Use of beat-to-beat ECG restitution for assessment of cardiac stress and arrhythmia vulnerability

Anthony Fossa, PhD
SPS, Webinar, May 7, 2015

Anthony@fossaconsulting.com
www.fossaconsulting.com
Outline

• What is restitution and why is it important?
• How has it been used
  – Clinically
  – Preclinically
• How can it be used in drug studies?
• How does it translate to risk of arrhythmia?
“We” means “Not possible without”

- Pfizer (or at least used to be)
  - Todd Wisialowski
  - Kim Crimin
  - Craig Trost

  - Jean-Philippe Couderc
  - Wojciech Zareba

- iCardiac
  - Meijian Zhou

- AMPS
  - Fabio Badilini

- VivaQuant
  - Brian Brockway
  - Marina Brockway
Too many false positives keeping good medications off the market

- Tamoxifen, amiodarone, chloroquine, erythromycin, most antipsychotics and antidepressants, quinolones would not be developed in today’s regulatory environment

FDA now recognizes this by starting CiPA initiative

FDA also open to new measures of risk assessment using ECG biomarker qualification process.
Restitution

• Restitution is the ability of the heart to recover from one beat to the next.
• Assessed through beat-to-beat relationship between the working phase of heart (APD or QT interval) and the preceding resting phase of heart (DI or TQ interval).
• Can be quantified to assess stress on heart at any heart rate (RR interval)
• Takes into consideration abnormal hysteresis and all changes in autonomic states
• Used in tandem with dynamic QT beat-to-beat analysis at usually no added resource expenditure.
Restitution: The ability to recover: Examples of work vs rest.

• Push-ups:
  – One per minute-relatively easy for most people-can sustain for long time
  – One per second- not so easy unless you’re a trained athlete.
  – The faster you go, the quicker you collapse (arms quivering).

• Heart beats pushing blood
  – Slow heart rate with low blood pressure: easy for most hearts
  – Faster heart rate with higher blood pressure: not so easy unless heart is trained (quivering heart is fatal arrhythmia)
  – QT interval measures work period of the heart while TQ interval measures rest period
  – As QT/TQ ratio gets > 1 (more work than rest) the heart gets tired more quickly in unhealthy hearts or drugs that impair restitution.
  – ECG restitution can accurately quantify this in over 100,000 heart beats/day.
Restitution in dog papillary muscle

Why restitution ratio of “1” is so important to arrhythmia vulnerability

Stability of spiral wave reentry

Ratio < 1: Suppresses oscillations to stabilize spiral wave.

Ratio > 1: Magnifies oscillations causing spiral wave break and re-entry

From: Qu et al., Front Physiol 29: 154, 2010
Heart rate increases in the last minute prior to TdP

Heart rate increase causes QT oscillations preceding pause and Torsades de Pointes

From Roden et al., Annu Rev Physiol 64: 431-475, 2002
Relationship of heart rate (RR), QT and Diastolic (TQ) intervals

Normal = RR $1000$ ms (60 BPM)

Tachycardia

RR = $400$ ms (150 BPM)

QT prolongation

$70$ ms QT prolongation (RR = $1000$ ms)

Tachycardia

QT Prolongation plus Tachycardia

RR = $400$ ms

Fossa et al., 2007 A.N.E. 12:338-349.
Restitution Parameters

- **Lower TQ 5\textsuperscript{th} quantile**: Rest period boundary of lower 5% of beats

- Median QT/TQ ratio: Median stress on the heart over any particular period.

- % **Beats with QT/TQ > 1**: Reflects relative time spent in on steep portion of restitution relationship

- **Upper 98% quantile of QT/TQ ratio**: reflects magnitude of steepness and temporal heterogeneity in restitution relationship for beats that may pose the greatest risk
Assessing stressed autonomic states

Sotalol improves restitution despite QT prolongation

Comparison of Cmax period to time-matched baseline

RR: ↑ 235 ms  
QT: ↑ 101 ms  
TQ: ↑ 134 ms  
QTc: ↑ 52 ms  

TQ 5th Quantile: ↑ 115 ms  
QT/TQ 98th Quant: ↓ 15%  
%QT/TQ beats >1: ↓ 30%

Fossa et al., 2007 A.N.E. 12:338-349.
Restitution is impaired prior to TdP

Comparison to Cmax period from normals

RR: ↓ 172 ms
QT: ↑ 53 ms
TQ: ↓ 225 ms
QTc: ↑ 95 ms

TQ 5th Quantile: ↓ 126 ms
QT/TQ 98th Quant: ↑ 58%
%QT/TQ beats >1: ↑ 722%

Fossa et al., 2007 A.N.E. 12:338-349.
Use of Beat-to-Beat and ECG Restitution in FDA TQT Study

CARCIAL SAFETY

Use of ECG Restitution (Beat-to-Beat QT-TQ Interval Analysis) to Assess Arrhythmogenic Risk of QTc Prolongation with Guanfacine

Anthony A. Fossa, Ph.D.,* Meijian Zhou, Ph.D.,* Antoine Robinson, M.Sc., M.B.A.,† Jaideep Purkayastha, Ph.D.,† and Patrick Martin, M.D.†

From the *iCardiac Technologies, Rochester, NY; and †Shire Pharmaceuticals, Chesterbrook, PA

Background: Guanfacine (Intuniv) is a centrally active alpha-2A adrenergic agonist for the new indication of attention-deficit/hyperactivity disorder. QTc (QTcF and QTcNi) was prolonged at both therapeutic (4 mg) and supratherapeutic (8 mg) doses of a thorough QT study even though guanfacine has had a safe clinical history of over 3 million prescriptions for the treatment of hypertension. In an attempt to understand this disparity, retrospective evaluation of the continuous ECG data utilized dynamic beat-to-beat and ECG restitution analyses was performed.

Methods: Sixty healthy subjects using 24-hour Holters were examined in a 3-arm, placebo-and positive-controlled, double-blind crossover study for effects on beat-to-beat QT, TQ, and RR intervals.

Results: ECG restitution analyses indicated that, at all time points, a disproportionate effect to increase the TQ interval (rest) occurred more in relationship to each QT interval lengthening resulting in a placebo-adjusted reduced QT/TQ ratio of 21% after 4 mg and 31% after 8 mg (both antiarrhythmic responses). Additionally, the percentage of time and magnitude of stress on the heart, as measured by the upper limits of the QT/TQ ratio, were reduced with guanfacine by 22% to 24%. In contrast to guanfacine, moxifloxacin did not show a significant improvement in any restitution parameters but reflected a trend toward proarrhythmia with an increase in the QT/TQ ratio of up to 11%. Conclusion: These results indicate that guanfacine causes a stabilizing effect on cardiac restitution that helps reconcile the clinical evidence for a lack of arrhythmia liability despite apparent increases in typical QT/QTc prolongation measures.


Also used in several other regulatory facing studies unable to disclose at this time.
QTc and QTcNi both undercorrect at low heart rate during peak drug concentration of guanfacine.
Restitution stabilized at peak drug concentration of guanfacine
Restitution changes from baseline at Tmax with guanfacine (T and ST) and moxifloxacin.
Effects on Heart Rate and QT Interval
The effect of two dose levels of immediate-release guanfacine (4 mg and 8 mg) on the QT interval was evaluated in a double-blind, randomized, placebo- and active-controlled, cross-over study in healthy adults.

A dose-dependent decrease in heart rate was observed during the first 12 hours, at time of maximal concentrations. The mean change in heart rate was -13 bpm at 4 mg and -22 bpm at 8 mg.

An apparent increase in mean QTc was observed for both doses. However, guanfacine does not appear to interfere with cardiac repolarization of the form associated with proarrhythmic drugs. This finding has no known clinical relevance.
Use of ECG restitution in preclinical studies
QT beat-to-beat and ECG restitution analyses in the same dog from a cross-over design study

Placebo vs. 24-hour Baseline

Drug vs. 24-hour Baseline

QT prolongation with no change in restitution (i.e. drug safe with no increased risk of arrhythmia).
QT beat-to-beat and ECG restitution analyses in the same dog from a cross-over design study

Placebo vs. 24-hour Baseline

Drug vs. 24-hour Baseline

QT prolongation with impaired restitution (i.e. drug has increased risk of arrhythmia).
Analysis at each time point so that PK/PD determinations can be made
## Translation of baseline values in humans, dogs and monkeys

<table>
<thead>
<tr>
<th>MEASURE</th>
<th>OUTCOME</th>
<th>VALUES</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normals median QT/TQ ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• humans</td>
<td>10-sec rest strips ¹</td>
<td>0.73</td>
<td>1.  Gross. Am J Physiol 170:121-125; 1952</td>
</tr>
<tr>
<td></td>
<td>2-hr sleep ²</td>
<td>0.65</td>
<td>2.  Fossa et al. ANE 12:338-348; 2007</td>
</tr>
<tr>
<td></td>
<td>24- hour baselines ²-⁴</td>
<td>0.73-0.85</td>
<td>3.  Fossa and Zhou. Cardiol J 17:230-243</td>
</tr>
<tr>
<td></td>
<td>24- hour baselines ⁵</td>
<td>0.6 ± 0.1</td>
<td>4.  Fossa et al., ANE 19:582-5994; 2014.</td>
</tr>
<tr>
<td></td>
<td>24- hour baselines ⁶</td>
<td>1.01± 0.1</td>
<td></td>
</tr>
<tr>
<td>• Dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Monkeys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Normals upper 98% QT/TQ ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• humans</td>
<td>2-hr sleep ²</td>
<td>1.23</td>
<td>1.  Unreported dog studies</td>
</tr>
<tr>
<td></td>
<td>24- hour baselines ²-⁴</td>
<td>1.31~1.52</td>
<td>2.  Unreported monkey studies</td>
</tr>
<tr>
<td></td>
<td>24- hour baselines ⁵</td>
<td>1.6 ± 0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24- hour baselines ⁶</td>
<td>1.85 ± 0.1</td>
<td></td>
</tr>
<tr>
<td><strong>Median QT/TQ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>% myocarditis patients with QT/TQ &gt; 1</strong></td>
<td>10-sec rest strips</td>
<td>74.5% cases</td>
<td>2.  Gittleman et alAm Heart J 41:78-90; 1951.</td>
</tr>
</tbody>
</table>
Methods

10 min walk on treadmill

N= 25 Normals
N = 20 HCVD and ASHD
N = 8  CHD
N = 24 PD

Translation to outcomes in humans

**Methods**

Programmed electrical stimulation through ICD pacing protocol.

R2I2 = SD of QT/TQ slope over 12 leads
PERS = Peak ECG restitution (max slope)

**Results**

Selectivity = 80%
Specificity = 95%
Relative Risk = 21.6X

Next steps

• Qualify restitution through FDA Drug Development Tools Process for use in all preclinical and clinical studies.
  
  – Compare PK/restitution outcomes to historical arrhythmia incidences for well characterized drugs (dofetilide, moxi, ranolazine, mexelitine)
  
  – Validation requires continuous ECG data from studies with known clinical outcomes
    • QT prolongation and arrhythmia
    • Cardiac Stress
    • Possibly Ischemia
  
  – Independent review of results by CDER
ECG restitution analysis may be able to differentiate safe vs dangerous QT prolongation

Define TI through PKPD analysis

May quantify cardiac risk during hemodynamic and contractility changes

Allow direct translation of data from animal studies to humans

Completely congruent with QT beat-to-beat analysis
THANK YOU FOR YOUR ATTENDANCE!
**Methods**

10 min walk on treadmill

N= 25 Normals
N = 20 HCVD and ASHD
N = 8 CHD
N = 24 PD

**Table V**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Endurance (in minutes)</th>
<th>Rest</th>
<th>Exercise</th>
<th>Early recovery</th>
<th>Late recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1½</td>
<td>1.25</td>
<td>2.31</td>
<td>1.42</td>
<td>1.40</td>
</tr>
<tr>
<td>2</td>
<td>1½</td>
<td>1.50</td>
<td>2.21</td>
<td>1.77</td>
<td>1.74</td>
</tr>
<tr>
<td>3</td>
<td>3½</td>
<td>0.83</td>
<td>1.91</td>
<td>1.74</td>
<td>0.95</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1.22</td>
<td>2.00</td>
<td>2.42</td>
<td>1.45</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>1.47</td>
<td>1.94</td>
<td>1.34</td>
<td>1.42</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>0.94</td>
<td>1.56</td>
<td>0.84</td>
<td>0.92</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>1.00</td>
<td>1.65</td>
<td>1.48</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Average 3.6 | 1.17 | 1.94 | 1.57 | 1.28

QT Prolongation and Torsades de Pointes (TdP)

- ↓ repolarizing $K^+$ current
- ↑ sodium current
- ↑ calcium current

TQ interval is analogous to DI. When approaching (i.e. R on T beat) EAD can occur leading to reentry and ventricular tachycardia.

Refractory period decreases with increasing heart rate in human restitution.

Assessing beat-to-beat restitution

- Normal QT-TQ boundary for all levels of autonomic tone
- Region of Arrhythmia Vulnerability
- Abnormal hysteresis boundary
- Restitution at Rest

normal QT-TQ boundary for all levels of autonomic tone
Effect of impaired repolarization on restitution in the same resting conscious dog

ASSESSMENT OF HETEROGENEITY OF ACCELERATION AND DECELERATION WITH ISOPROTERENOL IN NORMAL CONSCIOUS DOGS

<table>
<thead>
<tr>
<th></th>
<th>Acceleration</th>
<th>Deceleration</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle Baseline vs. Isoproterenol Challenge</td>
<td>Area = 11213 ms²</td>
<td>Area = 18273 ms²</td>
<td>Area = 35436 ms²</td>
</tr>
<tr>
<td>L-768,673 + E-4031 Baseline vs. Isoproterenol Challenge</td>
<td>Area = 28476 ms²</td>
<td>Area = 20434 ms²</td>
<td>Area = 51711 ms²</td>
</tr>
</tbody>
</table>

Compound N restitution stabilized at Cmax
Compound N 24-hour restitution stabilized
USE OF RESTITUTION PRECLINICALLY TO QUANTIFY ARRHYTHMIA RISK: THE GUINEA PIG ALTERNANANS MODEL
The Protocol: Anesthetized Guinea Pig Alternans Model

Instrument anesthetized open-chest guinea pig

Baseline Pacing Sequence
50 pulses @ 240 or 220 followed by:
(30 pulses @ 200, 190, 180, 170, 160, 150, 140 BCL)

Stabilize animal

Start infusion Dose Level 1

10

Pacing Sequence during last 5 min of every infusion level

Level 2

15

Level 3

15

Level 4

15

Time (min)
Effect on beat-to-beat alternans of E-4031 (BCL= 150 ms)

Therapeutic Use Level of E-4031 = 3.4 nM
(HERG IC20 = 4.6 nM)

E-4031 Baseline

SBE-CD Baseline

Discordant alternans?

[1.28 nM] [5.34 nM] [25.2 nM] [97.3 nM]
E-4031: Effect on mean alternans (vehicle corrected)

Ceff = 3.3 nM; HERG IC20 = 5 nM

Mean Alternans (ms)

Basic Cycle Length (ms)
Bepridil: Effect on mean alternans (vehicle corrected)

Ceff = 15 nM; HERG IC20 = 7.6 nM
Relationship of "Safe" vs "Dangerous" HERG blockers in the Guinea Pigs Alternans Model

Alternans in anesthetized guinea pig in relationship to hemodynamics and ventricular arrhythmias outcomes

- All compounds studied within clinical concentration range:
  - Positive and negative controls
    - E-4031, cisapride, verapamil, bepridil, terfenadine, risperidone
    - Antibacterials: Moxifloxacin, telithromycin, erythromycin
      - (J Pharmacol Exp Ther 318:352-359, 2006).
    - Antidepressants: fluoxetine, citalopram, venlafaxine
      - Reboxetine (manuscript submitted)
    - Antimalarial: Chloroquine and azithromycin alone and in combination
Mechanism of alternans leading to arrhythmogenesis

Adapted from Wilson LE and Rosenbaum DS. Europace 2007; 9:vi77-vi82.