Advanced waveform analysis of the electrocardiogram to characterise cardiac drug safety between caucasian and Japanese volunteers

AUTHORS:

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INTRODUCTION:

Safety assessment during clinical development of candidate drugs involves evaluation of their pro-arrhythmic propensity through detailed ECG studies. Moxifloxacin serves as a positive control in such studies.

ECG analysis is currently reduced to simplified biomarkers, such as rate, amplitudes and intervals, including QT.

A novel analysis method, Symmetric Projection Attractor Reconstruction (SPAR), highlights changes in the morphology of such waveforms which might provide further sensitivity of detection of cardio-activity beyond QT.

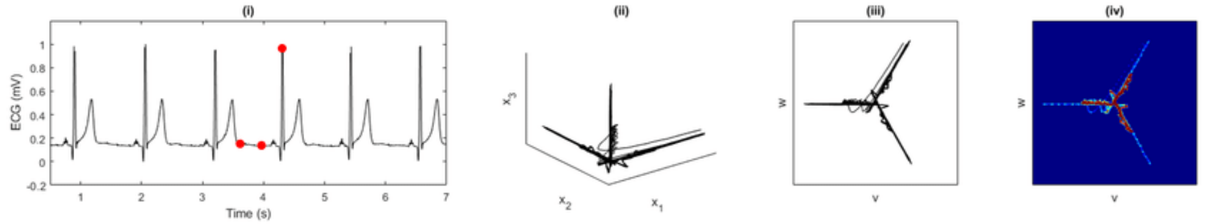
METHODS:

We carried out retrospective SPAR analysis of ECG data from a Moxifloxacin (400g) Ph1 study in healthy human volunteers. These included caucasian (n=13) and Japanese (n=19), male (n=18) and female (n=14) subjects.

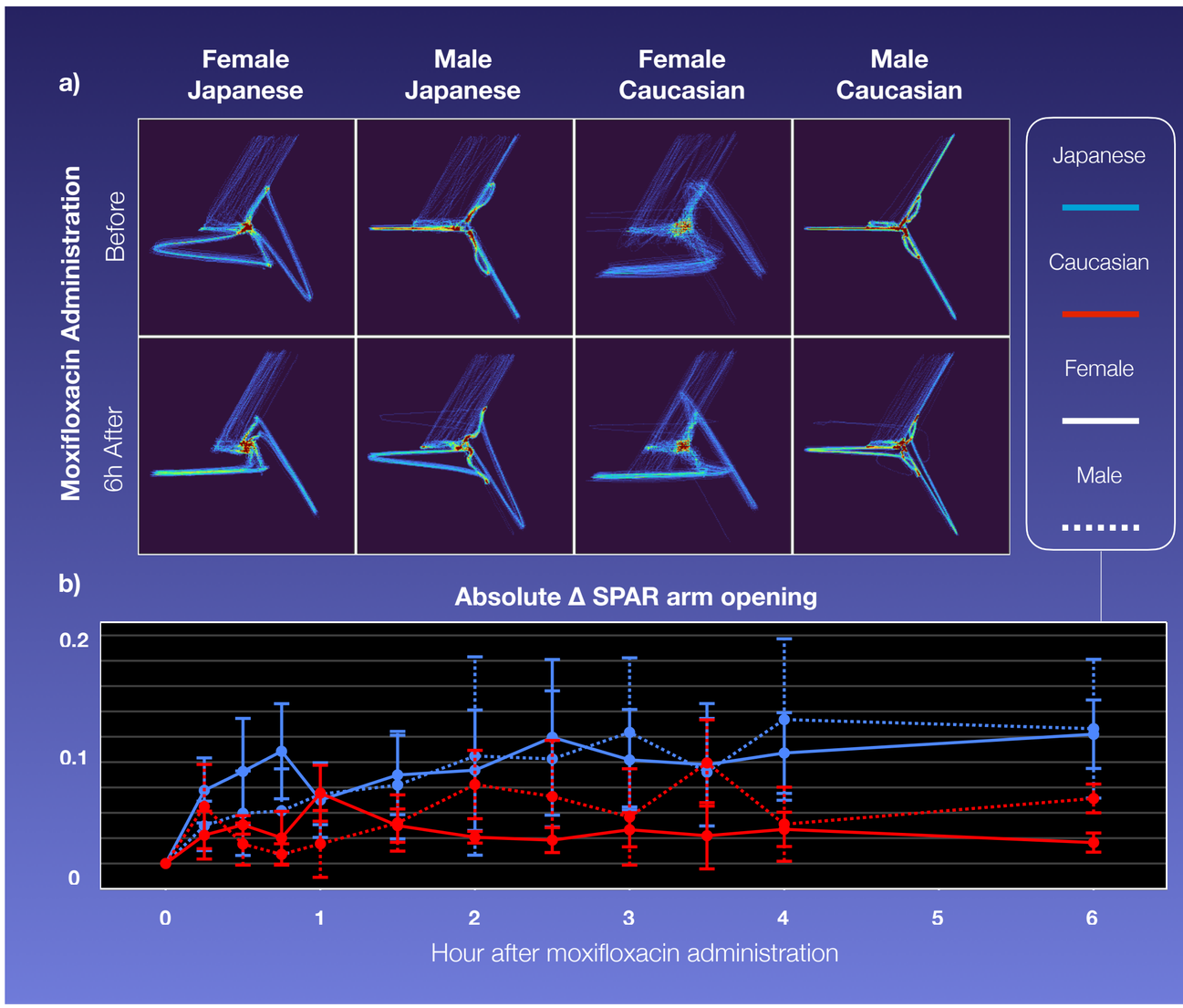
Symmetric Projection Attractor Reconstruction

SPAR transforms ECG signals by continuously measuring 3 moving equidistant points (1/3 of a cycle) and plotting their values in 3 dimensions, creating a loop for each wave

A final image (i.e. 'attractor') is then created by projecting the multi-wave 3D plot into a contained 2D plane, which highlights waveform morphology and variability changes



* WO2015121679A1 delay coordinate analysis of periodic data and state - KCL and University of Surrey IP



DATA PROCESSING:

10-second triplicate ECGs, measured at 0 and 6h after drug administration, were combined into single attractors.

RESULTS:

Consistent with previous studies, ECG attractors showed high inter-individual variability.

Moxifloxacin caused more evident ECG and SPAR attractor changes in Japanese populations over the 6 hours after administration, in a time-dependent manner (Fig. 1a).

These changes were quantified using secondary algorithms (Fig. 1b).

CONCLUSION:

This pilot study illustrates the ability of SPAR to describe an individual's whole-waveform ECG morphology and highlight drug-induced ECG changes.

Furthermore, it suggests that ECG drug monitoring data should be disaggregated to understand subpopulation risks.

Plasma drug concentration correlations to attractor metrics and and head-to-head comparisons with conventional ECG markers should now be performed to confirm the added benefit of SPAR analysis.

Figure 1
Exemplary SPAR attractors of the 4 study groups under different treatments and corresponding quantifications

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