Spectral Analysis Techniques of Surface Electrocardiograms in Atrial Fibrillation Research and Clinical Management

Andreas Bollmann, Daniela Husser, Martin Stridh, Leif Sornmo, Helmut U. Klein, S. Bertil Olsson

Otto-von-Guericke-University Magdeburg, Germany
Lund University, Sweden
Is Analysis of Fibrillatory Waves Useful for Treatment of Atrial Fibrillation?

SHIH-ANN CHEN, M.D., and CHING-TAI TAI, M.D.

„As our increasing understanding of the mechanism of AF forms the basis for new treatment strategies, we believe that noninvasive methods such as spectrum analysis of fibrillatory waves, which is capable of detecting or monitoring changes in the characteristics of fibrillatory waves due to interventional procedures, will be useful for treatment of AF.“

J Cardiovasc Electrophysiol 15(8):918 - August 2004
AF Prevalence

Significance of AF

- **Frequent Symptoms**
  - Palpitations (> 50 %)
  - Chest pain and Dyspnea (> 50 %)
  - Symptoms of cerebral hypoperfusion (25 %)

- **Increased Morbidity and Mortality**
  - 3 – 5-times increased risk for stroke
  - Development of heart failure

- **High Cost**
  - frequent office visits and hospitalizations
  - ca. 6.000 – 15.000 US Dollar per patient and year
General Treatment Options in AF

- Restoration and Maintenance of SR
  - Pharmacologic vs Non-pharmacologic

- Control of Ventricular Rate
  - Pharmacologic vs Non-pharmacologic

Anticoagulation

ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation 2001
General Treatment Options in AF

- Restoration and Maintenance of SR
- Control of Ventricular Rate

No treatment recommendations that “take the various mechanisms and patterns of AF into account”

Anticoagulation

ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation 2001
Issues in Clinical AF Management

How to quantify AF severity in the individual patient?

How to choose among the different treatment options for the individual patient?
AF is not a Homogenous Arrhythmia
Evidence From Epicardial Mapping

Konings et al. Circulation 1994
AF is not a Homogenous Arrhythmia
Evidence From Surface ECG

Holm, Dissertation 1997
Fibrillatory Rate as a Measure of Atrial Refractoriness

AF in Isolated Canine Atria

Kim et al. *Circulation* 1996

Induced Human AF

Capucci et al. *Circulation* 1995
Fibrillatory Rate as a Measure of AF Complexity

modified from Konings et al. Circulation 1994
FAF-ECG

Frequency Analysis of Fibrillation

Surface ECG lead

Fibrillatory signal after subtraction of averaged QRS-T-complexes

Frequency power spectrum

Determination of dominant fibrillatory rate

Rate (fpm) = Frequency (Hz) x 60

Bollmann et al. Am J Cardiol 1998
FAF-ECG
Examples

Patient 7 Channel 27

Patient 4 Channel 27

Peak Surface: 9 Hz
Atrial Fibrillatory Frequency, Atrial Fibrillatory Rate or Atrial Cycle Length – Does it Matter?

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th></th>
<th>Patient B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Rate</td>
<td>Cycle length</td>
<td>Frequency</td>
</tr>
<tr>
<td></td>
<td>(Hz)</td>
<td>(fpm)</td>
<td>(ms)</td>
<td>(Hz)</td>
</tr>
<tr>
<td>Pre-drug</td>
<td>6</td>
<td>360</td>
<td>166</td>
<td>9</td>
</tr>
<tr>
<td>Post-drug</td>
<td>5</td>
<td>300</td>
<td>200</td>
<td>8</td>
</tr>
<tr>
<td>Difference</td>
<td>1</td>
<td><strong>60</strong></td>
<td><strong>34</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

Bollmann et al. *Am J Cardiol* 2004
Time-Frequency Analysis

Dominant Rate (fpm)
Exponential Decay ($\gamma$) as Marker for AF Organization

Average Rate (fpm): Mean of Instantaneous Rates
Stability Index (%): Proportion With Differences of Consecutive Rates < 6 fpm (0.1 Hz)

Time-Frequency Analysis
Example

<table>
<thead>
<tr>
<th>Primary Investigator</th>
<th>Bollmann</th>
<th>Olsson</th>
<th>Stridh &amp; Sornmo</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation</td>
<td><strong>Comparison with intracardiac EGM (N=54)</strong></td>
<td><strong>Comparison with intracardiac and esophageal EGM (N=8)</strong></td>
<td><strong>Comparison with asystolic ECG segment (N=12)</strong></td>
<td><strong>Spatiotemporal QRST cancellation</strong></td>
</tr>
<tr>
<td>Method improvement</td>
<td><strong>Spatiotemporal QRST cancellation</strong></td>
<td><strong>Time-frequency analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproducibility</td>
<td><strong>Short-term-reproducibility (N=6)</strong></td>
<td><strong>Short-term-reproducibility (N=10)</strong></td>
<td><strong>Short-term-reproducibility (N=5)</strong></td>
<td><strong>24-hour reproducibility (N=20)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Long-term-reproducibility (N=10)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circadian rate variation</td>
<td><strong>Every 6 hours (N=30)</strong></td>
<td><strong>Every hour (N=20)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous AF termination</td>
<td><strong>Onset vs. mid-episode vs. termination (N=11)</strong></td>
<td><strong>i.v. sotalol (N=5)</strong></td>
<td><strong>10 min before termination vs. termination (N=19)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>i.v. ibutilide (N=15)</strong></td>
<td><strong>p.o. verapamil (N=10)</strong></td>
<td><strong>i.v. cibenzoline (N=5)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>p.o. amiodarone (N=5)</strong></td>
<td><strong>i.v. MgSO4 (+GIK) (N=13)</strong></td>
<td><strong>i.v. procainamide (N=3)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>p.o. sotalol (N=3)</strong></td>
<td></td>
<td><strong>p.o. bepidril (N=22)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>p.o. flecainide (N=18)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>p.o. verapamil (N=27)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring and predicting atrial drug effects</td>
<td><strong>Carotid sinus massage (N=19)</strong></td>
<td><strong>Head-up tilt test (N=14)</strong></td>
<td><strong>Controlled breathing + i.v. atropine (N=8)</strong></td>
<td><strong>External CV (N=29)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring autonomic maneuvers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicting ADFT</td>
<td><strong>Internal CV (N=19)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Internal CV (N=19)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>External, internal and drug-induced CV (N=44)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicting AF recurrence</td>
<td><strong>External CV (N=19)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rhythm differentiation</td>
<td></td>
<td></td>
<td></td>
<td><strong>Sinus rhythm vs. atrial fibrillation</strong></td>
</tr>
</tbody>
</table>

Husser et al. *Indian Pacing Electrophysiol J* 2004
Fibrillatory Rate as Predictor for Spontaneous AF Termination

AF Duration < 15 min
N=13

AF Duration ≥ 15 min
N=18

Fibrillatory Rate as Predictor for Internal Defibrillation Threshold

$R = 0.71$

$p = 0.001$

Bollmann et al. *PACE* 2002
Fibrillatory Rate as Predictor for AF Recurrence

- Frequency < 7 Hz
  - Patients in sinus rhythm (%): 64%
  - Cut-off: 420 fpm
  - p = 0.02

- Frequency > 7 Hz
  - Patients in sinus rhythm (%): 12%

Bollmann et al. *PACE* 2002
## Risk Stratification Based on Systolic LA Area and Fibrillatory Rate

<table>
<thead>
<tr>
<th></th>
<th>SR *</th>
<th>AF *</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(n=29)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(n=13)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 12</td>
<td>61 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Male/Female</td>
<td>15/14</td>
<td>10/3</td>
<td>NS</td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>12 ± 20</td>
<td>30 ± 35</td>
<td>.11</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>None</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>16</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>44 ± 5</td>
<td>47 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic LA area (cm²)†</td>
<td>24.9 ± 6.6</td>
<td>31.5 ± 5.4</td>
<td>.006</td>
</tr>
<tr>
<td>Diastolic LA area (cm²)†</td>
<td>19.6 ± 6.2</td>
<td>23.9 ± 5.5</td>
<td>.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>54±15</td>
<td>56 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Class I or III antiarrhythmics</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Flecainide</td>
<td>17</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fibrillatory rate (fpm)</td>
<td>386 ± 33</td>
<td>420 ± 41</td>
<td>.007</td>
</tr>
</tbody>
</table>

Risk Stratification Based on Systolic LA Area and Fibrillatory Rate


electro-mechanical index” = 0.176 x Systolic LA Area + 0.029 x Fibrillatory Rate – 17.674

Bollmann et al.
J Cardiovasc Electrophysiol
2003
Antiarrhythmic Drug Utilization in New-onset AF

Husser et al. Cardiovasc Drugs Ther 2004
Issues with Antiarrhythmic Drugs

Drug effects are not predictable in the individual patient

Drug monitoring is limited to plasma levels and ventricular ECG parameters (e.g. QT-Interval)
<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Dosage</th>
<th>Patients (N)</th>
<th>Drug effect (baseline vs after drug)</th>
<th>AF termination</th>
<th>Converters vs non-converters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecaïnide</td>
<td>300 mg bolus + 100 – 200 mg/day p.o.</td>
<td>18</td>
<td>- 108 fpm (6.2 ± 0.5 vs 4.4 ± 0.4 Hz)</td>
<td>50 %</td>
<td>Baseline fibrillatory rate 354 vs 384 fpm (5.9 ± 0.4 vs 6.4 ± 0.4 Hz)</td>
</tr>
<tr>
<td>Cibenzoline Procainamide</td>
<td>1.4 mg/kg i.v. (N=5) 10 mg/kg i.v. (N=3)</td>
<td>8</td>
<td>- 102 fpm (151 ± 17 vs 203 ± 21 ms)</td>
<td>100 %</td>
<td>-</td>
</tr>
<tr>
<td>Amiodarone Sotalol Flecaïnide</td>
<td>600 – 1200 mg/day p.o. (N=5) 240 – 480 mg/day p.o. (N=3) 200 mg/day (N=1)</td>
<td>8</td>
<td>- 66 fpm (6.9 ± 0.5 vs 5.8 ± 0.4 Hz)</td>
<td>0 %</td>
<td>-</td>
</tr>
<tr>
<td>Bepidril</td>
<td>200 mg/day p.o.</td>
<td>32</td>
<td>-</td>
<td>69 %</td>
<td>Fibrillatory rate change 31 ± 10 vs 17 ± 5 %</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1 mg (+ 1 mg if required) i.v.</td>
<td>15</td>
<td>- 114 ± 42 fpm</td>
<td>60 %</td>
<td>Baseline fibrillatory rate 338 ± 55 vs 436 ± 67 fpm</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1 mg (+ 1 mg if required) i.v.</td>
<td>19</td>
<td>- 82 ± 57 fpm</td>
<td>35 %</td>
<td>Fibrillatory rate change 108 ± 60 vs 68 ± 52 fpm</td>
</tr>
<tr>
<td>Sotalol</td>
<td>80 mg i.v.</td>
<td>5</td>
<td>Atrial cycle length increased in all patients</td>
<td>0 %</td>
<td>-</td>
</tr>
</tbody>
</table>

Husser et al. *Cardiovasc Drugs Ther* 2004
Monitoring Antifibrillatory Drug Effects Using Time-Frequency Analysis (1)

Baseline

Day 3 200 mg Flecainide p.o.
Monitoring Antifibrillatory Drug Effects Using Time-Frequency Analysis (2)

80 mg Sotalol i.v.

Husser et al. Cardiovasc Drugs Ther 2004
Influence of Antiarrhythmic Drugs on Fibrillatory Rate

Average Rate (fpm)

Baseline vs. Drug  \( p < .001 \) for Flec;  \( p < .001 \) for Amio

Change Flecainide vs. Amiodarone  \( p = .015 \)

Husser et al. *Am J Cardiol* 2005
Influence of Antiarrhythmic Drugs on Fibrillatory Rate Stability

Rate Stability (%)

Baseline vs. Drug $p=.001$ for Flec; $p=.011$ for Amio
Change Flecainide vs. Amiodarone $p=.002$

Husser et al. *Am J Cardiol* 2005
Influence of Antiarrhythmic Drugs on Exponential Decay

Exponential Decay

Baseline vs. Drug  
P = .001 for Flec; P = .001 for Amio

Change Flecainide vs. Amiodarone  
P = .272

Husser et al. *Am J Cardiol* 2005
Influence of Antiarrhythmic Drugs on Fibrillatory Rate and Its Variability
Results from Principal Component Analysis

Raine et al. J Cardiovasc Electrophysiol 2004
Fibrillatory Rate as Predictor for Drug-Induced AF Termination

Ibutilide 1g (+1g) i.v.

Flecainide 300 mg p.o.

Bollmann et al. *Am J Cardiol* 1998

Bollmann et al. *Am J Cardiol* 2002
Conclusions (1)

Determination of frequency measures from the surface electrocardiogram

• is possible in the vast majority of AF patients

• allows non-invasive monitoring of pharmacologic interventions

• seems to exhibit prognostic information
Conclusions (2)

AF with a low fibrillatory rate is more likely ...

• to terminate spontaneously

• to terminate after antiarrhythmic drug administration

• to remain in sinus rhythm after cardioversion

... than AF with a high rate