Abrupt changes in fibrillatory wave characteristics at the termination of paroxysmal atrial fibrillation in humans

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Aims We investigated the process of spontaneous termination of atrial fibrillation (AF) to determine its time course from the surface ECG.

Methods and results We studied fibrillatory waves in Holter recordings of paroxysmal and sustained AF. Following QRS-T cancellation dominant frequencies (DFs) were computed and the relationship of DF to termination was scrutinized. For 57 episodes of paroxysmal AF (PAF) in 24 patients, DF ranged from 4.4 to 6.5 Hz (5.2 ± 0.4 Hz) compared to 5.8 to 7.4 Hz (6.6 ± 0.6 Hz) for sustained AF recordings. Comparison of the atrial frequency of the ultimate to the penultimate second demonstrated a drop in frequency in 51 of 57 episodes, \( P < 0.00001 \). No comparable change was seen at longer time periods. Moments of comparably low frequency without termination were only occasionally seen in patients with PAF but not in patients with sustained AF.

Conclusion Low frequency fibrillation was found to be much more likely to terminate. Frequency changes preceding spontaneous termination were abrupt, in contrast to the gradual frequency drop reported with drug-induced termination. The analysis of fibrillatory wave characteristics and their change over time might be used to target specific moments for pacing therapy in patients with AF.

Introduction

The mechanisms of maintenance and termination of atrial fibrillation (AF) are not completely understood. It is not known why AF is self-terminating in certain individuals but not in others although electrophysiological and structural remodeling during AF are believed to play a part in the transition from paroxysmal (PAF) to permanent AF.1,2 The duration of episodes of spontaneously terminating AF varies from patient to patient and from episode to episode and it is not known why PAF self-terminates at a particular moment in time.

Pacemakers have had limited success in the prevention and termination of PAF.3–5 Understanding the mechanisms of spontaneous termination of AF may lead to improvements in treatment by identifying conditions to be promoted or avoided, or moments during PAF that are promising or ill-timed for intervention. The fibrillatory wave characteristics and their change over time might be used in determining a window of opportunity to pace-terminate AF.

The atrial activity during AF can be characterized through the study of the fibrillatory waves from the surface electrocardiogram (ECG).6–8 Spontaneous termination during PAF episodes is rarely encountered in the electrophysiology laboratory and therefore long-term surface ECG recordings provide the best way to document these events in humans.

There is a good correlation between surface ECG characteristics and simultaneously recorded endocardial signals.9

Although termination of AF with anti-arrhythmic drugs10–13 has been well studied and seems to depend on such factors as cycle length, organization, refractory periods and wavefront curvature, the spontaneous termination of AF remains poorly understood. In the multiple circulating wavelet model, termination probability relates to a decrease in the number of wavelets present, which is in turn a function of critical mass14 and wavelength.15 With models of AF based on focal firing,16 slowing or complete cessation of the firing foci would lead to termination, but the mechanisms involved are unknown. With models based on rotors,17 a change in wavefront curvature should result in termination. The time course of these events and whether they are registered in the surface ECG is unknown.

In this study, we evaluated 24-h Holter ECG recordings during episodes of PAF to determine if fibrillatory wave changes can be detected during the spontaneous termination of AF episodes. We investigated the process of termination to determine its time course from the surface ECG. We also investigated whether self-terminating AF episodes can be differentiated from sustained AF.

Methods

We retrieved analog 24-h ECG Holter recordings from 44 consecutive patients with AF. Patients were divided into those with PAF and those where AF persisted throughout the 24 h, which will be
referred to as sustained AF. Though the exact duration in patients with AF throughout the 24 h is unknown, most of these patients had permanent AF. From the PAF recordings, we analysed all episodes lasting longer than 1 min, and where termination was documented during the 24-h Holter recording.

Signal processing and data analysis

All analog data were digitized at a sampling rate of 128 Hz with a resolution of 16 bits. Digital signal processing was performed using MATLAB (The Mathworks Inc., Natick, MA). The signals were first band-pass filtered with cutoff frequencies of 1 and 50 Hz to avoid baseline wander and power line interference. To isolate fibrillatory waves, we used a template-matching QRS-T cancellation algorithm similar to the one previously described by Slocum et al. and validated by Xi et al. We performed QRS-T detection on the channel with a higher ratio of ventricular to atrial activity. QRS-T complexes were identified, and the point of maximum negative slope was chosen as the fiducial point. An adaptive median beat was then computed for the channel with a lower ratio of ventricular to atrial activity, and a template of median beats was generated and subtracted from the original signal. PVC and aberrant beat detection was performed by comparing the morphology of the median beat with all detected QRS-T complexes. The abnormal beats were zeroed out before template subtraction.

Following QRS-T cancellation, the power spectrum of each ‘remainder’ ECG was calculated using the Fast Fourier Transform. We analysed 1-min segments as well as shorter segments of 10-s, 2-s and 1-s duration. When the length of the signal was short, the signal was zero-padded to keep the frequency resolution at <0.1 Hz. Dominant frequency (DF) was defined as the peak of highest power in the 3-9 Hz band. Peak power was also recorded as a way to look at the amplitude change and organization of the signal. For patients with sustained AF, we analysed a sample minute selected from the middle of the 24-h recording. Figure 1 shows an example of a 10-s segment from a Holter lead, the remainder ECG obtained after QRS-T cancellation and the power spectrum of the remainder ECG.

We compared our measurements between groups of patients and within patients using Student’s t-test for unpaired or paired data, respectively. A P-value <0.05 was considered statistically significant.

All activities for this research were reviewed and approved by the Institutional Review Board of Evanston/Northwestern Healthcare.

Results

A total of 44 patients were included in this study, 24 with PAF and a control group of 20 patients with sustained AF. Patients with PAF ranged in age from 43 to 89 years (mean ± SD, 67 ± 11 years). There were 12 men and 12 women. Patients with sustained AF ranged in age from 39 to 87 years (66 ± 12 years). There were 15 men and 5 women. Twenty-six patients (pts) were not taking any cardioactive drugs. Eighteen patients were taking cardioactive medications including beta-blockers (10 pts), calcium channel blockers (6 pts), digoxin (1 pt) and amiodorone (1 pt).

Fifty-five episodes of PAF whose initiation and termination were documented lasted from 1 to 530 min (mean 87 ± 146 min, median 18 min). One episode was preceded by atrial flutter. Two additional episodes with only the termination but not the onset documented lasted longer than 470 and 550 min, respectively. Ten patients had only one episode, 14 patients had two or more episodes documented during 24 h. DF ranged from 4.4 to 6.5 Hz (5.2 ± 0.4 Hz) for PAF episodes compared to 5.8 to 7.4 Hz (6.6 ± 0.6 Hz) for sustained AF recordings (P < 0.00001).

Pre-termination characteristics for PAF

We investigated the process of termination in all 57 episodes of PAF. To study the time course of termination, we analysed different length segments (1-min, 10-s, 2-s and 1-s). No significant difference was found between the penultimate and ultimate 1-min segments or between the penultimate and the ultimate 10-s segments (NS). The penultimate 2-s segment DF ranged from 3.0 to 6.9 Hz (5.3 ± 0.7 Hz) compared to the ultimate 2-s segments that ranged from 3.0 to 6.6 Hz (4.9 ± 0.8 Hz). Thus, there was a significant decrease in DF only from the penultimate to the ultimate 2-s segment (P < 0.0001).

To determine if there was a decrease in frequency within the last 2-s segment, we further scrutinized the difference between the penultimate and the ultimate segments. DF in the penultimate second of PAF ranged from 3.9 to 6.6 Hz (5.3 ± 0.7 Hz). DF in the ultimate second of PAF ranged from 3.0 to 5.8 Hz (last-second-mean-dominant-frequency, 4.4 ± 0.7 Hz). Comparison of the atrial frequency of the ultimate to the penultimate second demonstrated a drop in frequency in 51 of 57 episodes with a mean drop of 0.8 Hz, (P < 0.00001) which is illustrated in Figure 2.
shows a comparison of the mean DF for the entire episodes of sustained vs. paroxysmal atrial fibrillation patients as well as the means of the penultimate and ultimate 2-s and 1-s segments of paroxysmal atrial fibrillation (mean ± SD). It can be observed that the mean for the ultimate 2-s segment is much lower than the mean for the penultimate 2-s segment and lower than the overall mean for paroxysmal atrial fibrillation episodes. Most of this is attributable to slowing during the ultimate second.

Does low frequency AF always lead to termination?

Because moments of termination of fibrillation were almost invariably preceded by low fibrillation frequency, we scrutinized the last minute of each paroxysmal episode lasting longer than 4 min for other 1-s segments with comparably low frequency to that of the final second. The number of segments per patient with equal or lower frequency ranged from 0 to 23 segments (mean 8 ± 6 segments, median 6) of the 59 possible for each episode. The duration of the frequency drop was on the order of 1 to 2 s. Only in three instances, we found consecutive segments with a comparable low frequency lasting 4 s.

For patients with sustained AF, we compared the frequency of each of the 1-s segments of the selected sample minute to the last-second-mean-dominant-frequency of the PAF patients (4.4 Hz). The number of seconds of sustained AF with frequency less than the last-second-mean-dominant-frequency for patients with PAF was only 36 out of 1200 possible seconds of AF (60 s for each of 20 patients with sustained AF). Figure 4 shows a histogram distribution of the percentage of 1-s segments over the entire range of frequencies for AF and illustrates the difference between paroxysmal and sustained AF with PAF segments clustered at a lower frequency compared to sustained AF segments and terminating segments clustered at an even lower frequency compared to non-terminating segments.

Discussion

Main findings

Our study confirmed that episodes of PAF have a lower overall DF than episodes of sustained AF.\textsuperscript{20} We found that frequency changes preceding spontaneous termination are abrupt, in marked contrast to the time course of such changes reported for anti-arrhythmic drug-induced termination. We observed a significant decrease in DF only in the last second or two of each episode, but no change in the organization of the signal. This abrupt change was nearly universal, being observed as a drop from the penultimate to the ultimate second in 51 of 57 episodes. Moments of comparably low frequency without termination were occasionally seen in patients with PAF. It was rare to find such moments of comparable low frequency in patients with sustained AF.

Pre-termination changes reflected in the surface ECG

It is known that termination of AF by anti-fibrillatory drugs is preceded by gradual slowing of fibrillatory frequency.\textsuperscript{9–12} Asano \textit{et al.} studied the termination of induced AF in humans and demonstrated that the mean FF intervals prolonged before termination when compared to initial values.\textsuperscript{21} Capucci \textit{et al.} determined in a pacing induced AF study in humans that the mean of 100 AF intervals prolonged before termination in episodes lasting less than 5 min.\textsuperscript{22} Sih \textit{et al.} reported that termination in three out of seven episodes of induced AF in humans was accompanied by a slight increase in atrial rate.\textsuperscript{23} These studies reported observations before termination of induced AF in comparison to onset, but the actual time course of changes produced by the spontaneous termination of PAF episodes was not investigated.

Unlike the process at onset and the slowing during drug-induced termination, which are progressive over a few minutes, the process of spontaneous termination of AF in our study occurred abruptly with changes in frequency...
only in the last few seconds before termination. The presence of other moments of comparably low frequency without termination suggests that low fibrillatory frequency reflects a necessary, but perhaps not a sufficient condition for termination.

Clinical studies have shown conflicting results about the effectiveness of AF pacing prevention and termination algorithms. The ADOPT trial demonstrated that overdrive atrial pacing with the AF Suppression Algorithm decreased symptomatic AF burden significantly in patients with sick sinus syndrome and AF. One limitation of this study was that only symptomatic AF was used as an end point. The ATTEST trial determined that atrial prevention and termination therapies combined did not reduce burden, total frequency, or symptomatic frequency of AF. Anti-tachycardia pacing (ATP) only achieves local capture in AF, and recordings provide the best way to document these events. For example, in the pulmonary veins. However, spontaneous recordings to allow for the detection of more local events from the surface ECG, it may be important to avoid pacing interventions, since spontaneous termination may occur.

Limitations

Although a list of medications was available for each patient, we do not know the timing of administration of different medications. We have previously reported in a larger group of patients the effect of medication on these parameters, as well as the relationship between the DF and the type and duration of AF. The course we have described in the present study seems much too short to be a direct effect of medications or meals.

Although the atrial activity during AF can be characterized directly from the surface ECG, it may be important to investigate the process of termination from intra-cardiac recordings to allow for the detection of more local events for example, in the pulmonary veins. However, spontaneous termination during PAF is rarely encountered in the electrophysiology laboratory and therefore long-term surface ECG recordings provide the best way to document these events.

Summary and clinical implications

Short-term changes that occur during the spontaneous termination of PAF are reflected in, and can be quantified from the surface ECG. Low frequency fibrillation was found to be much more likely to terminate. The process of spontaneous termination has a quite different time course than anti-arrhythmic drug-induced termination, and is reflected in an abrupt decrease in frequency just before termination. The analysis of fibrillatory wave characteristics and their change over time might be used in determining specific moments to target pacing therapy in patients with AF.

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References


