

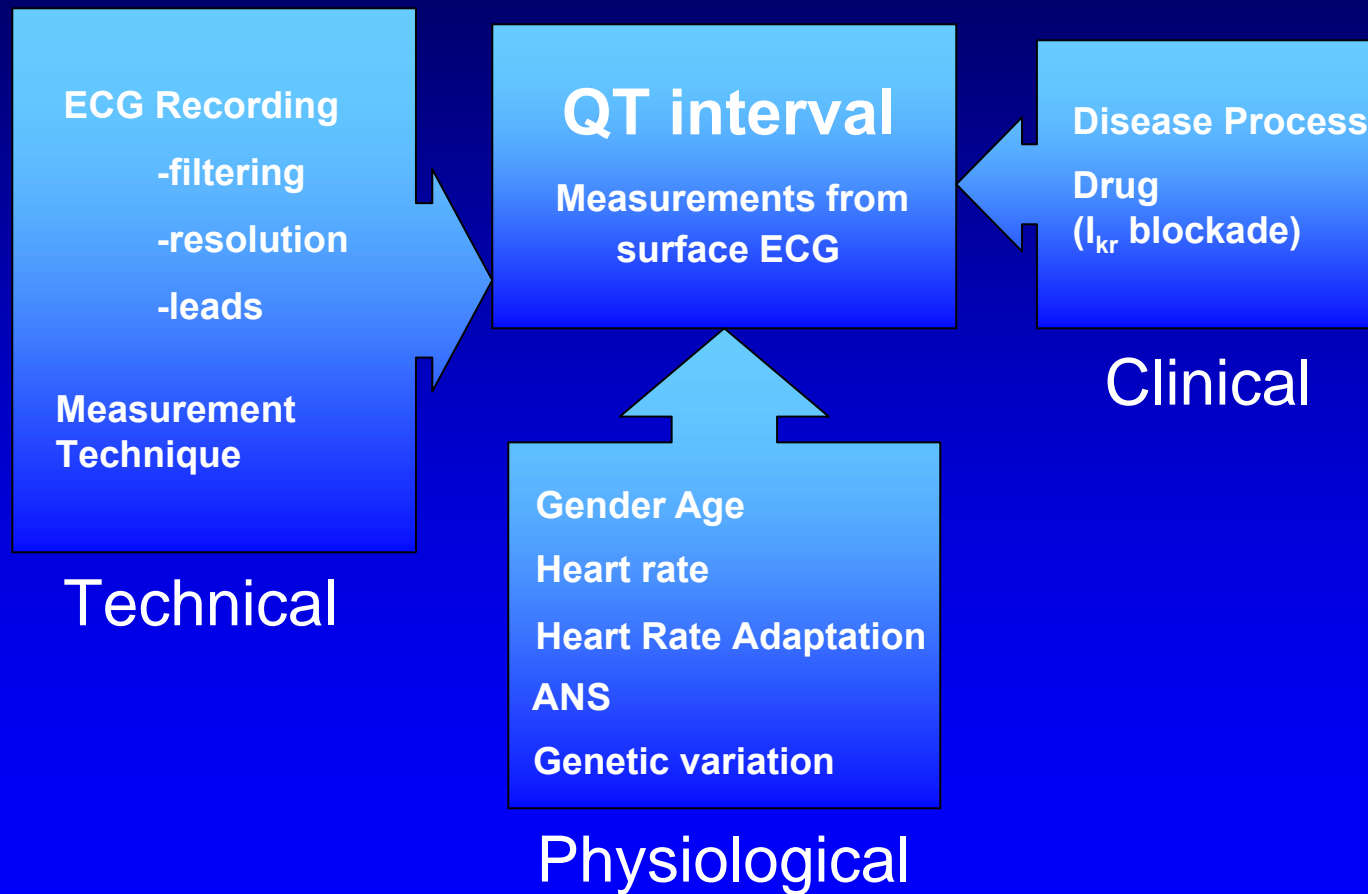
Holter-Based Methods for Improved Cardiac Safety Assessment

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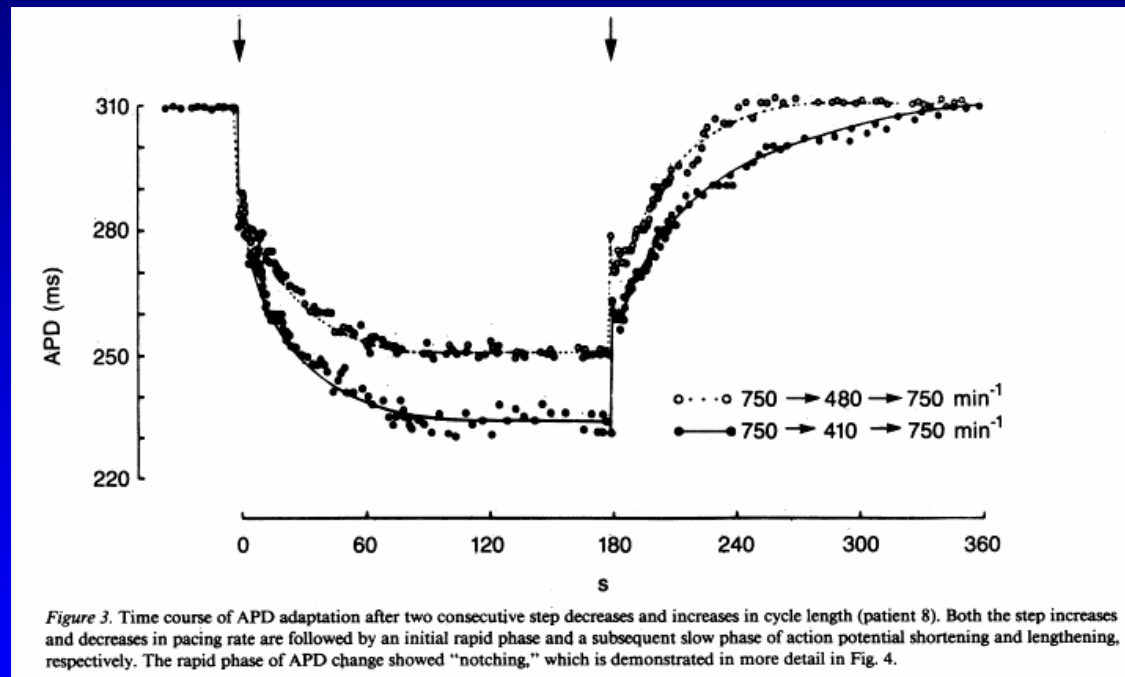


The Challenge of QT Interval Measurements



QT Adaptation - Non-Steady State

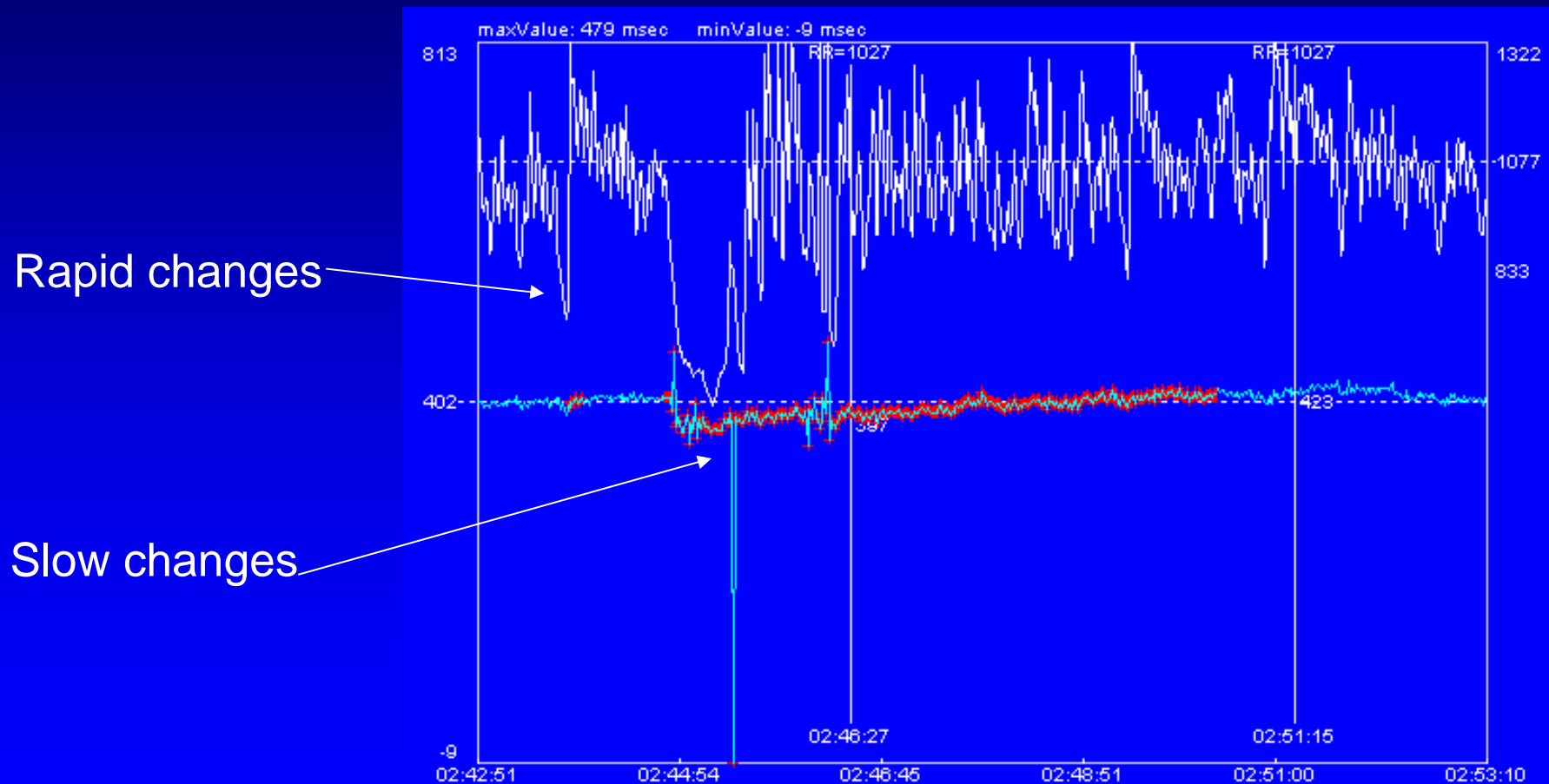
QT interval needs time to adapt to rapid heart rate changes. This is true for both acceleration and deceleration of the cardiac rhythm.



Franz et al. Cycle Length Dependence of Human Action Potential Duration in Vivo. Effects of Single Extrastimuli, Sudden Sustained Rate Acceleration and Deceleration, and Different Steady-State Frequencies. J.Clin.Invest 1988;82(3):972-9.

QT- RR adaptation

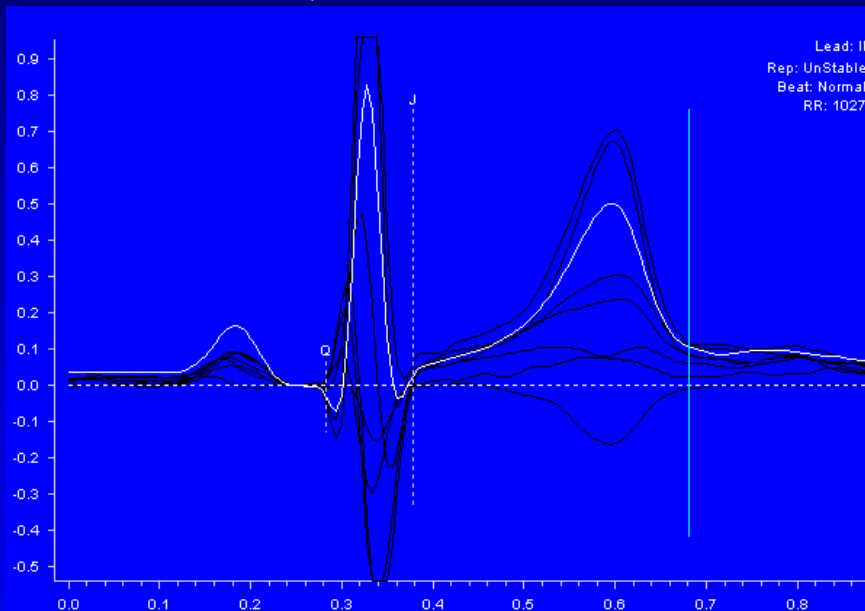
Holter ECG technology provides the ability to identify heart rate instability by reviewing the history of heart rate



QT Prolongation and Heart Rate Adaptation

Example of non-steady state of repolarization

QT= 397 msec

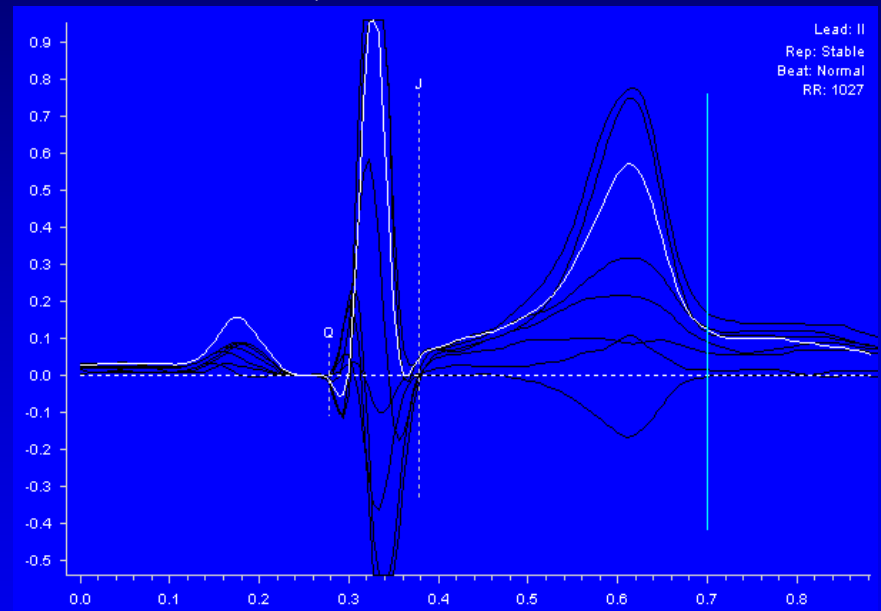


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QTOffset: 397	QTA50: 298	QTA97: 406
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<input checked="" type="checkbox"/> Show All Leads	<input type="checkbox"/> Show Tangent	<input type="checkbox"/> Show Previous Signal

ECG tracing at 02:46:27

RR=1027 msec

QT= 423 msec



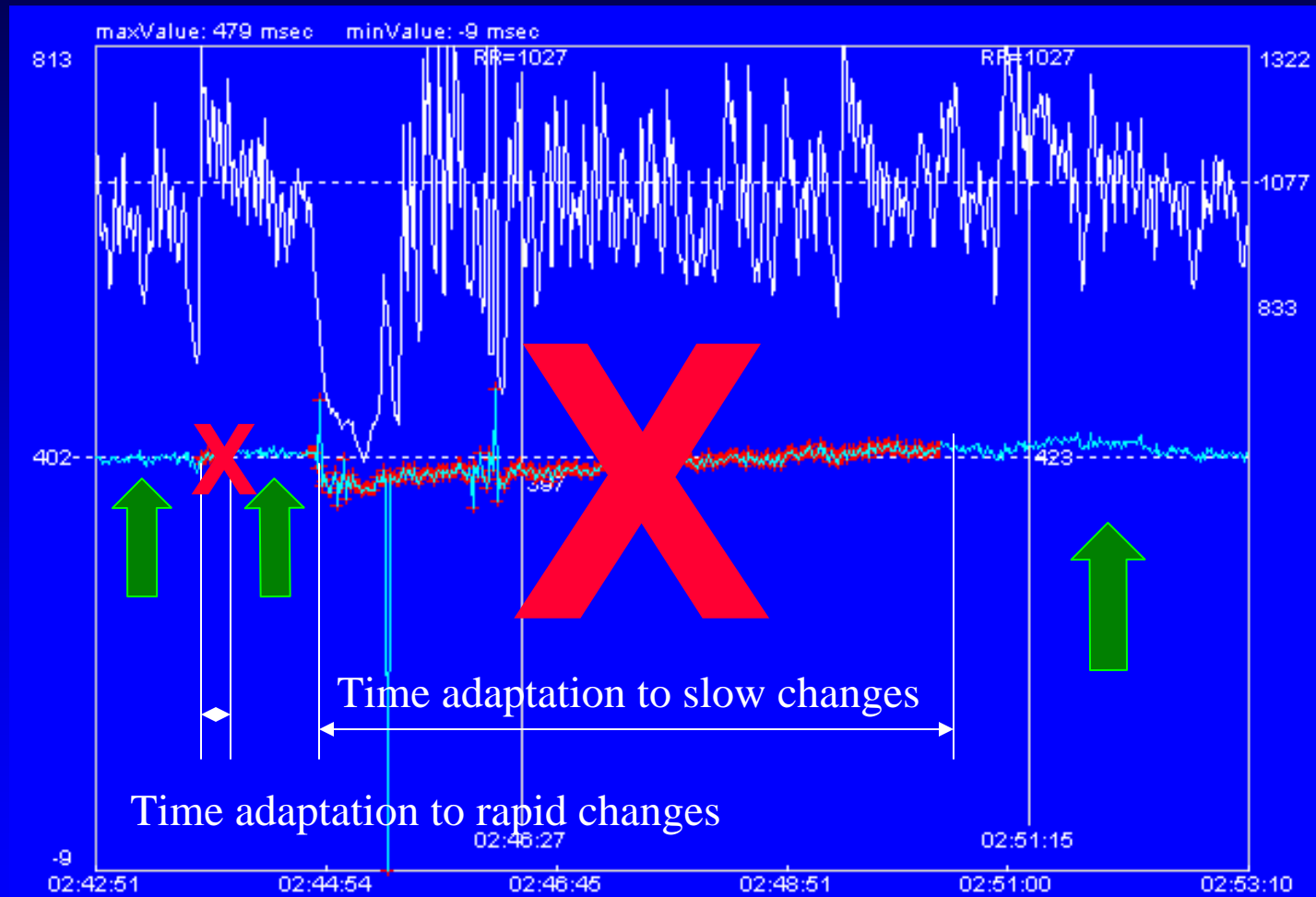
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ECG tracing at 02:51:15

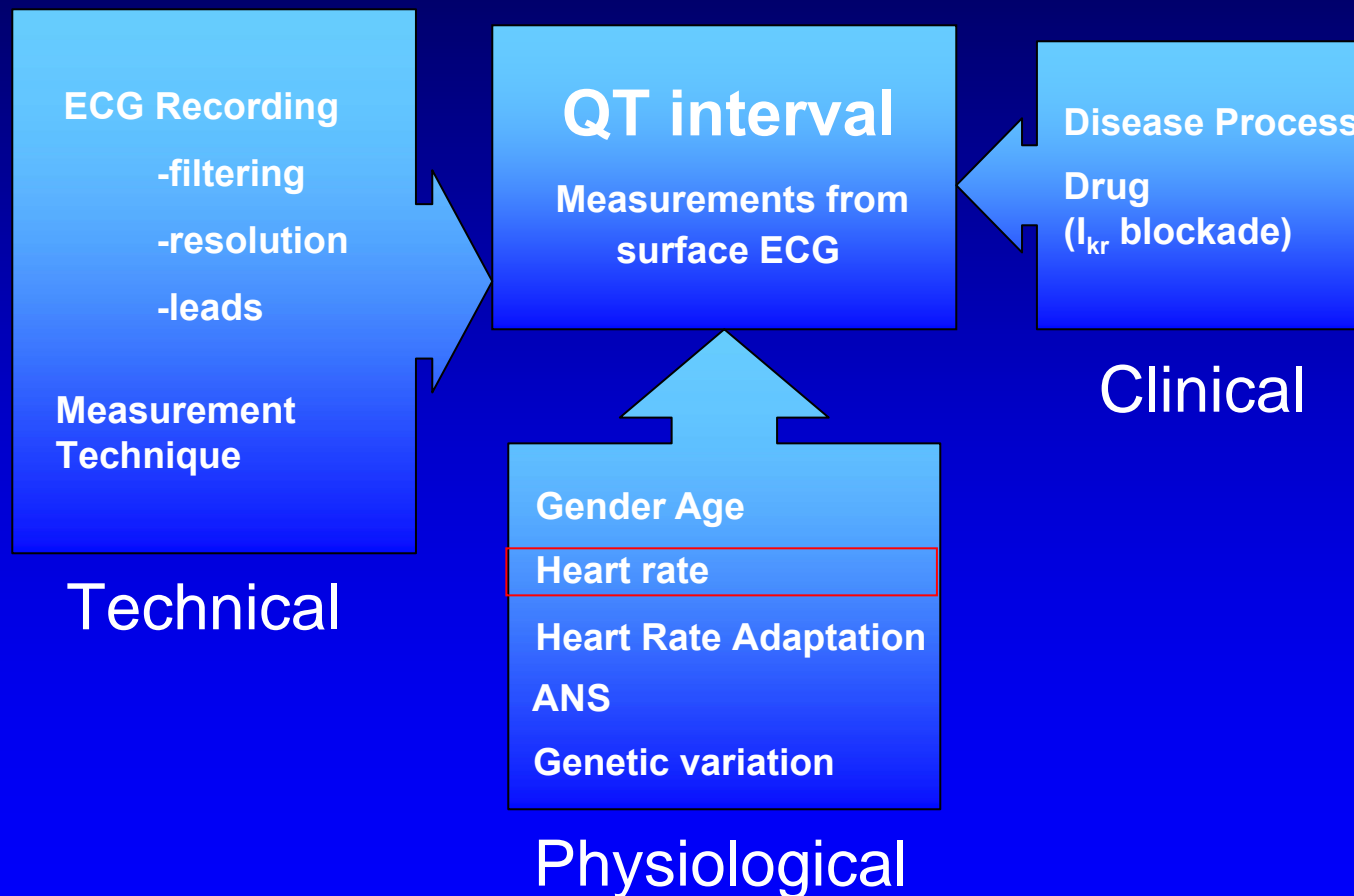
RR=1027 msec

Holter Approach

Removing Periods of Repolarization Instability

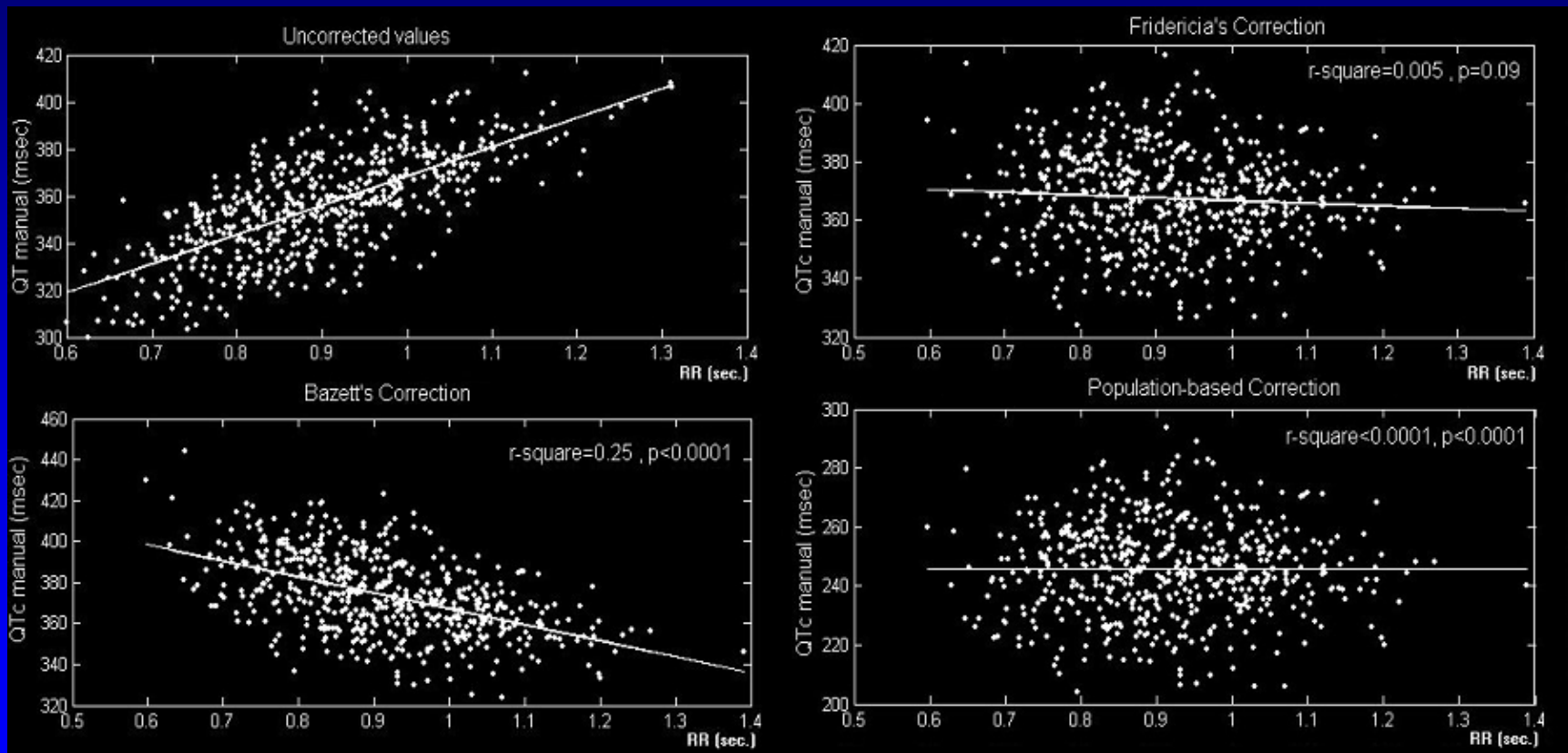


The Challenge of QT Interval Measurements



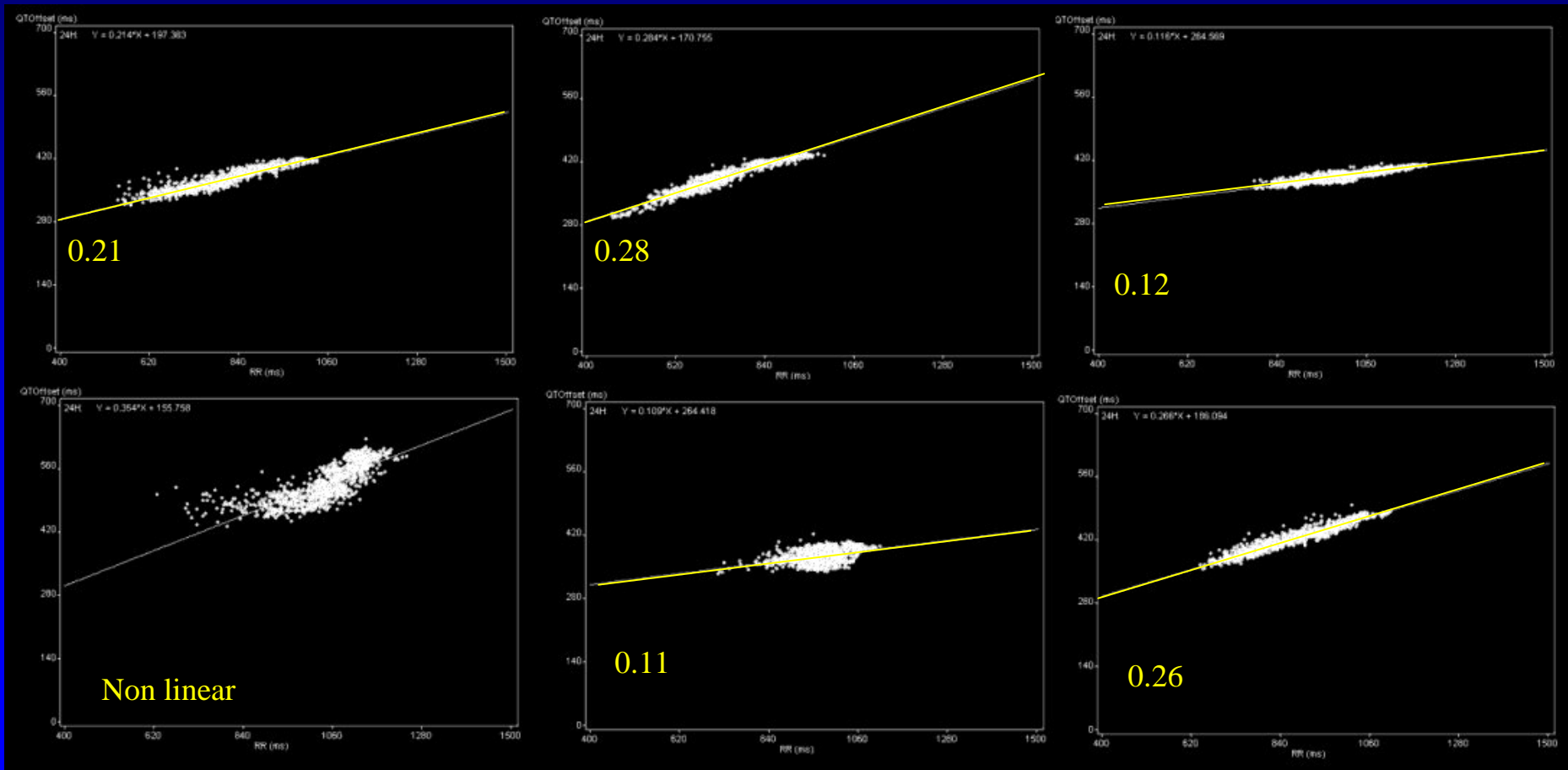
Heart Rate Dependency (1)

Formula-based correction



Heart Rate Dependency (2)

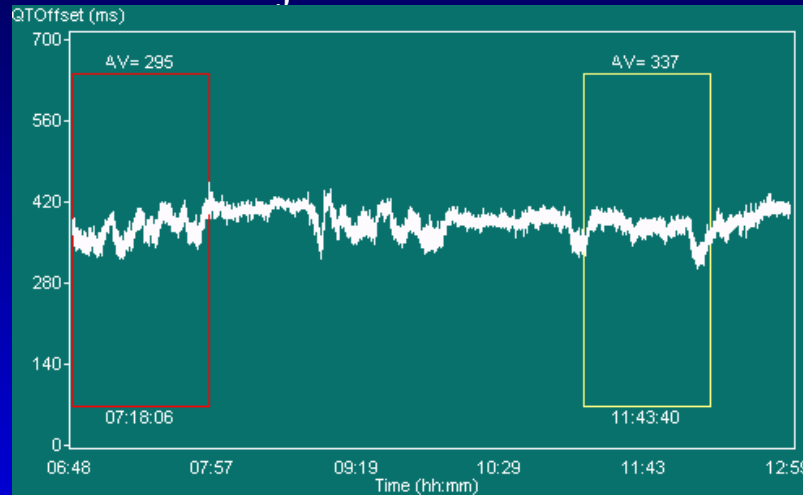
- Subject dependent QT/RR profile



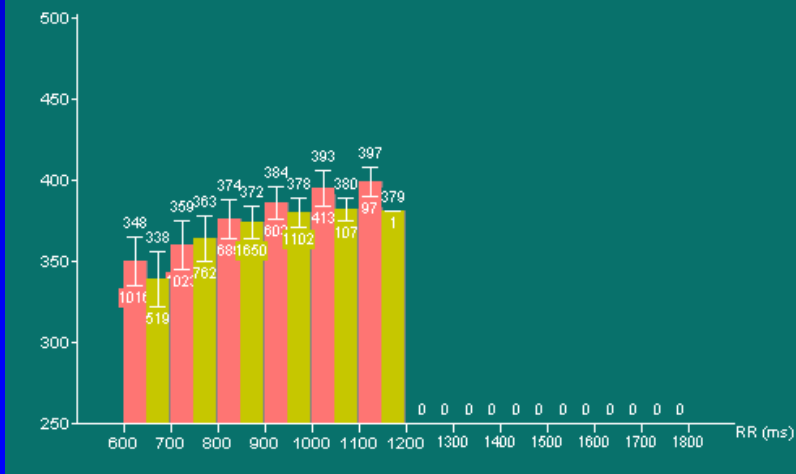
Beat-to-beat RR-Bin Method

Based on beat-to-beat measurements of the QT interval in Holter ECG recordings

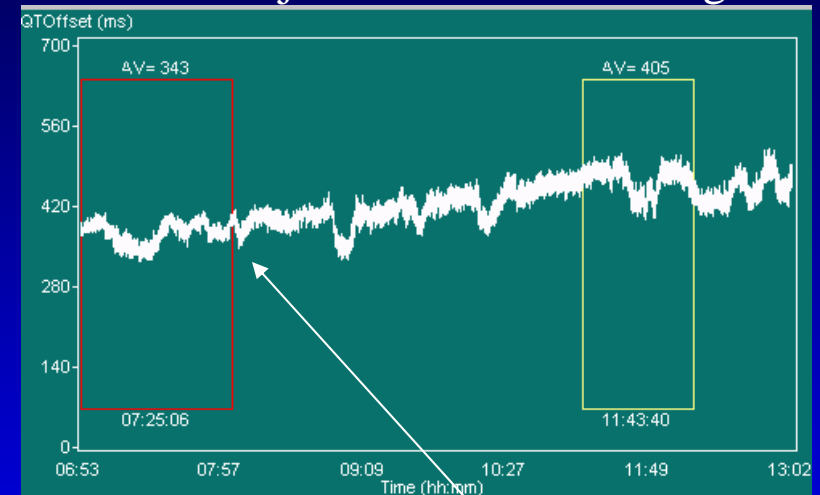
Subject #21: baseline



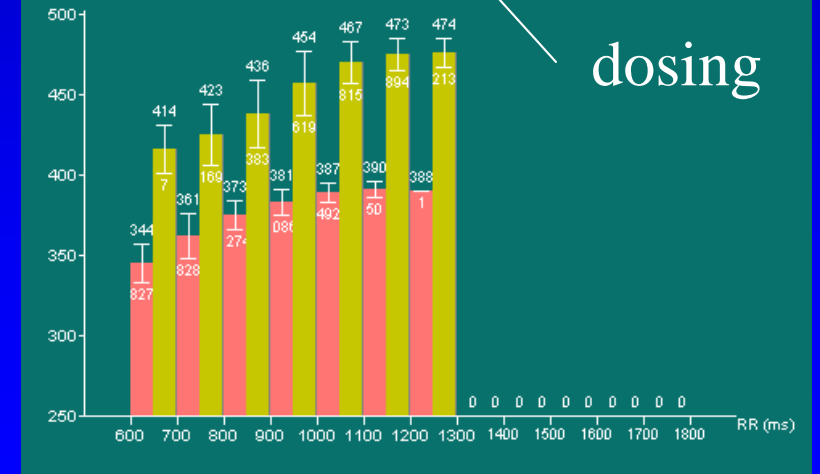
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Subject #21: sotalol dosing

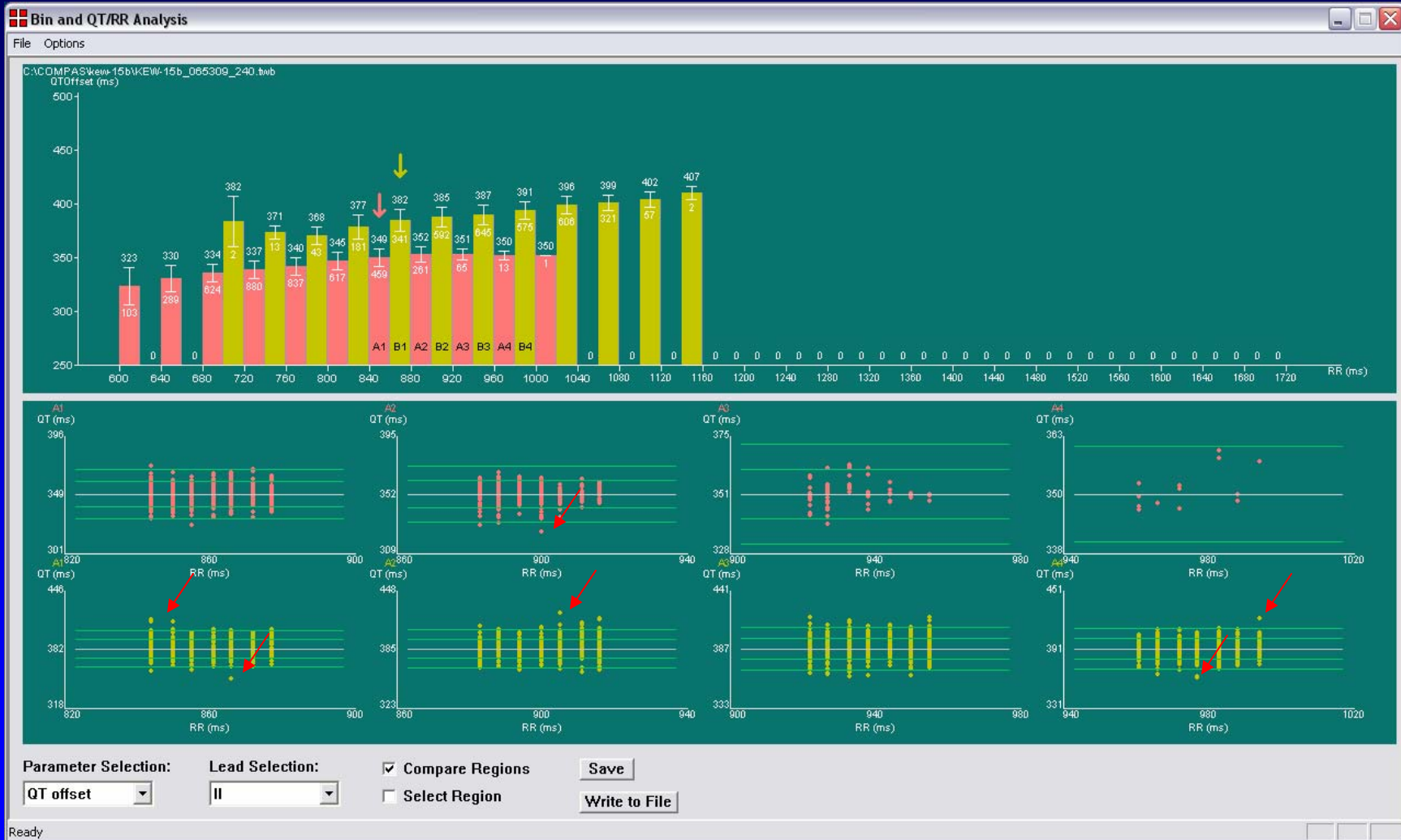


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Beat-to-beat RR-Bin Method

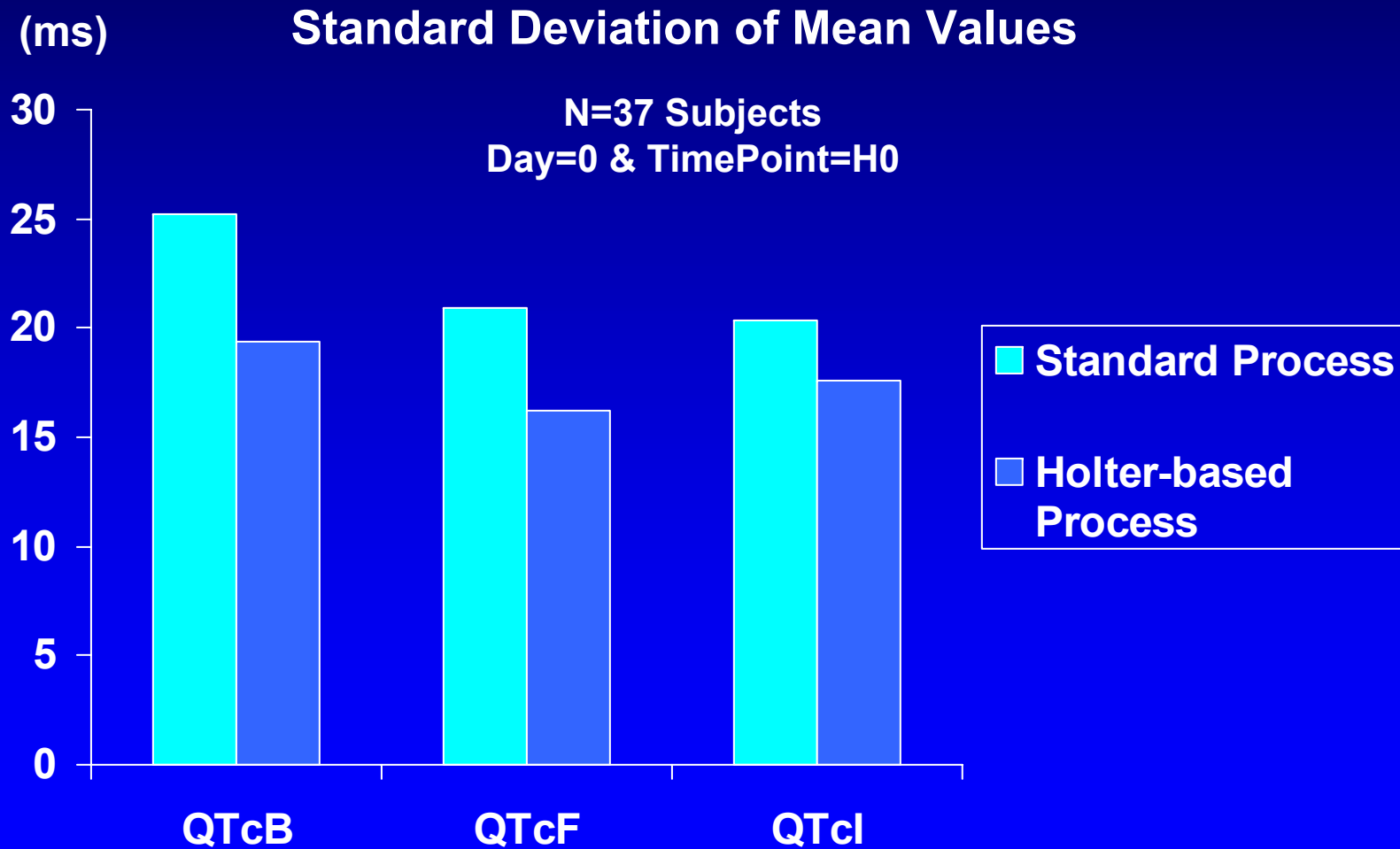
Assessing the quality of the automatic beat-to-beat QT measurements
(semi-automatic approach)



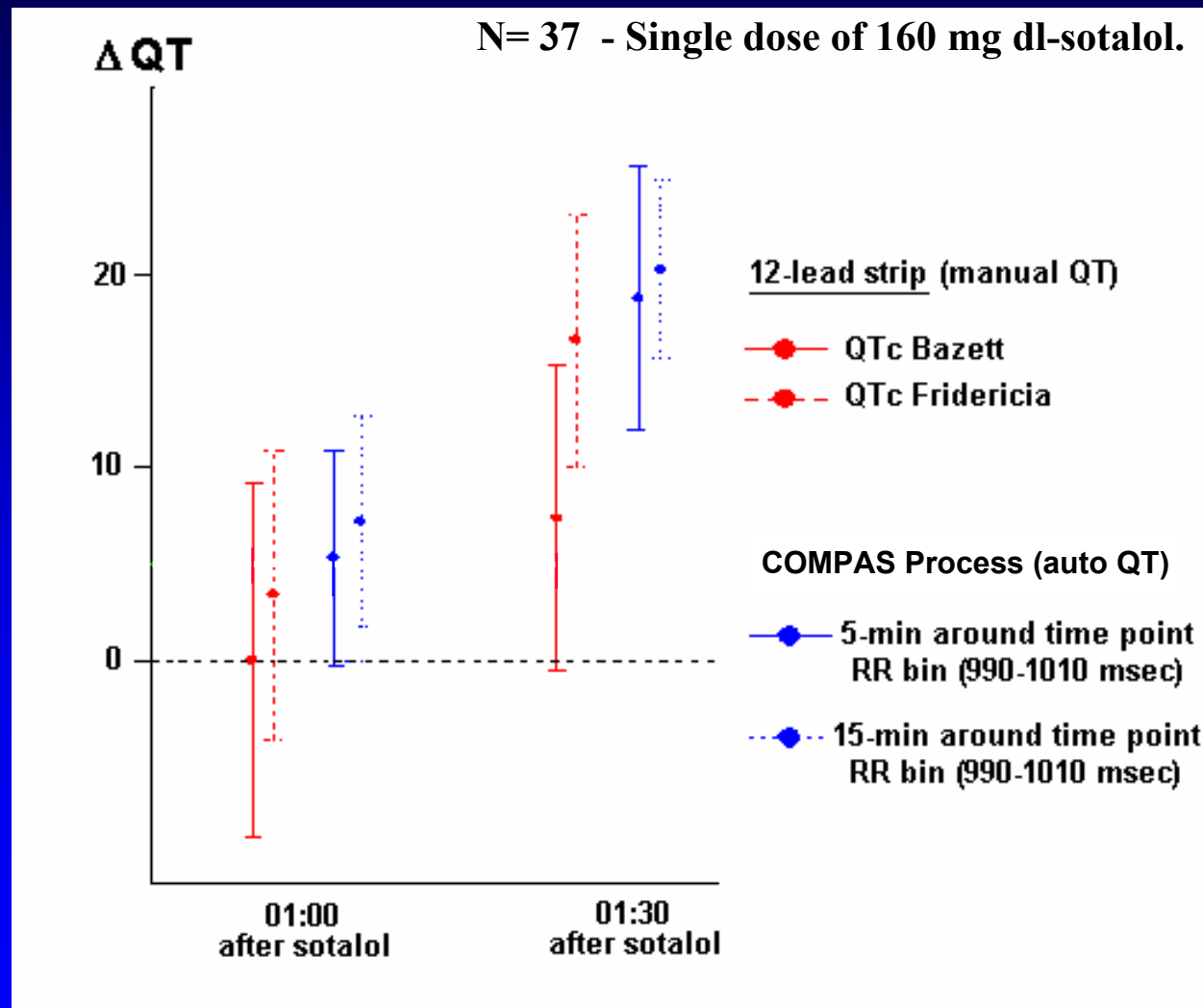
*Controlling for the Hysteresis
and
for the QT heart-rate Dependency*

Assessing the effect on the QT measurements

Reduction in QT Variability vs. Standard Core Lab Process



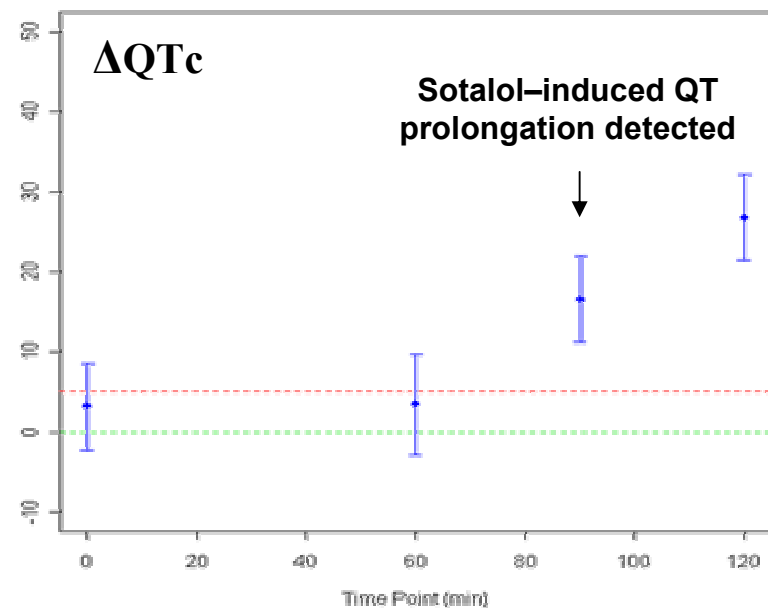
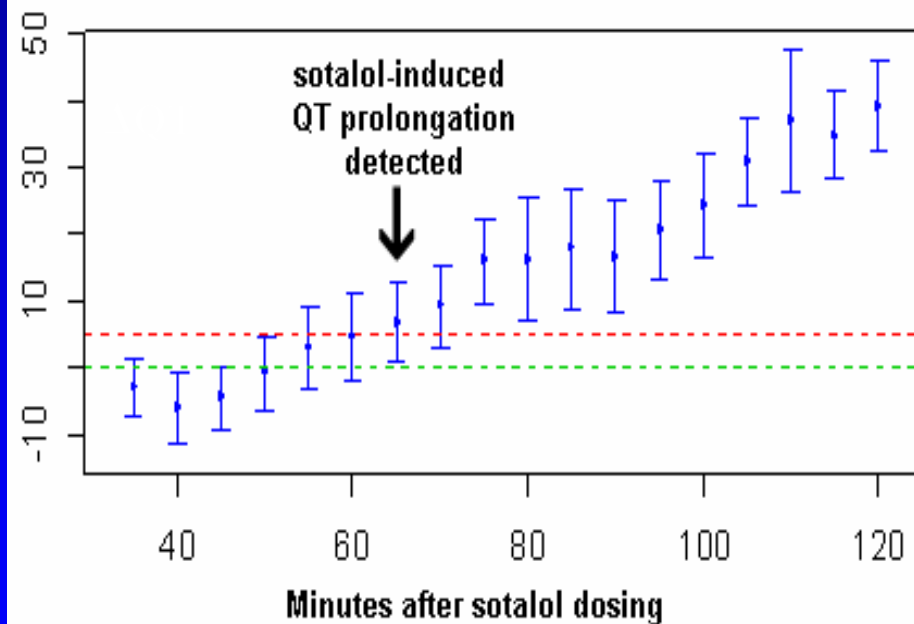
Reduction in QT Variability Associated with beat-to-beat RR-bin Technique



Early Detection of QT Prolongation Using beat-to-beat RR-bin Technique

Five-minute interval RR binning reporting RR bin (990-1010 msec) (Fully automatic QT)

ECGs extracted and $\Delta QTcF$ calculated at 4 timepoints (manual QT)



Conclusions

- Advanced Holter-based technologies have potential to greatly improve cardiac safety assessment
- The Telemetric and Holter ECG Warehouse project is an important initiative to further develop advanced cardiac safety approaches