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LETTER TO THE EDITOR

WILEY

Novel arrhythmic risk markers incorporating QRS dispersion: $QRS_d \times (T_{peak} - T_{end})/QRS$ and $QRS_d \times (T_{peak} - T_{end})/(QT \times QRS)$

Dear Editor,

We read the excellent article by Robyns et al. (2015) with great interest, validating the Index of Cardio-Electrophysiological Balance (iCEB) as a reliable marker for predicting arrhythmogenicity in humans. Risk stratification of patients who might develop life-threatening ventricular arrhythmias remains difficult. Several risk markers based on repolarization have been proposed. QT interval (corrected, QT_c) prolongation is a widely used marker but its use is limited by a low sensitivity and specificity, arrhythmias can develop despite a normal or even shortened QT interval. Other markers include QT dispersion (QT_d), interval from the peak to the end of the *T* wave ($T_{peak} - T_{end}$) and ($T_{peak} - T_{end}$)/QT ratio.

However, the major problem with the above repolarization markers is that abnormal depolarization, which contributes to arrhythmogenesis, is largely ignored. For example, in heart failure and Brugada syndrome, conduction velocity (CV) is reduced. This increases the likelihood of reentry by shortening the excitation wavelength, λ (CV × effective refractory period). λ must be determined invasively by electrophysiological studies. Therefore there is a need for noninvasive markers that are good approximates of λ: the index developed by Lu, Yan, and Gallacher (2013) iCEB, is one of such markers.

Based on the concept of λ and iCEB, and the observations that $T_{peak} - T_{end}$ and ($T_{peak} - T_{end}$)/QT are superior to the QT interval in predicting arrhythmogenicity, Tse recently proposed two novel indices that may have a higher accuracy in risk stratification: ($T_{peak} - T_{end}$)/QRS and $T_{peak} - T_{end}$/(QT × QRS) (Tse, 2016a,b). Both can easily be determined from the electrocardiogram and are firmly based on electrophysiological principles that λ is critical in determining arrhythmogenicity (Tse, Lai, Tse, & Yeo, 2016; Tse, Lai, Yeo, Tse, & Wong, 2016; Tse, Lai, Yeo, & Yan, 2016; Tse, Sun, Wong, Tse, & Yeo, 2016; Tse, Wong, Tse, & Yeo, 2016a,b). Although these have not been validated clinically, they have the potential of having superior predictive values than ventricular repolarization markers such as QT_c, QT_d, $T_{peak} - T_{end}$, or ($T_{peak} - T_{end}$)/QT ratio.

Nevertheless, a downfall of Tse's indices is that they do not account for increased CV dispersion in arrhythmogenesis. This can refer to phase difference in conduction latencies of neighboring regions, difference in CV across the myocardial wall, and coefficient of dispersion using standard deviation of the mean CV. A method of measuring CV dispersion clinically is increased QRS dispersion (QRS_d). QRS_d has been defined as the maximum difference between QRS durations measured in the right and left precordial leads. Here, we further propose two indices incorporating QRS_d: (1) $QRS_d \times (T_{peak} - T_{end})/QRS$, and (2) $QRS_d \times (T_{peak} - T_{end})/(QT \times QRS)$. The term QRS_d/QRS is proposed to serve as a surrogate marker of CV dispersion coefficient based on the standard deviation of the mean CV. These indices may have good predictive value for arrhythmic outcome and cardiovascular mortality in clinical conditions with increased CV dispersion, such as heart failure and Brugada syndrome.

In conclusion, clinical markers such as iCEB, Tse's conduction-repolarization indices of ($T_{peak} - T_{end}$)/QRS and $T_{peak} - T_{end}$/(QT × QRS), as well as the two novel indices presented here will further aid identification of patients at risk of developing ventricular arrhythmias.

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REFERENCES

Lu, H. R., Yan, G.-X., & Gallacher, D. J. (2013). A new biomarker – Index of Cardiac Electrophysiological Balance (iCEB) – plays an important role in drug-induced cardiac arrhythmias: Beyond QT-prolongation and Torsades de Pointes (TdPs). *Journal of Pharmacological and Toxicological Methods*, *68*, 250–259.

Robyns, T., Lu, H. R., Gallacher, D. J., Garweg, C., Ector, J., Williams, R. … Nuygen, D. (2015). Evaluation of Index of Cardio-Electrophysiological Balance (iCEB) as a new biomarker for the Identification of Patients at Increased Arrhythmic Risk. *Annals of Noninvasive Electrocardiology*, *21*, 294–304.

Tse, G. (2016a). (Tpeak-Tend)/QRS and (Tpeak-Tend)/(QT x QRS): Novel markers for predicting arrhythmic risk in Brugada syndrome. *Europace*, in press.

Tse, G. (2016b). Novel conduction-repolarization indices for the stratification of arrhythmic risk. *Journal of Geriatric Cardiology*, in press.

Tse, G., Lai, E. T., Tse, V., & Yeo, J. M. (2016). Molecular and electrophysiological mechanisms underlying cardiac arrhythmogenesis in diabetes mellitus. *Journal of Diabetes Research*, in press.

Tse, G., Lai, T. H., Yeo, J. M., Tse, V., & Wong, S. H. (2016). Mechanisms of electrical activation and conduction in the gastrointestinal system: Lessons from cardiac electrophysiology. *Frontiers in Physiology*, *7*, 182.

Tse, G., Lai, E. T., Yeo, J. M., & Yan, B. P. (2016). Electrophysiological mechanisms of Bayés syndrome: Insights from clinical and mouse studies. *Frontiers in Physiology*, *7*, 188.

Tse, G., Sun, B., Wong, S. T., Tse, V., & Yeo, J. M. (2016). Ventricular anti-arrhythmic effects of hypercalcaemia treatment in hyperkalaemic, Langendorff-perfused mouse hearts. *Biomedical Reports*, in press.

Tse, G., Wong, S. T., Tse, V., & Yeo, J. M. (2016a). Monophasic action potential recordings: Which is the recording electrode? *Journal of Basic and Clinical Physiology and Pharmacology*. doi:10.1515/jbcpp-2016-0007 [Epub ahead of print].

Tse, G., Wong, S. T., Tse, V., & Yeo, J. M. (2016b). Depolarization vs. repolarization: What is the mechanism of ventricular arrhythmogenesis underlying sodium channel haploinsufficiency in mouse hearts? *Acta Physiologica*. doi:10.1111/apha.12694 [Epub ahead of print].