Rapid fluctuations in atrial fibrillatory electrophysiology detected during controlled respiration

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Submitted 25 January 2005; accepted in final form 18 April 2005


Rapid fluctuations in atrial fibrillatory electrophysiology detected during controlled respiration. Am J Physiol Heart Circ Physiol 289: H754–H760, 2005; doi:10.1152/ajpheart.00075.2005.—Heart rate during sinus rhythm is modulated through the autonomic nervous system, which generates short-term oscillations. The high-frequency components in these oscillations are associated with respiration, causing sinus arrhythmia, mediated by the parasympathetic nervous system. In this study, we evaluated whether slow, controlled respiration causes cyclic fluctuations in the frequency of the fibrillating atria. Eight patients (four women; median age 63 yr, range 53–68 yr) with chronic atrial fibrillation (AF) and third-degree atrioventricular block treated by permanent pacemaker were studied. ECG was recorded during baseline rest, during 0.125-Hz frequency controlled respiration, and finally during controlled respiration after full vagal blockade. We calculated fibrillatory frequency using frequency analysis of the fibrillatory ECG for overlapping 2.5-s segments; spectral analysis of the resulting frequency trend was performed to determine the spectrum of variations of fibrillatory frequency. Normalized spectral power at respiration frequency increased significantly during controlled respiration from 1.4 (0.76–2.0) (median and range) at baseline to 2.7 (1.2–5.8) (P = 0.01). After vagal blockade, the power at respiration frequency decreased to 1.2 (0.23–2.8) (P = 0.01). Controlled respiration causes cyclic fluctuations in the AF frequency in patients with long-duration AF. This phenomenon seems to be related to parasympathetic modulations of the AF refractory period.

Cyclic fluctuations in heart rate during sinus rhythm vary in response to a range of physiological regulatory systems. These fluctuations have been utilized to study autonomic regulation of human cardiovascular physiology (2, 12, 28). The origin of variations in the sinus interval is not fully explained but appears to be predominantly determined by interactions between the autonomic nervous system, hormonal effenter systems, and cardiac pacemaker cells (12, 28). Analysis of heart rate variability by spectral methods (frequency domain analysis) is widely used to study autonomic tone and variations thereof. For example, fluctuations in the so-called high-frequency (HF) band (0.15–0.4 Hz) correspond to normal respiratory frequencies and are thought to reflect parasympathetic tone (26). These fluctuations have been shown to be abolished by parasympathetic withdrawal (1, 2, 28).

Although variations in beat-to-beat intervals (i.e., RR intervals) are usually examined in frequency domain analysis studies, it is assumed that during sinus rhythm the variability of heart rate is determined by changes in autonomic input to the sinoatrial node [i.e., it is assumed that variations in the atrioventricular (AV) interval do not significantly influence total heart rate variation]. Studies on heart rate variability in settings outside of sinus rhythm are sparse, but a few studies on atrial tachycardia (15) and atrial fibrillation (AF) (34, 35) have been performed. These studies utilized analyses of RR interval data, which represent a potential significant weakness (8). During AF, rhythmic fluctuations in RR intervals are potentially determined by both AV nodal conduction and atrial input frequency (23). Thus spectral analyses of RR intervals during AF cannot be assumed to reflect solely or predominantly atrial events because it may be primarily determined by AV nodal factors.

This study set out to explore whether, in patients with AF, vagally induced changes in atrial electrophysiology can be detected during rhythm-controlled respiration. This is a time frame much shorter than previously examined for autonomic influences on refractoriness. We utilized time-frequency analysis (14, 16, 24, 27, 32), which examines atrial electrophysiological changes rather than the RR interval.

METHODS

Study Population

Patients with permanent AF and complete heart block treated by permanent pacemaker were recruited. Exclusion criteria were pharmacological treatment with sympathomimetic or anticholinergic drugs, AF duration exceeding 3 yr, or clinical conditions that could affect the autonomic nervous system, such as diabetes, hyperthyroidism, alcohol abuse, smoking, or recent cardiovascular or cerebrovascular events. All patients gave written, informed consent; this study was approved by the local ethics committee and complied with the Declaration of Helsinki.

Study Protocol and Data Acquisition

In line with recommended practices for autonomic studies, all studies were performed during the morning, and patients were instructed to abstain from eating for 4 h and from caffeine for 24 h before the study commenced. Cardiovascular drugs, other than direct sympathomimetic or anticholinergic drugs, were not discontinued. On arrival, the patients’ pacemakers were programmed to

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Fig. 1. Schematic illustration of the derivation of the modulation spectrum of the ECG, via QRST subtraction and two subsequent fast Fourier transforms. The original ECG (A) is subsequently subjected to pacemaker spike removal (B) and QRST cancellation (C). By repeated measurements of the continuous recording, a time-frequency distribution is obtained (D) from which the frequency trend is extracted (E). A final fast Fourier transform produces the modulation spectra of the different study phases (F). resp. Respiration.

Original ECG (10 s)

After pacemaker spike removal (10 s)

After QRST cancellation (10 s)

Time-frequency distribution (entire recording, 28 min)

Frequency trend (entire recording, 28 min)

Modulation spectra
pace at 60 beats/min in unipolar VOO mode for the duration of the study.

After ECG electrodes were attached and other preparations were completed, patients rested supine for 15 min in a quiet, temperature-controlled room. ECG acquisition was then begun, and 5 min of baseline data were acquired. Subsequently, we initiated controlled respiration with 4-s inspiratory and 4-s expiratory phase durations with the use of auditory guidance (i.e., 8-s cycles, respiratory frequency = 0.125 Hz), and a second 5-min period of data for analysis was acquired once the patient was in a stable synchronized respiratory pattern. Finally, full vagal blockade was induced by intravenous administration of atropine (0.02 mg/kg). After a 5-min interval, 0.125-Hz controlled respiration was again commenced and a final 5-min period of ECG for analysis was acquired. Real-time ECG was monitored throughout the study, and blood pressure was manually measured every 1 min.

Data Analysis

ECG acquisition. We acquired standard 12-lead ECG using a custom-made optically isolated PC card (Siemens Elema, Solna, Sweden). The digital signal (1-kHz sampling rate, 16-bit analog-to-digital conversion, 0.6-μV amplitude resolution) was transferred to a personal computer, where the data were written to a file for subsequent off-line processing. ECG signal acquisition was continuous throughout the study, but the periods for subsequent analyses were noted at the time of recording.

Pacing spike and QRST removal. The initial stage comprised identification and digital subtraction of the unipolar pacing spike. Subsequently, QRST cancellation was performed using a spatiotemporal approach (33), which involves multiple templates, allowing an improved matching to each individual complex and leaving less ventricular residua than conventional processing.

In this study, only data from lead V1 were used for further analysis, although V2 and V3 data were used in the QRST cancellation process. Frequency analysis to detect fluctuations at respiratory cycle lengths. A new method for fibrillatory frequency (FF) trend estimation was used based on the logarithmic Fourier transform of overlapping (one every second) 2.56-s segments of “atrial fibrillatory ECG” (32). An example of the resulting time-frequency distribution is shown in Fig. 1D. The frequency estimation was performed by aligning the spectrum of each new signal segment to a template spectrum with a known main peak position. The advantage of such a procedure is that the entire energy of the signal (both fundamental frequency and harmonic pattern representing the rate and waveform shape of the signal, respectively) is used to obtain detailed frequency estimation. Estimation accuracy was ensured by requiring that both the peak magnitude and the ratio of the peak magnitude to the noise level of the spectrum exceeded certain thresholds. For each new spectrum, a template spectrum was formed by averaging frequency-aligned versions of previous spectra. All frequency estimates were used to provide a time series (see the frequency trend in Fig. 1E) for a second spectral analysis, using the fast Fourier transform to detect fluctuations of the peak frequency value within the band 0.04–0.4 Hz (see Fig. 1F for an example of such modulation spectra). This range was chosen such that it corresponds to the range of the conventionally tested HF and low-frequency (LF) bands (HF: 0.15–0.4 Hz; LF: 0.04–0.15 Hz) examined in heart rate variability studies and contains the frequency of interest (0.125 Hz). The spectra were estimated from segments of 5-min duration from each of the three intervals of interest for analysis, namely, the initial period of quiet rest (baseline), the period of controlled respiration, and the period of controlled respiration postatropine administration.

Figure 1 illustrates the process from ECG via “residual ECG” to final spectral analyses.

Postprocessing Analyses and Statistics

From each power spectrum, we calculated total power (0.04–0.4 Hz), LF power (0.04–0.15 Hz), HF power (0.15–0.4 Hz; P_HF), and power at the frequency of controlled respiration (0.125 Hz; P_0.125).

All values are expressed as median and range. Wilcoxon’s matched pairs test was used for comparison between paired samples; otherwise, Spearman’s ranked correlation coefficient was used. P < 0.05 was significant.

Table 2. Measured parameters

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Gender</th>
<th>EF, %</th>
<th>Left Atrial Diameter, mm</th>
<th>AF Duration, mo</th>
<th>Number of Cardioversions</th>
<th>Heart Active Drugs</th>
<th>Comorbidity</th>
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<tr>
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</table>

AF, atrial fibrillation; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HT, hypertension.

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<td>4</td>
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<td>None</td>
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<tr>
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<td>24</td>
<td>7</td>
<td>Enalapril</td>
<td>HT</td>
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AF, atrial fibrillation; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HT, hypertension.

$^*P < 0.01$ compared with baseline, $^†P < 0.01$ compared with controlled respiration, $^‡P < 0.02$ compared with controlled respiration (Wilcoxon’s matched pairs test).
controlled power, the data were modeled by normalizing for this observation. To correct for the significant variability in total spectral power, the data were modeled by normalizing for this baseline.

It is well known that fluctuations in heart rate during sinus rhythm are mainly determined by autonomic effects on the sinoatrial node. Specifically increased sympathetic tone increases and parasympathetic tone decreases the depolarization frequency of the specialized atrial pacemaker cells by, respectively, increasing and decreasing the rate of the spontaneous diastolic depolarization (2, 6). However, the situation in the fibrillating atria is fundamentally different. The cycle length is the sum of the atrial myocyte effective refractory period, any possible excitability gap that may exist during AF (3, 19), and the action potential upstroke time, which is related to the conduction velocity. FF is the inverse of the fibrillatory cycle length. Thus rhythmic fluctuations in atrial FF may result from dynamic changes in the refractory period, as well as changes in the conduction velocity or of the excitable gap.

### Observations in Individual Patients

The response to controlled respiration was heterogeneous. Although all patients showed increased P0.125/PHF during controlled respiration followed by a decrease after vagal blockade, the amount of response was variable (Table 3). A spectrum from a single patient is illustrated in Fig. 3. In this patient, and in some but not all of the other patients, there appears to be significant LF spectral power exhibited in the LF band. Some of this energy might represent artifacts; at present, however, quantification of absolute power in both the LF and HF band, as can be done during sinus rhythm, is not validated. No differences in patient characteristics in terms of age, AF duration, left atrial diameter, previous cardioversions, heart drugs, and other diseases could be found between marked responders and the less responsive patients.

### RESULTS

#### Study Population

Eight patients (four women, median age 63 yr, range 53–68 yr) were included. Four patients were taking renin-angiotensin-aldosterone inhibitors, one patient was taking a β-blocker and one a calcium channel antagonist, and two patients were not using any heart active drug. Echocardiography demonstrated a median left atrial diameter of 42 mm (32–53 mm) and a median ejection fraction of 55% (35–55%). The median AF duration was 17 mo (range 5–32 mo, defined as the elapsed time since last documented sinus rhythm), and the patients had undergone a median of nine prior cardioversions (range 4–26) (Table 1).

#### Data Availability

All patients were able to satisfactorily perform the rhythm-controlled respiration, and all provided recordings were suitable for analyses.

#### Population Observations

The median FF of patients at baseline was 6.9 Hz (6.1–8.2 Hz); at controlled respiration, this was 7.0 Hz [6.0–8.2 Hz, P = not significant (NS)], and after atropine injection, this was 6.8 Hz (6.1–8.1 Hz, P = NS). P0.125 rose significantly during controlled respiration, from 0.15 ms² (0.06–0.25 ms²) at baseline to 0.36 ms² (0.11–0.58 ms²) (P = 0.01). After vagal blockade, P0.125 decreased to 0.13 ms² (0.02–0.42 ms²) (P = 0.02), which was not significantly different compared with baseline.

Inspection of full spectra demonstrated that there was considerable but variable leakage of LF noise into the region of interest. To correct for the significant variability in total spectral power, the data were modeled by normalizing for this value. The resultant trends were similar (Table 2). The ratio of P0.125 to PHF (0.15–0.4 Hz) (P0.125/PHF) was found to best reflect actual shifts in power and also corrected for the absolute pollution of the spectrum. P0.125/PHF rose significantly during controlled respiration from 1.4 (0.76–2.0) at baseline to 2.7 (1.2–5.8) (P = 0.01); this ratio fell to 1.2 (0.23–2.8) (P = 0.01) after atropine administration (Fig. 2). There was no significant difference between the baseline and postatropine P0.125/PHF (P = 0.40). There were no significant changes in other measured parameters.

### DISCUSSION

#### Comparison of Dynamic Changes in the Electrophysiological Properties of the Fibrillating Atria to Other Scenarios

A spectrum from a single patient is illustrated in Fig. 3. In this patient, and in some but not all of the other patients, there appears to be significant LF spectral power exhibited in the LF band. Some of this energy might represent artifacts; at present, however, quantification of absolute power in both the LF and HF band, as can be done during sinus rhythm, is not validated. No differences in patient characteristics in terms of age, AF duration, left atrial diameter, previous cardioversions, heart drugs, and other diseases could be found between marked responders and the less responsive patients.

### Table 3. Changes in power at the frequency of controlled respiration

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline P0.125/PHF</th>
<th>Controlled Respiration P0.125/PHF</th>
<th>Postatropine P0.125/PHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1.00</td>
<td>5.76</td>
<td>0.23</td>
</tr>
<tr>
<td>b</td>
<td>1.85</td>
<td>2.43</td>
<td>1.73</td>
</tr>
<tr>
<td>c</td>
<td>1.83</td>
<td>2.39</td>
<td>0.80</td>
</tr>
<tr>
<td>d</td>
<td>2.01</td>
<td>2.93</td>
<td>1.85</td>
</tr>
<tr>
<td>e</td>
<td>1.85</td>
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<tr>
<td>f</td>
<td>0.95</td>
<td>1.23</td>
<td>1.03</td>
</tr>
<tr>
<td>g</td>
<td>1.05</td>
<td>3.63</td>
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<tr>
<td>h</td>
<td>0.76</td>
<td>2.42</td>
<td>0.27</td>
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</table>

All values represent the absolute values of power calculated at the frequency of respiration divided by the mean power value in the high frequency band (P0.125/PHF).
The derived parameter of the method for frequency analysis of the fibrillatory ECG, dominating atrial cycle length (inverse of FF), from lead V1 has been shown to closely correlate to an invasively measured spatial mean of right atrial free wall cycle length (14). This in turn has been shown to reflect atrial refractoriness (7, 18, 36). In this study, FF is used as an index of atrial refractoriness.

Although enhanced parasympathetic tone prolongs the ventricular refractory period (17), it has the opposite effect in the atria during sinus rhythm (17, 21, 31). The effect on atrial myocardium during AF is less studied, but the evidence that exists suggests that acetylcholine and enhanced vagal tone shorten the effective refractory period (16, 34), as occurs during sinus rhythm. Consequently, enhanced vagal tone would lead to a higher FF; however, this could not be verified in this study.

The response of vagal discharge is believed to be heterogeneous, as the right atrium has more extensive parasympathetic innervation than the left atrium (22, 37). This is consistent with the response of acetylcholine administration or vagal stimulation, demonstrating a more marked shortening of the refractory period in the right atria than in the left atria (31, 37).

Experimental studies are limited, but those available have not shown an effect of acetylcholine on conduction velocity (20, 31).

Mechanism of Shift in Spectral Power in Response to Slow Controlled Respiration and Attenuation by Atropine

Physiologically, the atrial refractory period adapts automatically to changes in heart rate (i.e., depolarization rate). These changes occur immediately (11). The autonomic nervous system and cardioactive drugs may also alter the electrophysiological properties of the atria (24, 31). It has been demonstrated in previous experimental studies that cholinergic stimulation leads to a response within milliseconds, in contrast to the marked delay of response in the sympathetic modulation (30). Moreover, it is well known that the length of the monophasic action potential can show rapid changes (i.e., beat-to-beat changes) even during high rate atrial depolarizations (29). Thus we conclude that it is theoretically possible for the atrial FF (i.e., the atrial refractory period) to be modulated at frequencies corresponding to respiration.

The shifts in spectral power after atropine administration occurred without any changes in respiration pattern, ventricular rate, blood pressure and body posture, or body movements. Finally, although parasympathetic modulation was specifically examined in this study, the human autonomic nervous system is in practice a complex interaction. Simultaneous afferent inputs occur from both sympathetic and parasympathetic limbs and are influenced by the central nervous system modulation. However, the methodology employed has demonstrated a detectable role of parasympathetic efferents during longstanding AF.

Atrial stretch (5) may also have been involved; cyclic changes in left and right atrial pressure would have been accentuated by slow breathing. A direct effect of stretch on atrial electrophysiology was disproved as a mechanism for our observations by its abolition with atropine. This indicates that reflex arches involving cholinergic receptors are involved. It is likely that the efferent limb of these arches is parasympathetic, but an involvement of baroreceptors and sympathetic fibers in the afferent limb cannot be excluded.
Preserved Dynamic Electrophysiological Changes in Chronic AF and Possible Mechanisms for Interpatient Variability

Two very interesting aspects of the present study are 1) the fact that dynamic changes in AF rhythm were detectable among patients with long duration AF and 2) the observed interpatient variation. All patients had long durations of AF; thus, by present understanding, electrical remodeling would be expected to be “complete” (4, 13). The degree of spectral power shift to 0.125 Hz with controlled respiration was variable.

Previous studies have shown that, after pharmacological interventions (and autonomic modulation), the change in FF is more pronounced in those who have a lower initial value (24, 25). This implies that the atrium is only susceptible to modulation if the FF is low. However, there was no such trend seen in the present study.

The present study is too small and the population too heterogeneous to draw conclusions regarding the importance of the above factors, but the variable preservation of responsiveness to autonomic stimuli is an important observation.

Methodological Issues and Study Limitations

Although all patients had long durations of AF and complete heart block, the population was heterogeneous in ways that may be relevant. Complete heart block and AF are associated with, or directly caused by, a range of conditions such as congestive heart failure, other heart diseases, and advanced age. All of these conditions are associated with attenuation of parasympathetic tone (10), some of which were present in our patients. Conversely, half the patients in our study were taking renin-angiotensin-aldosterone inhibitors, and blockade of the renin-angiotensin system is known to increase the activity in the LF band and to decrease the fluctuations at respiratory frequencies (1, 2). One patient was taking a β-blocker, which has been shown to shift the frequency distribution toward higher frequencies (9); although the exact effects are complex, the shift may be induced by augmentation of vagal tone.

We excluded conditions and drugs that might have abolished autonomic modulation, but this compromise was made for logistical (patient recruitment) and ethical (inadmissibility of drug withdrawal in elderly patients with cardiac comorbidity and without gain from participation in our study) reasons.

In this study, we estimated changes in atrial FF using time-frequency analysis, which is an indirect assessment of atrial refractoriness. This method cannot discriminate between changes in atrial refractoriness and conduction velocity; the latter, however, is likely to change after atropine administration. The response of conduction velocity to controlled, slow respiration is uncertain; however, because atropine attenuated the induced change (it is assumed that atropine does not affect the conduction velocity), it is likely that the observed change in atrial refractoriness is genuine.

Time-frequency analysis from the V1 lead correlates to the fibrillatory cycle length of the right atrial free wall; therefore, direct deductions about the rest of the atria cannot be made. Equally, this study recruited patients with longstanding AF. Therefore, inferences about shorter duration AF cannot be made, although it would be expected that the dynamic responsiveness of less remodeled atria would be more pronounced.

The respiration was controlled by the use of auditory guidance, but the definite respiration frequency was not objectively assessed during the study. Therefore, it is possible that the full extent of the parasympathetic modulation of FF via respiration may be larger than that found in the present study.

Conclusions

We found that slow, controlled respiration causes cyclic alterations of AF rhythm at the respiratory frequency in patients with long-lasting AF. The attenuation of this phenomenon by vagal blockade confirms that the observation is genuinely related to parasympathetic modulations of atrial electrophysiology. Our utilization of paced patients with complete heart block excludes any mechanism related to autonomic effects on the AV node, and the cancellation of ventricular components of the ECG rules contributions of ventricular depolarization to the spectral analysis.

ACKNOWLEDGMENTS

The authors thank Prof. S. Bertil Olsson, Department of Cardiology, Lund University, for valuable guidance in the preparation of the manuscript and Birgit Simeberg, Department of Cardiology, Lund University, for skillful technical assistance.

GRANTS

This study has been supported by grants from the Lund University, the Swedish Heart and Lung Foundation, and the Bergquist Foundation. The British Heart Foundation supported J. E. P. Waktare during this work.

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