A Multi-Scale Computational Framework for Human-Based Modelling and Simulation of Adverse Cardiac Remodelling in Type 2 Diabetes

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Abstract

Type 2 diabetes causes adverse cardiac remodelling at subcellular, tissue, and whole-organ level. This can lead to severe cardiac complications if left uncontrolled, notably cardiac arrhythmias and heart failure. A timely identification of cardiac abnormalities and a rigorous understanding of underlying mechanistic causes are therefore crucial to prevent further cardiac deterioration in patients with type 2 diabetes. Our goal is to identify and mechanistically explain subclinical abnormalities in the diabetic heart, by combining Big Data analysis at population-level followed by patient-specific multi-scale modelling and simulation. Rich in quantity and diversity of data, the UK Biobank is an ideal resource to quantify those changes in such a high-risk yet understudied population before the development of overt cardiac disease. While cohort studies do not offer mechanistic insight, modelling and simulation approaches provide a reliable virtual testbed to investigate possible pathophysiological mechanisms underlying those changes. In this work, we present a computational framework to characterise cardiac remodelling in type 2 diabetes in the absence of cardiovascular disease, using human-based multi-scale modelling and simulation to explain possible mechanisms underlying the differences observed in clinical biomarkers at population level.

1. Introduction

Characterised by chronically high blood sugar, type 2 diabetes (T2D) is a complex metabolic disease that affects over half a billion adults worldwide [1]. It is responsible for an increase in risk of cardiovascular disease of up to 4-fold and risk of sudden cardiac death of up to 10-fold due to changes in cardiac electrophysiology, structure, and function driven by T2D [2].

Subclinical abnormalities may be captured via non-invasive clinical modalities such as ECG and cardiac imaging. Indeed, the ECG forms part of the clinical screening process for heart failure and atrial fibrillation in T2D [2]. While cardiac magnetic resonance (CMR) captures structural and functional characteristics of the heart in high-resolution, its costly nature limits its use in routine clinical settings, including cardiac screening in T2D. Previous studies have suggested the presence of subclinical cardiac abnormalities in T2D using ECG and cardiac imaging, however the scarcity of multi-modal data and small cohort sizes limit the generalisability of these findings. Furthermore, cohort studies remain limited in their ability to identify the mechanisms underlying the changes observed clinically.

By merging experimental and clinical data into biophysically-detailed computational models, advanced simulations can now reproduce and unravel key mechanisms of human cardiac electrophysiology *in silico*, in healthy and diseased populations, from subcellular to whole-organ scale [3]. These methods represent an exciting avenue to generate and test new hypotheses, however their application to study the cardiac effects of T2D remains largely unexplored.

In this work, we present a fully multi-scale study of subclinical cardiac remodelling in T2D in the absence of overt cardiovascular disease. Harnessing the breadth and depth of data in the UK Biobank, we first quantify changes in ECG and imaging-derived biomarkers in T2D at population-level, then propose a framework to recapitulate key abnormalities and explain underlying mechanisms, using existing state-of-the-art multi-scale human-based modelling and simulation methods.

2. Methods

2.1. Dataset

The UK Biobank study is a multi-centre, prospective, longitudinal cohort study of over half a million adults living in the UK, recruited between 40 and 69 years old. Following an initial baseline clinical assessment, about

10% of participants underwent a further assessment which included a CMR scan coupled with a 12-lead resting ECG [4]. The UK Biobank is also linked to primary healthcare records and hospital episode statistics, where diagnoses are recorded using International Classification of Diseases codes.

For this study, we selected a cohort of 1,781 patients with available CMR and ECG data, and with prevalent T2D and no diagnosed cardiovascular disease at the time of the assessment. We also selected a control cohort without T2D matched on age, sex, body mass index, and cardiovascular outcomes. A full description of the cohort selection process is available in [5]. We then chose a single representative case from the T2D cohort to demonstrate the modelling and simulation framework.

General ethical approval was granted for UK Biobank studies by the United Kingdom's National Health Service Research Ethics Service (11/NW/0382). All participants gave written informed consent for their data to be stored and used for research purposes. The study was conducted under UK Biobank Application Number 40161.

2.2. Identification of electrophysiological, structural and functional abnormalities at population level

To identify subclinical cardiac abnormalities in T2D, we performed a matched cross-sectional cohort study, comparing ECG biomarkers (ventricular rate, QRS duration, QTc interval, Sokolow-Lyon index, ST segment amplitude, T wave amplitude) and CMR-derived biomarkers (left ventricular ejection fraction (LVEF), LV end-diastolic volume, LV end-systolic volume, LV stroke volume, cardiac output, LV myocardial mass, LV global average wall thickness) of our patient cohort with T2D, relative to biomarkers in the control cohort. We also quantified the association between T2D and each biomarker by using multivariate multiple linear regression models adjusted sequentially to account for possible confounders. Further details of these analyses can be found in [5].

2.3. Experimentally-informed modelling of subcellular-level changes in type 2 diabetes

Electrophysiological and contractility behaviour was simulated at single-cell level using the ToR-ORd ventricular cardiomyocyte model, coupled to the Land contractility model [3]. Based on published data from experimental studies, we propose an adaptation of this model to represent a type 2 diabetic cellular phenotype (Table 1). Human gene expression data suggest changes in certain cardiac ionic channels, corresponding to increases in the L-type calcium current (I_{CaL}), current through the sodium-calcium exchanger (I_{NaCa}), sodium and late-sodium currents (I_{Na}, I_{NaL}), a decrease in rapid, slow and transient outward potassium currents (I_{Kr}, I_{Ks}, I_{to}), and a decrease in sarcoplasmic reticulum Ca^{2+} release via the SERCA pump and ryanodine receptors (RyR), corresponding to a decrease in ionic fluxes J_{up} and J_{rel} [6]. This is the only comprehensive dataset of its kind available in human; multiple animal studies on ionic current changes in type 2 diabetes have been conducted, however results are heterogenous. Further evidence, including in human, suggests that CaMKII is also upregulated in T2D [7]. The extent of CaMKII activation changes as the disease progresses, from normal activation to a chronically activated state following post-translational modifications by O-GlcNAcylation [7].

Table 1: Proposed ToR-ORd model parameter changes to model ionic remodelling in type 2 diabetes (T2D), at early and chronic stages, capturing changes in CaMKII activation states. Current multipliers are based on human data from [6]. Asterisks (*) highlight parameter changes in the chronic stage vs. early stage T2D ionic remodelling scenarios.

	EARLY	CHRONIC
Parameter	**Multiplier**	**Multiplier**
I_{NaL}	1.21	2.00*
I_{Na}	1.21	1.21
I_{CaL}	1.14	1.14
I_{tof}	1.26	1.26
I_{Kr}	0.70	0.70
I_{Ks}	0.95	0.95
I_{NaCa}	1.50	1.50
J_{rel}	0.90	0.90
J_{up}	0.80	0.65*
α_{CaMKII}	(1)	1.50*

2.4. 3D cardiac anatomy reconstruction

Using a previously validated pipeline [8], we reconstructed a patient-specific 3D bi-ventricular cardiac surface geometry embedded in a corresponding torso mesh with ECG electrode positions, based on the 2D DICOM image slices of the representative case selected from our T2D cohort. Myocardial fibre orientation was included in the cardiac geometry using a rule-based method, recapitulating experimental findings [9]. The cardiac surface mesh was processed to produce tetrahedral and hexahedral meshes, providing the anatomical basis for whole-organ electrophysiological simulations in 3D.

2.5. Simulating cardiac electrophysiology at organ-level

Based on the ECG's QRS complex, we estimated sites of earliest electrical activation in the ventricles (i.e. root nodes of the cardiac Purkinje network) and tissue conduction velocities, adapting a previously developed framework that uses reduced-order Eikonal simulations

and an inference approach [10]. The cardiac geometry, root nodes and conduction velocities, along with the T2D-specific ToR-ORd model form the inputs to MonoAlg3D, an open-source GPU-enabled solver that performs biophysically detailed electrophysiological simulations of cardiac electrical propagation in 3D using the monodomain model and the finite volume method [11].

2.6. Calibration and validation

The ToR-ORd single-cell model was calibrated on human and animal data using an extensive range of experimental parameters, and independently validated [3]. We validated simulated outputs for the single-cell model adapted to T2D using experimental action potential duration (APD) biomarkers reported in the literature.

3. Results and discussion

3.1. Population-level biomarker analysis suggests increased QTc interval, lower LV stroke volume, and higher LV wall thickness in type 2 diabetes

Among 49,001 UK Biobank participants with imaging and ECG datasets, we identified 2,304 patients with prevalent type 2 diabetes, of which 1,781 were retained after excluding cases with a record of cardiovascular disease. The majority of patients were male (63.6%), elderly (median age = 67 years) and overweight (median BMI = 27.8 kg/m^2). Compared to controls, patients in the T2D cohort had a higher resting heart rate (66 vs. 61 beats per minute, $p < 0.001$), longer QTc interval (424 vs. 420ms, $p < 0.001$), reduced T wave amplitude (0.33 vs. 0.37mV, $p < 0.001$), lower stroke volume (72 vs. 78ml, $p < 0.001$) and thicker left ventricular wall (6.1 vs. 5.9mm, $p < 0.001$). After fully adjusting the regression models for clinical covariates, T2D was independently associated with higher heart rate ($\beta = 3.11$, 95% CI = [2.11, 4.10], $p < 0.001$), lower stroke volume ($\beta = -4.11$, 95% CI = [−6.03, −2.19], $p < 0.001$) and thicker left ventricular wall ($\beta = 0.133$, 95% CI = [0.081, 0.186], $p < 0.001$). Further information on cohort characteristics, biomarker differences and subgroup analyses can be found in [5].

3.2. Patient-specific anatomical mesh reconstruction

We selected one patient from the T2D cohort with the following clinical characteristics: male, 64 years old, BMI of 25.6 kg/m^2, with a record of T2D for 12½ years prior to assessment. This patient had no records of QT prolonging medication. Reconstructed torso and cardiac surface meshes with corresponding ECG electrode locations are illustrated in Figure 1.

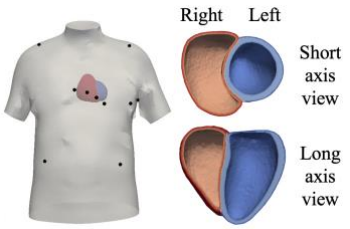

Figure 1: 3D reconstruction of a UK Biobank patient's heart and torso, with the ECG electrodes' positions shown by black dots.

3.3. Modelling and simulation of human ventricular cardiomyocytes suggests that type 2 diabetes prolongs the action potential duration, and diminishes calcium transient and active tension

The simulated APD was prolonged (Figure 2A), both in the early stage and chronic T2D cardiac remodelling scenarios. APD prolongation is consistent with the QTc prolongation observed at population-level. Simulated peak calcium transient amplitude (Figure 2B) and peak active tension (Figure 2C) were diminished in the early stage, but not chronic, T2D cardiac remodelling scenario. This finding suggests as decrease in contractility, which may explain the lower LV stroke volume observed in the T2D cohort. In the chronic remodelling scenario, we hypothesise that the lack of change may be explained by the CaMKII-dependent phosphorylation of the Na^+ channel which increases I_{NaL} and influx of sodium ions into the cell. This would cause a reduction of calcium efflux via I_{NaCa} and lead to an increase in intracellular calcium and subsequent improvement in contractility.

3.4. Personalised simulation of cardiac electrophysiology at organ-level to recapitulate ECG changes in type 2 diabetes

Figure 3 shows the cardiac activation time maps that were simulated using the personalised root node locations and conduction velocities computed by the inference process, based on the QRS complex of the selected patient's ECG. These simulations produce physiologically accurate estimations of the propagation of electrical waves across the myocardium. The ECG is then reconstructed from the simulated cardiac activation sequences using the pseudo-bidomain approach, first with a baseline cellular model as a control case, then applying T2D-specific remodelling. The T2D ECG exhibits delayed repolarisation and a slightly flattened T wave (see Figure 3), consistent with population-level clinical findings.

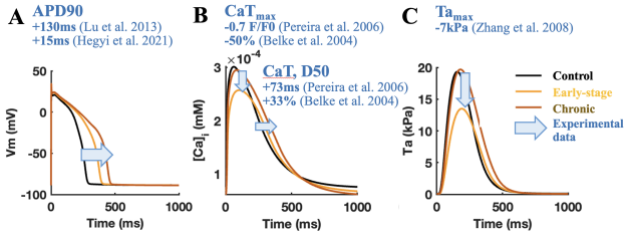

Figure 2: Simulated action potential (A), $[Ca^{2+}]_i$ (B) and active tension (C) for early stage and chronic type 2 diabetes cardiac remodelling in an endocardial cardiomyocyte. Experimental validation data is indicated in blue. APD90: action potential duration at 90% repolarization, $[Ca^{2+}]_i$: intracellular calcium, CaT: calcium transient, D50: duration at half-maximum amplitude, Ta: active tension, Vm: membrane voltage.

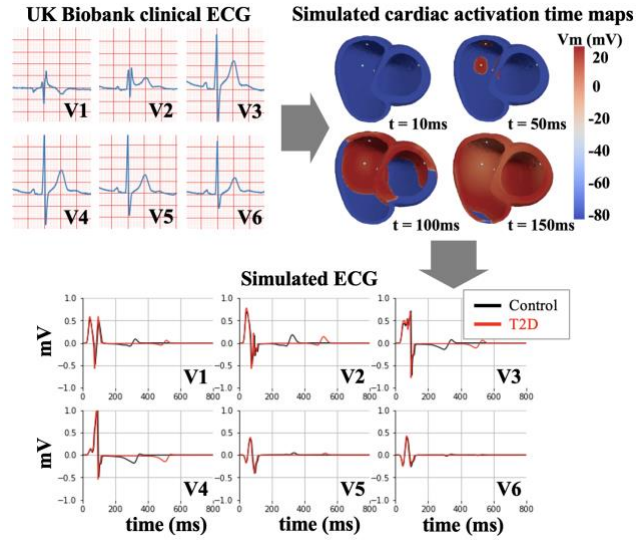

Figure 3: Simulated cardiac activation time maps and ECG using personalised estimated root node locations and tissue conduction velocities. ECG traces simulated using the baseline cellular model (control) and chronic type 2 diabetes model. Vm: membrane voltage, T2D: type 2 diabetes.

3.5. Limitations

The UK Biobank is a predominantly white cohort, limiting the relevance of our results to other ethnic backgrounds. Diabetes is a chronic condition that progresses gradually; the earliest reported date of a diagnosis in a patient's medical record may not reflect the actual time of disease onset; and there is no strict clinical staging of T2D once symptomatic and diagnosed. These factors make it challenging to quantify the true underlying duration and severity of disease in patients.

4. Conclusion

Using a multi-scale, human-based cardiac modelling and simulation framework, we have provided mechanistic insight into the role of T2D-induced cardiac remodelling on ECG and LV hemodynamic abnormalities observed at population level, notably supporting the link between APD and QTc interval prolongation, and reduced active tension and stroke volume, in patients with T2D and no diagnosed cardiovascular disease. Subject to further development and validation, this computational framework paves the way toward human-based *in silico* investigations of the diabetic heart, improving our mechanistic understanding of adverse cardiac changes identified clinically in T2D, ultimately enhancing patient risk stratification and helping to prevent further cardiac decline.

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