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Determination of action potential wavelength restitution in *Scn5a*$^{+/-}$ mouse hearts modelling human Brugada syndrome

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Brugada syndrome is a primary electrical disorder of the heart, predisposing affected individuals to potentially lethal, ventricular tachy-arrhythmias.[1–7] A number of mechanisms have been identified as being important increasing the risk of these rhythms.[8] Wavelength (λ) restitution has been suggested to predict the onset of action potential duration (APD) alternans in mouse *Scn5a*$^{+/-}$ hearts modelling Brugada syndrome.[9] Classical APD restitution analysis yielded mixed success in its ability to predict the onset of APD alternans and arrhythmogenicity. APD restitution relates APD to the previous diastolic interval (DI). APD restitution gradients > 1 is associated with the emergence of APD alternans,[10] and increased arrhythmogenicity in a number of different genetic and pharmacological mouse models, such as Brugada syndrome, long QT syndrome type 3 and hypokalaemia.[11–13] Matthews and colleagues previously demonstrated a non-linear relationship between APD alternans and APD restitution gradient and underestimated the extent of APD alternans, suggesting that it may partly underlie its lack of success in predicting arrhythmogenicity.[14] Another reason is that effective refractory period (ERP) can be altered independently of APD.[15]

The lack of predictive power of APD restitution led Matthews and colleagues to devise a novel λ restitution analysis by recording monophasic action potential (MAP) recordings in wild-type and *Scn5a*$^{+/-}$ hearts during dynamic pacing, which introduced a stepwise increase in pacing rate.[9] The MAP method is an *ex vivo* recording technique that has widely been used to study whole heart electrophysiology in Langendorff systems. Activation latencies and APDs were derived from the MAPs obtained from the ventricles, with conduction velocity (θ) approximated by the reciprocal of activation latency, θ'. This in turn enabled the calculation of λ', which was approximated by θ' × APD, with the explicit assumption that ERP was equal to APD.

Whilst we do not doubt the important role of wavelength in determining arrhythmogenicity, the method chosen by Matthews and colleagues may not be accurate in estimating wavelength for the following reasons. Firstly, the discordance between APD and ERP are apparent from the data generated by the authors' own group, but this has not been highlighted. Specifically, Martin and colleagues showed that APD is longer than ERP in wild-type hearts, whereas it is shorter than ERP *Scn5a*$^{+/-}$ hearts.[16]

Secondly, estimation of wavelength using the authors' method requires accurate measurements of APD. Yet, the group's data on APD values have been highly discrepant, as can be seen in their own studies on Brugada syndrome.[17,18] For example, in the left ventricular (LV) epicardium, APD_{70} and APD_{50} were not significantly altered by quinidine.[17] However, the authors later found that these were increased by quinidine.[18] In the LV endocardium, APD_{90}, APD_{70} and APD_{50} were decreased by quinidine.[17] Their later study found that these were increased by quinidine.[18] Given these discrepancies, λ did not appear to be accurately determined.

Together, the current evidence clearly shows that λ reduction,[19] and increased APD restitution[20] are important mechanism by which cardiac arrhythmias are generated and maintained. However, the role of λ restitution is unclear, but more accurate methods of determining this parameter experimentally need to be devised before a more definite conclusion can be reached.

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