil. **A.N.E. 2002;7(2):92-97**

atrial fibrillation; electrical remodeling; verapamil; ECG

Verapamil, being frequently prescribed in persistent atrial fibrillation (AF) in order to achieve adequate rate control, seems to exhibit different actions on atrial electrophysiology depending on the time and the mode of its administration during the course of AF.

While there is agreement that verapamil attenuates the AF-induced refractory period shortening when given before AF induction,^{1,2} controversy exists regarding its effects when given after the onset of persistent AF.

By administering oral verapamil to patients with chronic AF, Sato et al.³ found similar atrial postcardioversion refractory periods in treated and untreated patients, whereas Pandozi and co-workers⁴ noted even shortened refractory periods in their verapamil group. During chronic AF, the atrial rate was increased immediately after acute verapamil infusion in one study,⁵ whereas it decreased following treatment with slow release oral verapamil in another study.⁶

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Several groups⁷⁻⁹ have documented that the rate of atrial activation during AF can be assessed from the surface ECG. This precisely reflects the average rate of AF recorded directly from the endocardium, and serves as a marker of atrial refractory periods and subsequently AF complexity.¹⁰

The purpose of this study was to compare atrial fibrillatory frequency and its diurnal variability obtained from the surface ECG in patients with persistent AF using oral verapamil to those without this treatment.

METHODS

Patients

The subjects of this study were 57 patients with persistent AF (> 7 days). All patients are part of an observational database in which AF is characterized using echo and electrocardiography (including 12-lead and Holter ECG). Patients with concomitant use of class I or III antiarrhythmic drugs at entry, with mitral stenosis, severe mitral regurgitation, valve prosthesis or pacemaker implantation, and a history of rheumatic fever were excluded from this analysis.

Based on their continuous use of verapamil during the last 7 days, they were selected as group I (use of verapamil) or group II (without verapamil). The specific medication depended on the referring physician's preference and on concomitant heart disease.

In all patients a transthoracic echocardiogram was performed, and left ventricular function and left atrial diameter were quantified using conventional techniques. All patients provided written informed consent before study participation.

ECG Recording and Signal Processing

Continuous ECG recordings were performed in all patients with the subject relaxed in a supine position after a 5-minute equilibration period. In each subject a high-gain, high-resolution electrocardiogram (Predictor, Dr. Kaiser Medizintechnik GmbH) was recorded and lead V¹ was subjected to further signal processing.

In a subset of 20 randomly selected patients (10 with, 10 without verapamil treatment) a 24-hour Holter ECG recording was performed using Tracker II or Tracker III systems (Reynolds Medical, Edinburgh, U.K.). Holter ECG recordings of

lead MCL1 were displayed using Pathfinder 700 (Reynolds Medical, Edinburgh, U.K.). Selected for analysis were four one-minute ECG segments (4 PM, 10 PM, 4 AM, and 10 AM) with times for analysis being assigned to measure day versus night differences.¹¹ In these segments the ventricular rate was calculated.

All ECG segments were digitized at a sampling rate of 1000 Hz with a resolution of 12 bits and transferred to a personal computer for frequency analysis.

The frequency content of the fibrillatory baseline was quantified using digital signal processing. After high-pass filtering, the QRS complexes were subtracted using a template matching algorithm. The resulting fibrillatory baseline signal was subjected to Fourier transformation, displayed as a frequency power spectrum, and peak frequency was determined in the 3 to 12 Hz range (Fig. 1). The algorithm has been described in detail previously.⁷⁻⁹

Data Analysis

All continuous variables are presented as mean $\pm$ one standard deviation. For comparison of continuous variables, Student's *t*-test for unpaired data was used. To evaluate differences between groups of discrete variables, chi-square test was used. Uni- and multivariate ANOVA with repeated measurements was performed to detect the possible influence of clinical variables including verapamil use on fibrillatory frequency obtained from Holter recordings.

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. There were 34 males and 23 females, their mean age being 59 ± 11 years. Cardiovascular conditions associated with AF included one or more of the following: essential hypertension ($n = 30$), coronary artery disease ($n = 11$), dilated cardiomyopathy ($n = 4$), degenerative valvular heart disease ($n = 6$). Lone AF was present in 11 patients (19%). At the time of the study, 27 patients were treated with oral verapamil (120 mg/day, $n = 7$, or 240 mg/day, $n = 20$), while the other 30 patients were not on any calcium channel blocker. There were no statistical differences in clinical characteristics with respect to age, gender, AF duration, underlying

Figure 1. Signal processing technique used to estimate the atrial fibrillatory frequency from ECG recordings. Top panel: ECG segments (10 second segment for presentation) from a patient with AF. Middle panel: Typical appearance of the signal after filtering and subtraction of averaged QRST complexes using a template matching algorithm. Bottom panel: Frequency power spectrum produced by Fourier transformation of the fibrillatory baseline.

ing heart disease, echocardiographic parameters, and concomitant digoxin or beta blocker intake between patients with or without verapamil treatment.

Atrial Fibrillatory Frequency and Verapamil Treatment

Among all patients, mean fibrillatory frequency was 6.7 ± 0.9 Hz. In 27 patients with verapamil treatment (group I), mean fibrillatory frequency measured 6.4 ± 0.2 Hz. This was significantly lower when compared with 7.0 ± 0.4 Hz ($P = 0.012$) in 30 patients without verapamil treatment (group II, Fig. 2). Only 9/27 (33%) group I patients

had a fibrillatory frequency > 7 Hz, compared to 19/30 (63%) group II patients ($P = 0.024$). Verapamil dosage did not show an influence on fibrillatory frequency.

Frequency measurements obtained over the 24-hour observation period are depicted in Figure 3. While there was a significant reduction in fibrillatory frequency at night ($P = 0.011$) in group I, it remained constant over time in group II. During all measurements group I patients had a lower fibrillatory frequency than group II patients ($P = 0.028$). No other variable including age, gender, AF duration, underlying heart disease, echocardiographic parameters, and concomitant treatment affected the fibrillatory frequency. In contrast, mean ventricular rate (77 ± 13 vs 81 ± 16 beats/minute) as well as ventricular rate at all four measurement periods was similar between both groups (Fig. 3).

DISCUSSION

This study evaluated a signal processing technique where the fibrillatory frequency was determined from surface ECG recordings in patients with persistent AF. It could be demonstrated that patients taking oral verapamil for at least 7 days had a lower fibrillatory frequency and exhibited a frequency decrease at night compared to patients without this treatment.

Verapamil and Atrial Electrical Remodeling

Experimental and clinical studies have indicated that AF is based on multiple reentrant wavefronts wandering throughout the atria. If the atrial wavelength, defined as the product of conduction velocity and refractory period, is relatively short, a higher number of circulating wavelets can be sustained and AF may be perpetuated.¹²

Recently, it has been demonstrated that a progressive shortening of atrial refractoriness occurs even after brief AF episodes. This electrical remodeling process results in shorter wavelengths with increased stability of the arrhythmia.^{13,14} The mechanisms behind electrical remodeling have been attributed at least partially to intracellular calcium loading.^{1,2} More recently, calcium channel antagonists have been suggested to prevent a shortening in the atrial refractory period and subsequently reduce the atrial electrical remodeling pro-

Table 1. Characteristics of the Study Population

	Total n = 57	Verapamil + n = 27	Verapamil – n = 30	P Value
Age (years)	59 ± 11	62 ± 9	57 ± 12	NS
Male/Female	34/23	14/13	20/10	NS
AF duration (months)	18 ± 24	22 ± 32	14 ± 15	NS
Underlying heart disease	46	23	23	NS
Lone AF	11	4	7	NS
LAD (mm)	45 ± 5	45 ± 5	45 ± 5	NS
LVEF (%)	55 ± 11	54 ± 11	55 ± 11	NS
Digitalis and/or beta-blocking agents	39	19	20	NS

LAD = left atrial diameter; LVEF = left ventricular ejection fraction.

cess in humans,^{1,2} when given prior to the AF onset.

Different results were obtained, however, when oral verapamil was given to patients with persistent AF. Either no effect on atrial refractory periods but a delayed recovery from electrical remodeling³ or shorter atrial refractory periods in verapamil treated patients were noted.⁴ It was speculated that early verapamil administration prevents refractory period shortening by preventing intracellular calcium overload which is known to reduce the L-type Ca^{2+} current. In contrast, a later administration at a time when electrical remodeling has already occurred cannot reverse the calcium overload. This in turn, and the additional calcium channel blockade, reduce the L-type Ca^{2+} current further,

thereby leading to a shorter action potential duration and subsequently shorter refractoriness.⁴

We have found a lower fibrillatory frequency in patients taking long-term oral verapamil when compared to patients without this drug. Similarly, Meurling et al., by using a comparable ECG processing technique, observed a significant reduction in fibrillatory frequency (maximum after 5 days with steady state thereafter) in 10 patients with persistent AF after oral verapamil administration.⁶ While there was a significant day–night difference in fibrillatory frequency in our verapamil-treated group, it was absent in patients without verapamil. This finding is supported by another study from Meurling et al.,¹⁵ who noted no diurnal frequency fluctuation in patients with a high mean frequency (comparable to our untreated patients), as opposed to a significant nightly decrease in patients with a lower mean frequency (comparable to our treated patients).

The lower frequency found in these studies after long-term oral verapamil is in contrast to an increase in both atrial rate and dispersion of atrial refractoriness immediately after a 10-minute verapamil infusion.⁵ In this study performed by Rammanna and colleagues⁵ in 15 patients with chronic AF (> 1 year) no measurements were obtained, however, after a longer treatment period (e.g., after 1 or 7 days). An acute frequency increase may therefore not preclude a chronic frequency decrease. Differences in the study protocols may contribute to the different findings. For instance, the observed increase in fibrillatory frequency after acute verapamil infusion⁵ might be mediated by an increased sympathetic tone following hemodynamic alterations.¹⁶ From previous investigations it

Figure 2. Atrial fibrillatory frequency and verapamil usage among 57 patients.

Figure 3. Atrial fibrillatory frequency (left) and ventricular rate (right) obtained every 6 hours from Holter ECG among 20 patients.

is known that this autonomic change contributes to higher atrial rates.^{11,17}

Furthermore, the mechanisms of drug-induced fibrillatory frequency reduction have just recently been questioned.¹⁸ Interestingly, Wijffels et al.¹⁸ found in the goat that the increase in atrial cycle length following cibenzoline, quinidine, flecainide, and sotalol, could only be in part attributed to an increase in atrial refractory periods. This group speculated that rather a reduction in conduction velocity at pivot points (where the circulating wavelet makes a sharp U-turn) might be responsible for the observed cycle length increase. Whether verapamil exhibits a similar action is not known. Finally, verapamil could suppress pulmonary vein foci and/or exert favorable long-term effects on the reversal of morphological remodeling.¹⁹

Study Limitations

There are several limitations when interpreting our findings. Most importantly, this study has an observational, rather than a randomized study design, with respect to verapamil as well as concomitant cardiac drug use.

Previous investigations^{13,20} have suggested that fibrillatory frequency increases in long-lasting AF episodes as a result of progressive shortening in

refractory period. Whether the time course of changes in fibrillatory frequency is attenuated by calcium channel blockers of the verapamil type or the treatment onset or dosage influences the remodeling process is still unclear. Finally, when the patients entered the study they were already taking verapamil, though that we had no chance to obtain a baseline fibrillatory frequency off medication. The fibrillatory frequencies obtained in both groups were, however, comparable, to those reported by Meurling et al. pre- and postverapamil treatment.⁶

CONCLUSION

In patients with persistent AF, fibrillatory frequency assessed by spectral analysis of the surface ECG is lower in patients taking verapamil.

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