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A basis for human QT interval prolongation and arrhythmia risk in type 2 diabetes?

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Diabetes is well-established to be a major healthcare problem. Preclinical and clinical data suggest that diabetes influences the heart and may be associated with cardiac repolarisation abnormalities and pro-arrhythmia. For example, a recent (2017) retrospective review of patients admitted to hospital at least twice in a 4-year period with type 1 or 2 diabetes, found prolonged rate-corrected (QT_c) QT intervals in ~67 % of type 1 and ~51 % of type 2 patients (Lu *et al.*, 2017). In the same study, more than 60 % of diabetic patients exhibited a modest, but significant reduction in left ventricular ejection fraction (LVEF) between first and second admissions (Lu *et al.*, 2017). In preclinical experiments, potassium channel current reduction has been reported in ventricular myocytes from type 2 diabetic (*db/db*) male but not female mice of 12 weeks of age (Shimoni *et al.*, 2004); this suggests that type 2 diabetes in mice is associated with sex-specific K^+ channel remodelling. However, the relevance of such findings to human diabetes is unclear because small rodents and humans rely on different K^+ channels for ventricular repolarisation. In contrast, whilst *in vivo* measurements from rabbits with type 2 diabetes induced by a high fat diet have shown QT_c interval prolongation and augmented QT interval dispersion (Zarzoso *et al.*, 2014), corresponding *in vitro* measurements from isolated hearts with normal extracellular potassium showed no changes in repolarisation, suggesting that (an) extrinsic factor(s) may be involved in producing repolarisation abnormalities in that model (Zarzoso *et al.*, 2014). This differs from data from a rabbit model of type 1 diabetes, showing both QT_c prolongation and reduced ventricular rapid delayed rectifier K^+ current, I_{Kr}, attributed to oxidative stress damage to the myocardium and reversible with insulin (Zhang *et al.*, 2006). Of course, what is really needed to understand effects of diabetes on *human* ventricular repolarisation and arrhythmia risk is information on ion channel/transporter function in *human* ventricular myocardium. This is problematic, however, due to issues in obtaining

and making measurements from human healthy control and diabetic ventricular tissue. In this volume of the journal, Ashrafi *et al* (2017) have taken an alternative approach to the issue: measurement of myocardial gene expression from type 2 diabetic patients undergoing surgery for aortic valve replacement, with controls represented by patients undergoing the same surgery, but lacking type 2 diabetes. The combination of this approach with computer modelling has given rise to potentially important new information on proarrhythmic electrical remodelling in human type 2 diabetes (Ashrafi *et al*, 2017).

In this new study, left ventricular myocardial biopsies were taken from 9 control and 7 diabetic patients at the time of aortic valve surgery and quantitative polymerise chain reaction (qPCR) was used to measure levels mRNA for a range of major ion channels and transporters (Ashrafi *et al*, 2017). QT_c intervals for control and diabetic groups were 451 ms and 467 ms respectively. Modest changes (up to ± 26%) in mRNA for a number of ion channel subunits were found, with substantial changes observed for three genes. Thus, mRNA levels for hERG (the *human Ether-à-Go-Go-related Gene* encoded I_{Kr} channel α-subunit) were decreased by ~65%, whilst those for *KCNJ2* encoded Kir2.1 (a key component of channels responsible for inwardly rectifying K^+ current, I_{K1}) were increased by ~85% and for the cardiac isoform of the sodium-calcium exchanger (NCX1) by ~244%. The relevant current densities in ventricular epicardial and endocardial action potential (AP) models were then scaled by the observed % differences in mRNA levels. Both epi- and endocardial 'diabetic' APs were longer than control APs. Additionally, the modelled endocardial APs exhibited cellular pro-arrhythmic events, early after-depolarisations (EADs). Further simulations were performed in which changes to individual conductances were incorporated and these revealed that the most functionally significant changes were those to I_{Kr} and NCX

current. Altered I_{K1} had only a small effect - a small acceleration of terminal repolarisation. The two groups of subjects were similar in terms of age, left-ventricular ejection fraction, and drug treatments (metformin and sulphonylureas aside). For both groups longitudinal strain values fell into a range consistent with the presence of some fibrosis, albeit with a slightly lower longitudinal strain value for the diabetes group. Thus, the differences in gene expression and corresponding electrophysiological simulations were considered to be a consequence of diabetes/hyperglycaemia rather than caused by a pathway linked to fibrosis and left-ventricular hypertrophy (Ashrafi *et al*, 2017).

Whilst some caution is warranted in interpreting simulation results based on mRNA data alone, without corresponding protein expression or function data, the approaches adopted in the study by Ashrafi and colleagues are justified in light of the challenges in obtaining the required comparative functional data from human ventricular myocytes. Their results are consistent with human type 2 diabetes leading to an "acquired" form of QT_c interval prolongation akin to that produced by hERG blocking drugs (Hancox *et al.*, 2008), potentially exacerbated by NCX-linked changes in Ca^{2+} handling. This could have important implications in terms of arrhythmia risk and drug selection for such patients. However, as the authors acknowledge, the sample sizes here are relatively small and the subjects elderly (mean ages of >70 for both groups). Future work is needed to determine whether these results are borne out by studies of larger diabetic cohorts and for subjects of different ages. Also, there are intrinsic differences in repolarisation between males and females (James *et al.*, 2007) and the study of larger control and diabetic cohorts would enable evaluation of sex-linked differences in type 2 diabetic remodelling. The results presented here provide an important platform upon which such larger studies can build. They also provide a basis for the

selection for mechanistic studies of animal models that mimic most closely the ion channel/transporter remodelling seen here for humans. This study also lays the foundation for further future simulation work: to determine model-dependence of the delayed repolarisation seen here; to investigate rate dependence of the observed effects and, at the 'intact' tissue level, to probe arrhythmia mechanisms and to explore the potential for antiarrhythmic approaches targeted to specific diabetic remodelling.

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