Title: **Further evidence on how to measure local repolarization time using intracardiac unipolar electrograms in the intact human heart**

Running Title**: Wyatt vs Alternative methods for ERP estimation**

M. Orini[1,2], PhD, Neil Srinivasan[1], PhD, Adam J Graham[1], MRCP, Peter Taggart[2], MD DSci, Pier D. Lambiase[1,2,] PhD, FRCP, FHRS

1. Barts Heart Centre, St Bartholomew's Hospital, London, UK

2. Institute of Cardiovascular Science, University College London, London, UK

Corresponding author: Dr Michele Orini, +447845068446, 5 University St, WC1E 6JF, Lodon, UK, m.orini@ucl.ac.uk

Subject Terms: Electrophysiology, Information Technology

Keywords: Repolarization, Cardiac Mapping, Unipolar electrograms, In-vivo human studies

Non-standard Abbreviations and Acronyms: Repolarization time (RT); Unipolar electrogram (UEG); Effective refractory period (ERP); Activation-recovery intervals (ARI)

There are currently two methodologies for measuring local repolarization time (RT) from the unipolar electrogram (UEG). The standard method (or Wyatt method [1]), where RT is measured on the upslope of both upright and inverted T-waves, is widely used, has a solid theoretical background, correlates with the effective refractory period (ERP) in patients [2] and has been validated in animal studies [2,3]. An alternative method in which RT is also taken on the upslope of inverted T-waves, but on the downslope of upright T-waves, has been suggested to provide better correlation to RT derived from monophasic action potentials in human hearts [4], which has made it the method of choice in several recent human studies [5]. Although the Wyatt method is supported by solid evidence and more widely used, further data from the intact human heart is therefore needed to bring closure to the controversy. This is increasingly relevant as advances in cardiac mapping are rapidly providing access to more and more human data. Importantly, no direct comparison between these two methods and the ERP, the most robust measure of refractoriness, has ever been conducted. In this first retrospective comparative study, the local ERP was more accurately measured with the Wyatt than the alternative method.

Eleven patients (47±12 years old, 6 women) with structurally normal hearts and normal ECG underwent electrophysiology studies for supraventricular tachycardia ablation conducted under minimal conscious sedation. The study was approved by the local ethics committee and all patients gave informed consent. Programmed electrical stimulation was performed via the distal electrodes of Decapolar catheters, with electrode spacing equal to 2-5-2 mm, at a pulse width of 2 ms and stimulus strength of twice the diastolic threshold. Pacing was delivered from the RV apex (n=10), LV base (n=10) and coronary sinus (LV epicardial base, n=4). Following steady state pacing at 600 ms for 3 minutes, S_1S_2 restitution protocols were performed from at least 2 of these 3 sites. Eight drive trains at 600 ms were followed by an extra stimulus at coupling interval S_1S_2 decrementing from 1000 to 400 ms in 50 ms steps, from 400 to 300 ms in 20 ms steps and from 300 to ERP in 5 ms steps. The S_2 stimulus was then decremented in 1 ms steps from 10 ms above the point of loss of capture to define the ERP (Figure A). UEGs were recorded with a BARD EP system with sampling frequency equal to 2 KHz and band-pass filtered at 0.05-500 Hz using the Wilson Central terminal as reference. UEGs were subsequently low-pass filtered off-line at 80 Hz and 25 Hz for activation and repolarization measurements, respectively. Activation-recovery intervals (ARI), a surrogate for action potential duration, were measured as repolarization time minus actitation time. As upright T-waves occur adjacent to the pacing site but become inverted at sites more distant to it, analysis for upright T-waves used ARI measured from the electrode adjacent to the pacing site where ERP was being determined, while analysis for inverted T-waves used ARI measured from the site where ERP had been previously assessed while pacing at a distance from it.

Data are available from the corresponding author upon reasonable request.

No patient developed ventricular tachycardia or signs of myocardial ischemia therefore excluding the possibility of underlying post-repolarization refractoriness.

ERP across all patients was 240±15.9 ms (mean ± standard deviation).

A representative example showing a positive T-wave, where the Wyatt and alternative method differ, is shown in Figure B. The ARI measured with the Wyatt and alternative methods were 4 ms and 61 ms longer than the ERP, respectively. When pacing from the site of ERP measurement, all sites adjacent to it exhibited an upright T-wave, with the ERP occurring during its upslope (i.e. between its onset and peak). Across all 24 sites where upright T-waves were recorded, the Wyatt method closely approximated the ERP, with difference between ERP and ARI equal to 10.1±15.5 ms, whereas the alternative method provided ARI always much longer than the local ERP, with differences between ERP and ARI equal to -56.8±16.2 ms ($P=1.8x10^{-5}$, Wilcoxon signed-rank test).

UEGs with inverted T-waves were recorded at the site of ERP measurement in 17 out of 24 cases while pacing at sites distant from it (Figure C). In these inverted T-waves, the Wyatt and alternative methods coincide and the difference between ARI and ERP was -0.7±12.8 ms.

In conclusion, in the intact human heart the Wyatt method provides a reliable approximation of local ERP regardless of pacing site and T-wave morphology, whereas the alternative method provides ARI estimates that in UEGs exhibiting up-right T-waves largely exceed ERP.

Sources of Funding

Part of this work was supported by a British Heart Foundation Clinical Research Training Fellowship (FS/14/9/30407). PDL is supported by University College London Hospital Biomedicine National Institute of Health Research (UCLH-NIHR), NIHR Barts Biomedical Research Centre and Stephen Lyness Research Fund.

Conflict of interest: none declared

References

1. Wyatt RF, Burgess MJ, Evans AK, Lux RL, Abildskov JA, Tsutsumi T. Estimation of ventricular transmembrane action potential durations and repolarization times from unipolar electrograms. *Am J Cardiol*. 1981;47:488.

2. Chinushi M, Tagawa M, Kasai H, Washizuka T, Abe A, Furushima H, Aizawa Y. Correlation between the effective refractory period and activation-recovery interval calculated from the intracardiac unipolar electrogram of humans with and without dl-sotalol treatment. *Jpn Circ J*. 2001;65:702–706.

3. Coronel R, de Bakker JMT, Wilms-Schopman FJG, Opthof T, Linnenbank AC, Belterman CN, Janse MJ. Monophasic action potentials and activation recovery intervals as measures of ventricular action potential duration: Experimental evidence to resolve some controversies. *Heart Rhythm*. 2006;3:1043–1050.

4. Yue AM, Paisey JR, Robinson S, Betts TR, Roberts PR, Morgan JM. Determination of human ventricular repolarization by noncontact mapping: Validation with monophasic

action potential recordings. *Circulation*. 2004;110:1343–1350.

5. Leong KMW, Ng FS, Yao C, Roney C, Taraborrelli P, Linton NWF, Whinnett ZI, Lefroy DC, Davies DW, Boon Lim P, Harding SE, Peters NS, Kanagaratnam P, Varnava AM. ST-elevation magnitude correlates with right ventricular outflow tract conduction delay in Type I Brugada ECG. *Circ Arrhythmia Electrophysiol*. 2017;10.

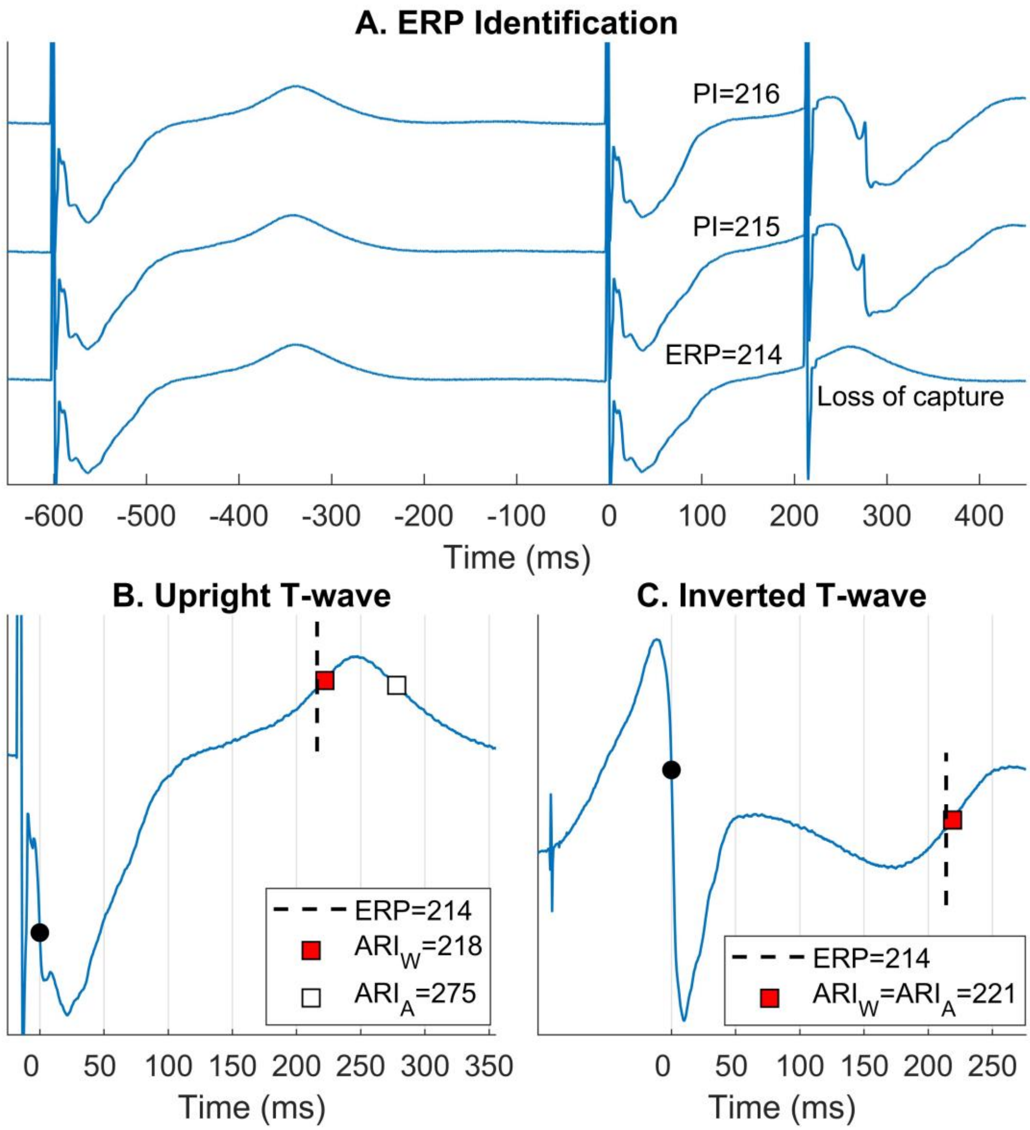

Figure: ERP and ARI measured with the Wyatt and Alternative methods. A: The last 2 S_1 beats of the drive train followed by the S_2 premature beat are shown for the last 3 drive trains prior to loss of capture, aligned vertically. Vertical lines represent pacing artefacts. S_1S_2 pacing interval (PI) decrements with loss of capture at 214 ms (bottom) defining the effective refractory period (ERP). B: Unipolar electrogram (UEG) simultaneously recorded from the electrode adjacent to the pacing site shows an up-right T-wave. C: UEG recorded from the site where ERP was measured, while pacing at a distance, shows an inverted T-wave. Both UEGs are aligned to the local activation time. Vertical dashed lines represent the local ERP, which is better estimated by the ARI obtained using the Wyatt (ARI_W) than the alternative (ARI_A) method. PI, ARI_W, ARI_A and ERP are reported in ms.