Understanding the mechanisms of atrial fibrillation in diabetes using human tissue resources, animal models, and big data

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Project outline

Background: Diabetes mellitus (DM) is an important risk factor for atrial fibrillation (AF) and heart failure with preserved ejection fraction, although the mechanisms underlying these associations remain unclear. Both type 1 and type 2 DM have been associated with an increased risk of AF, independent of other risk factors, and in both cases the excess risk conferred by DM was much greater in women than in men. In contrast with obesity, genetic studies to date have failed to support a causal relationship between type 2 DM and AF and the mechanism by which SGLT2 inhibition lowers the risk of AF in patients with DM and multiple cardiovascular risk factors is unclear. Whether there is a causal relationship between type 1 DM and AF remains to be explored.

In a model of stable type 1 DM in male mice, we found that increasing myocardial tetrahydrobiopterin (BH4) content by overexpressing GTP-CH1 or by oral BH4 supplementation prevents or reverses, respectively, the impaired cardiomyocyte relaxation and rate of intracellular calcium decay, and the *in vivo* LV dysfunction that develop post-DM induction. The protective effect of BH4 is abolished by CRISPR/Cas9-mediated knockout of the "neuronal" isoform of nitric oxide synthase (NOS1). Augmenting BH4 availability in cardiomyocytes induced a nitric oxide-dependent increase in glucose uptake *via* the insulin-independent glucose transporter, GLUT-1, which was instrumental in preserving myocardial mitochondrial creatine kinase activity, oxygen consumption rate, LV energetics (by ^{31}P MRS), and myocardial function (Carnicer *et al.* 2021). In addition, the probability of AF induction by burst pacing was greatly increased in the presence of DM. The rate of AF induction was positively correlated with plasma glucose levels but not with LV function. Atrial histology showed localised fibrosis and *ex-vivo* voltage mapping demonstrated conduction delay limited to this area, with no differences in action potential characteristics.

Aim: To understand the mechanisms responsible for the increase risk of AF in the presence of DM using human tissue resources, animal models, and genetic tools. We hypothesise that DM-induced atrial metabolic alterations and inflammation impact the electrical characteristics of the atrial myocardium, induce fibrosis, and promote AF.

To achieve our aim we plan to combine insights from experimental and big data 'omics and:

a) to assess the impact of hyperglycaemia on stromal and immune cell composition in human and murine atrial tissue by generating bulk and single-cell RNA-sequencing / proteomic data from fresh

and frozen samples of atrial tissue from diabetic and euglycaemic mice and patients and (in mice) evaluate the reversibility of these findings upon reversing DM (see b.). We have already undertaken bulk RNAseq in 440 atrial samples from patients in sinus rhythm with and without DM.

b) to evaluate the relative role of myocardial metabolic alterations *vs.* fibrotic remodeling in increasing AF risk in the presence of DM. This will be accomplished by using an inducible murine model of human DM (the bV59M with Prof F Ashcroft in Oxford).

c) These experiments will be complemented by epidemiological studies that consider genetic proxies for DM and diabetic therapies and their impact on AF and related phenotypes using big data resources such as UK Biobank, genome-wide consortia data, and comprehensive bioinformatic tools.

Supervisor's recent relevant publications:

Barbara Casadei

1. Carnicer R, Duglan D, Ziberna K, Recalde A, Reilly S, Simon JN, Mafrici S, Arya R, Roselló-Lletí E, Chuaiphichai S, Tyler D, Lygate CA, Channon KM, **Casadei B**. BH4 Increases nNOS Activity and Preserves Left Ventricular Function in Diabetes. Circ Res. 2021 Mar 5;128(5):585-601.
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4. Wijesurendra RS, Liu A, Eichhorn C, Ariga R, Levelt E, Clarke WT, Rodgers CT, Karamitsos TD, Bashir Y, Ginks M, Rajappan K, Betts T, Ferreira VM, Neubauer S, **Casadei B**. Lone Atrial Fibrillation Is Associated With Impaired Left Ventricular Energetics That Persists Despite Successful Catheter Ablation. Circulation. 2016 Oct 11;134(15):1068-1081. *(published with an Editorial)*
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Jemma Hopewell

1. Aragam *et al*; CARDIoGRAMplusC4D Consortium. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. Nat Genet. 2022 Dec;54(12):1803-1815.
2. Mishra et al. Stroke genetics informs drug discovery and risk prediction across ancestries. Nature. 2022 Nov;611(7934):115-123.
3. Gajendragadkar PR, Von Ende A, Ibrahim M, Valdes-Marquez E, Camm CF, Murgia F, Stiby A, **Casadei B*, Hopewell JC*.** Assessment of the causal relevance of ECG parameters for risk of atrial fibrillation: A mendelian randomisation study. PLoS Med. 2021 May 13;18(5):e1003572.
4. Camm CF, Lacey B, Massa MS, Von Ende A, Gajendragadkar P, Stiby A, Valdes- Marquez E, Lewington S, Wijesurendra R, Parish S, **Casadei B*, Hopewell JC***. Independent effects of adiposity measures on risk of atrial fibrillation in men and women: a study of 0.5 million individuals. Int J Epidemiol. 2022 Jun 13;51(3):984-995.

5. **Hopewell JC**, Ibrahim M, Hill M, Shaw PM, Braunwald E, Blaustein RO, Bowman L, Landray MJ, Sabatine MS, Collins R; HPS3/TIMI55 - REVEAL Collaborative Group. Impact of ADCY9 Genotype on Response to Anacetrapib. Circulation. 2019 Jul 23;140(11):891–8.