Cardiac repolarisation and heart rate variability during experimental hypoglycaemia in healthy subjects and patients with type 2 diabetes

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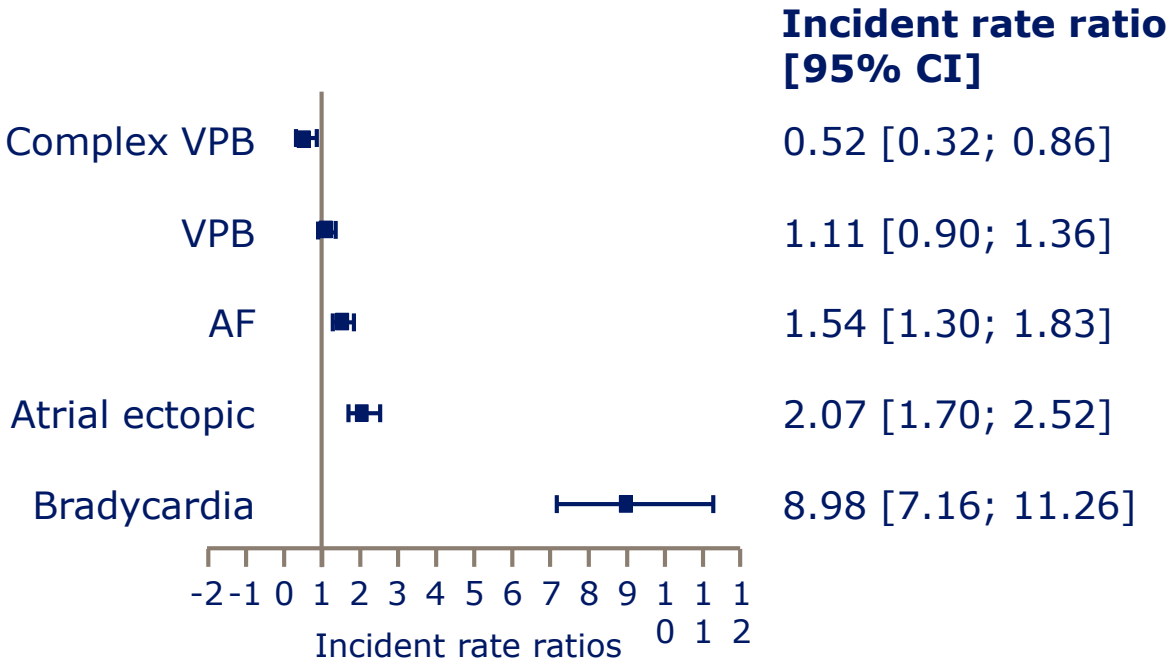
Introduction

- Diabetes: dysfunctional regulation of sugar (glucose) in the blood – glucose level often too high
- Large trials of intensive glucose control (lowering) in type 2 diabetes resulted in severe hypoglycaemia (low blood glucose)
- Hypoglycaemia associated with adverse CV conditions and mortality, including arrhythmic death
- Potential mechanism could involve
  - dysfunctional cardiac autonomic activity (regulation of the heart rate)
  - dysfunctional cardiac repolarisation (electrical activity of the heart)

Zoungas et al. *N Eng J Med* 2010
Mellbin et al. *Eur Heart J* 2013

Introduction

- Higher incidence of cardiac arrhythmias during **spontaneous hypoglycaemia** vs euglycaemia (normal BG) in type 2 diabetes
- Underlying mechanisms are uncertain



AF: atrial fibrillation, VPB: ventricular premature beats

Chow et al. Diabetes 2014

Aim

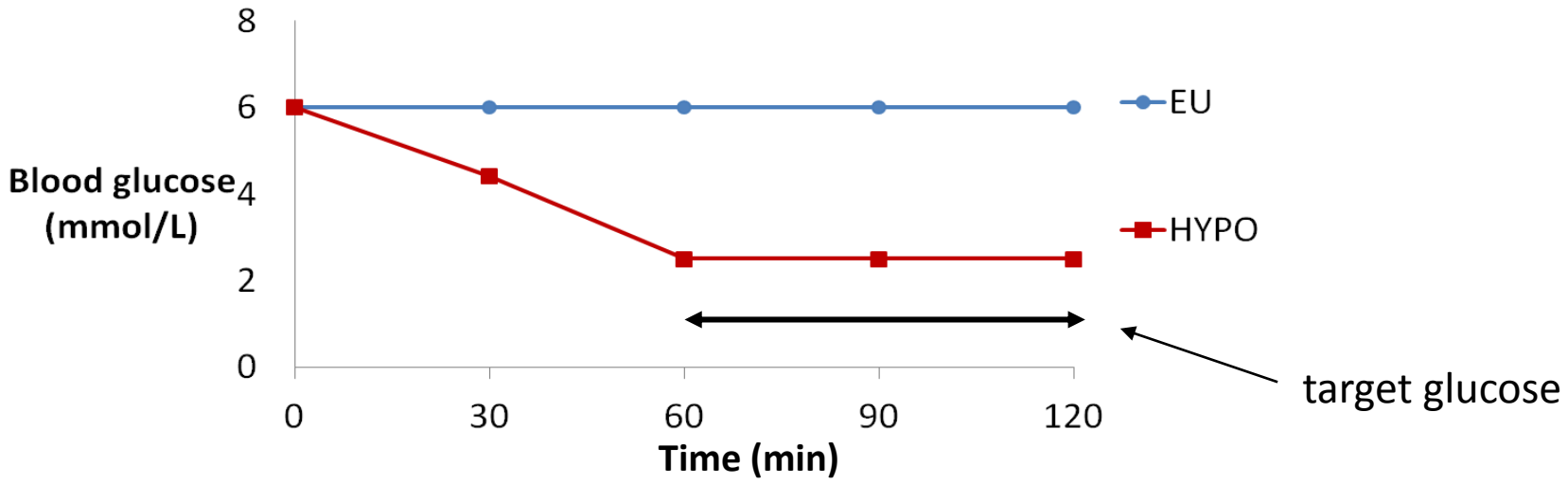
To investigate the changes in heart rate variability and cardiac repolarisation during sustained experimental hypoglycaemia

- Changes during euglycaemia (normal blood sugar) vs hypoglycaemia (low blood sugar)
- Effects investigated in patients with type 2 diabetes and healthy controls

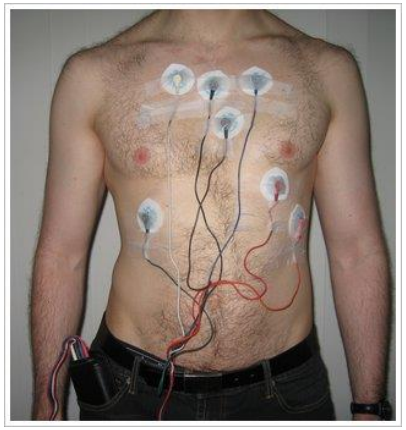
Participants and protocol

- Type 2 **diabetes subjects** with no CVD (**n=12**)
  - age 54(37-64) years, duration of diabetes 11±7 years
- Nondiabetic **controls** (**n=11**)

- Paired hyperinsulinaemic clamp studies at least 4 weeks apart
  - Constant rate insulin infusion together with variable glucose infusion
  - **Euglycaemic** clamp (EU): glucose at normal 6 mmol/L, for 60min
  - **Hypoglycaemic** clamp (HYPO): glucose at 2.5 mmol/L, for 60min

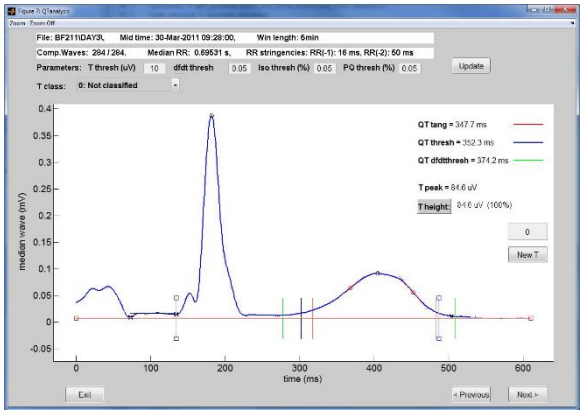


Recordings



- 12 lead ECG @1000 Hz
  - 5 min stable resting ECG segments at timepoints: 0, 30, 60, 120min and recovery after clamp
- Blood pressure: SBP, DBP, respiration
- Plasma electrolytes (Na, K), catecolamines (adrenaline, noradrenaline) at 0 and 120min
- Glucose sample taken every 5min
  - Arterialised blood, retrograde cannula

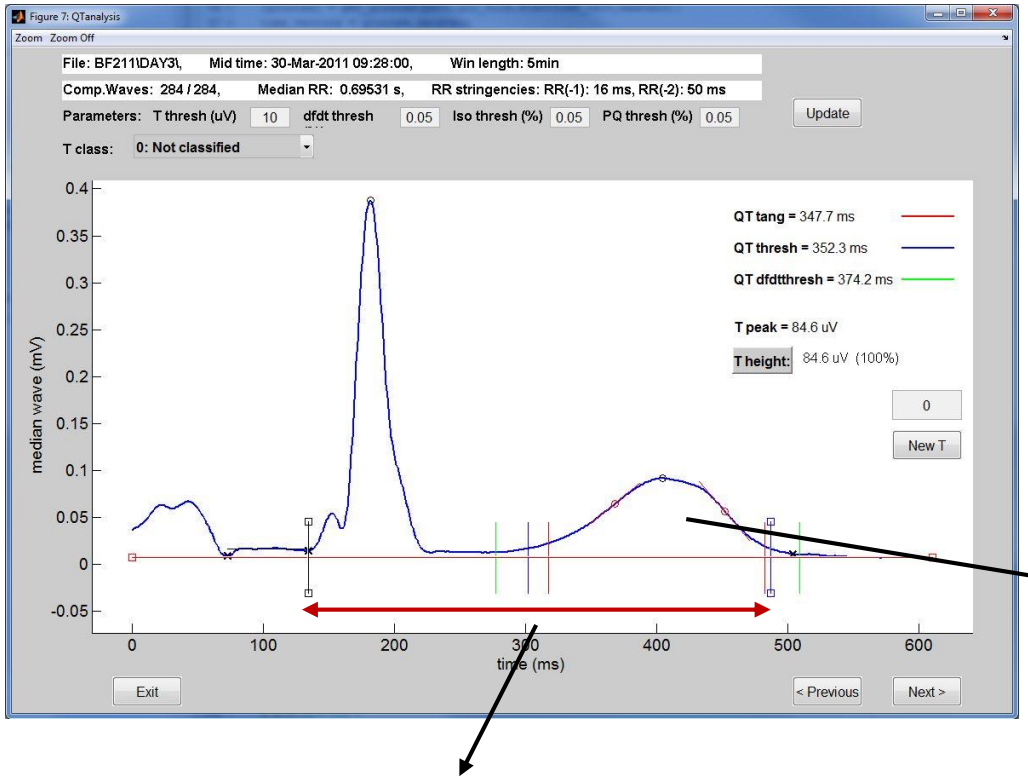
Methods



- Heart rate and heart rate variability
  - Spectral power from 5min segments
    - 0.15 – 0.4 Hz (HF): breathing frequency
    - 0.04 – 0.15 Hz (LF): around 0.1Hz
- Cardiac repolarisation
  - Restoration of the action potential in cardiac muscle cells
  - Indication of the electrical/mechanical activity of the heart
  - **QT interval** (prolongation associated with risk of arrhythmias and fatal ventricular fibrillation), common for testing drug safety
  - **T wave morphology** (repolarisation of ventricles)
  - **Heterogeneity** of repolarisation (spatial and temporal variability between standard ECG leads)
    - Calculated from 9 ECG leads using principal component analysis (PCA)
  - Parameters predictors of CV and all-cause mortality

Methods: Cardiac repolarisation

- Composite wave from three orthogonal leads: lead I, II and V5

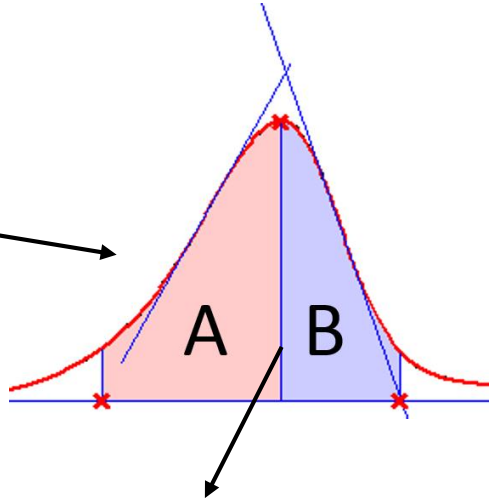


QT interval: duration of ventricular depolarisation and repolarisation

T wave symmetry: TS = A / B

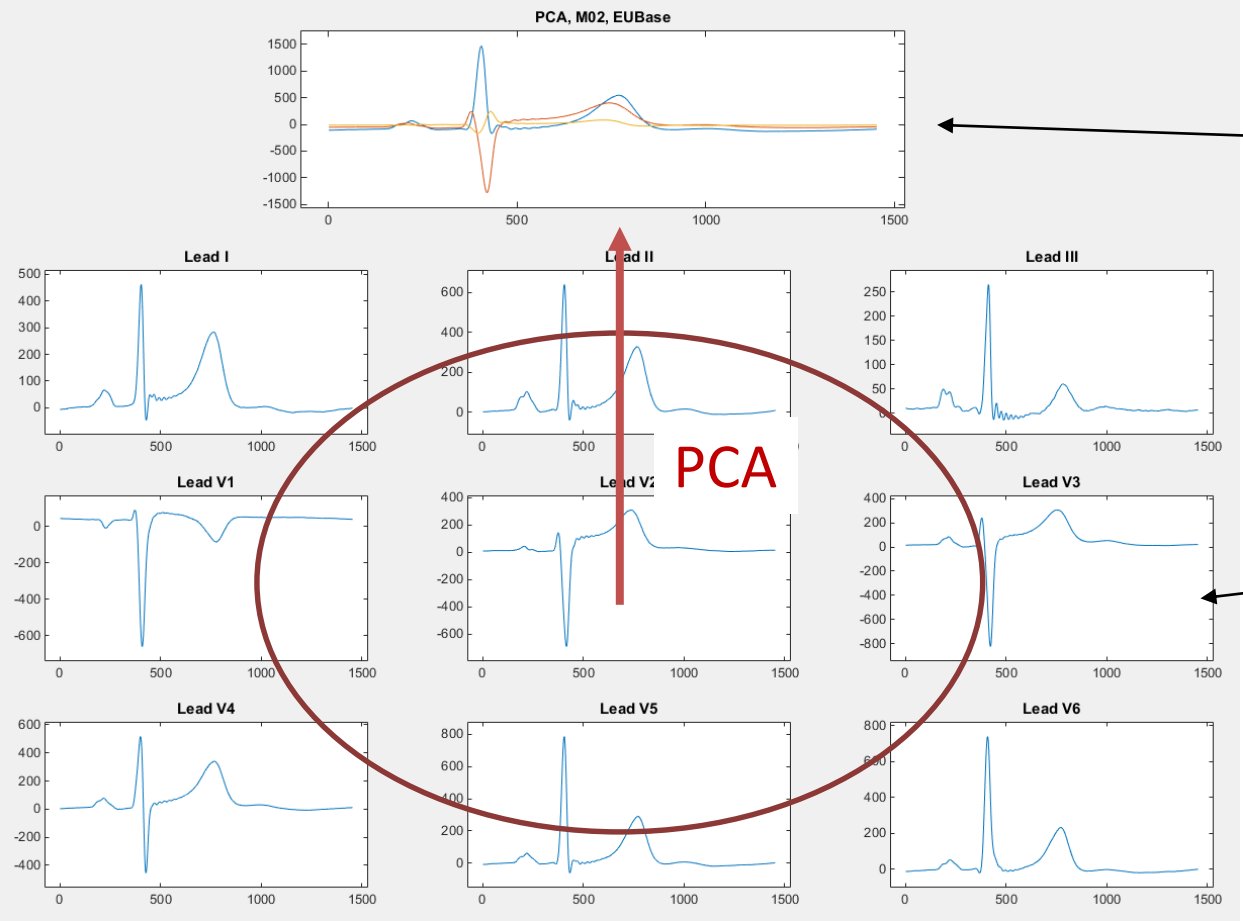
TS ~ 1.5 : *normal non-symmetric T wave*

TS ~ 1 : *symmetrical T wave - abnormal repolarization*



T wave amplitude

Methods: Principal component analysis



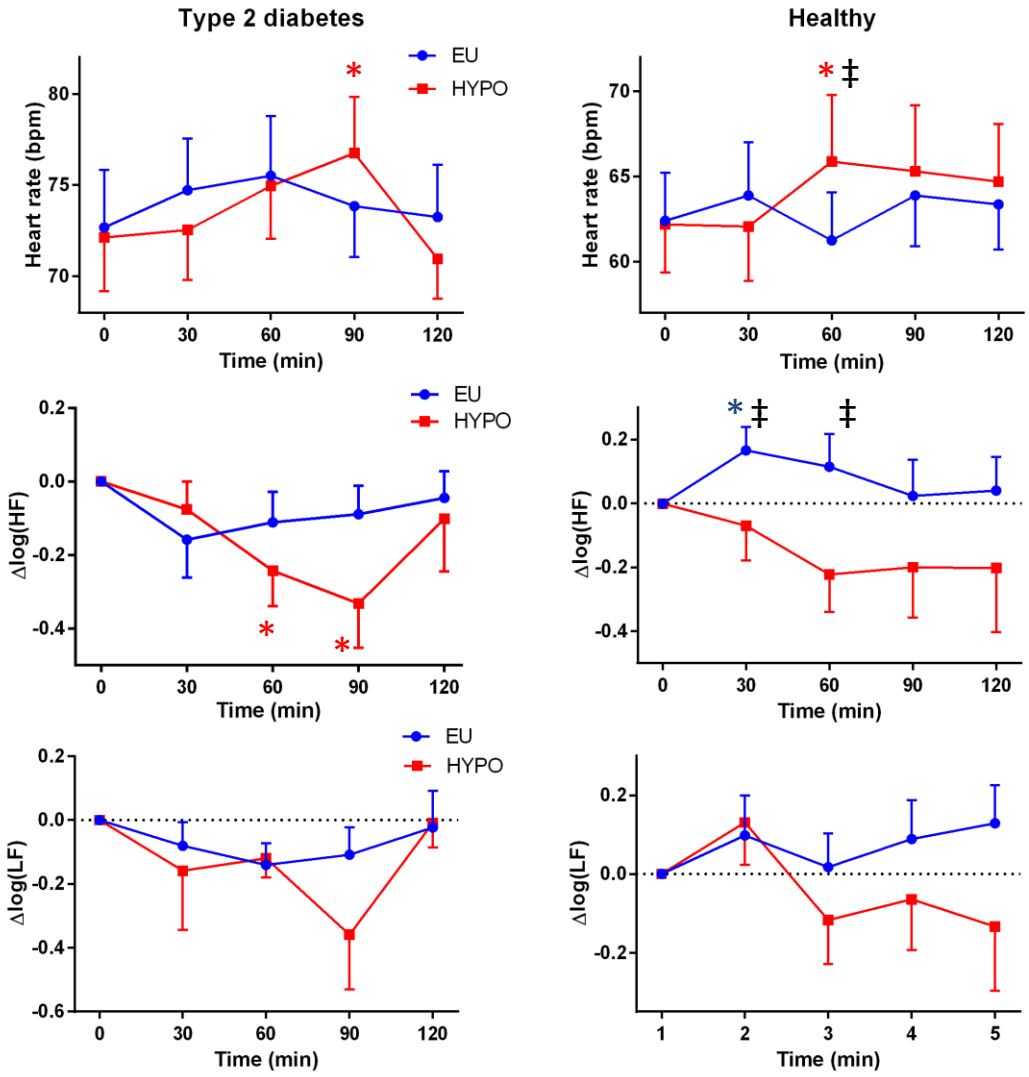
First 3 principal components: 'compressed ECG leads'

- PC1 – PC3 ~ 98 % energy

Standard ECG leads

Parameters of repolarisation variation (heterogeneity) calculated from principal components

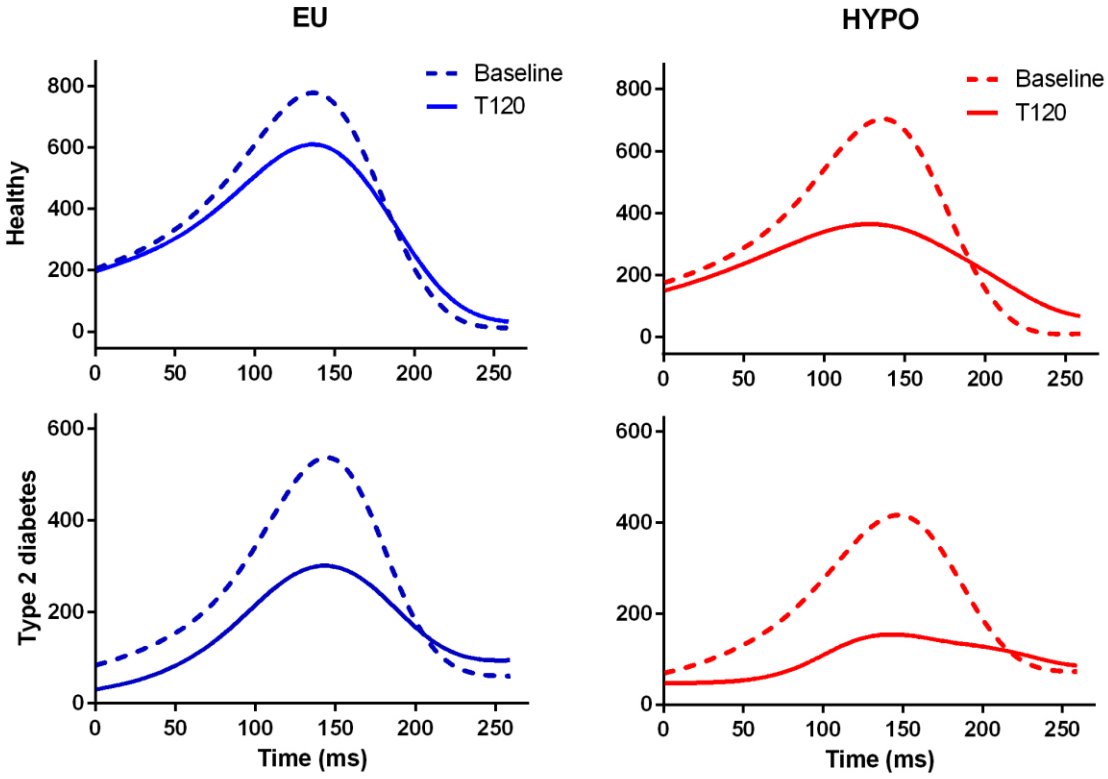
Results: HR and HRV



- Smaller non-significant changes during EU
- HR increase during HYPO, slower and greater in diabetes vs healthy
- HR reversed at T120 in diabetes, not in controls despite maintained HYPO
- HF power decreased during HYPO, reversed in diabetes not in controls
- Trend: increased LF and HF power during EU in controls

* P<0.05 vs baseline
‡ p<0.05 HYPO vs EU

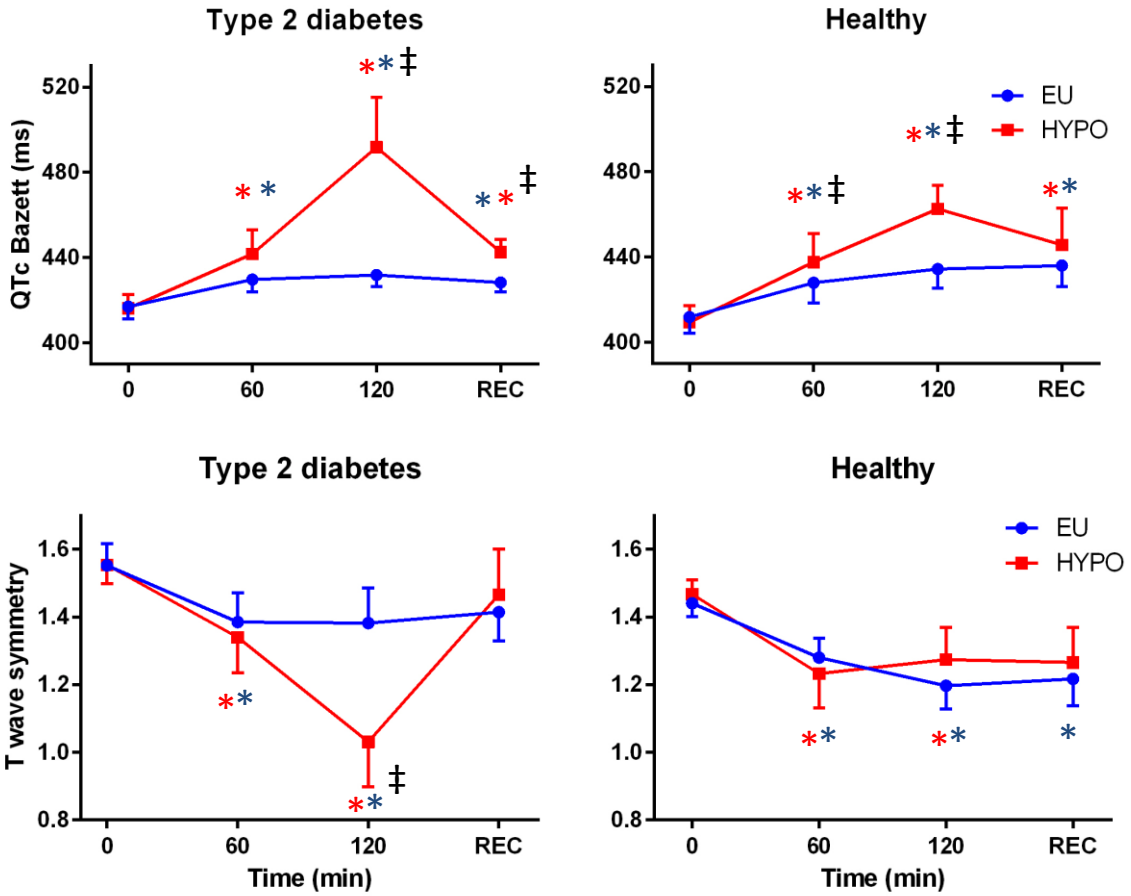
Results: Ventricular repolarisation



- T wave amplitude decrease during clamps
- T waves more symmetric
- QT interval prolongation
- Changes bigger in HYPO vs EU and in diabetes vs controls

Results: QT and T wave symmetry

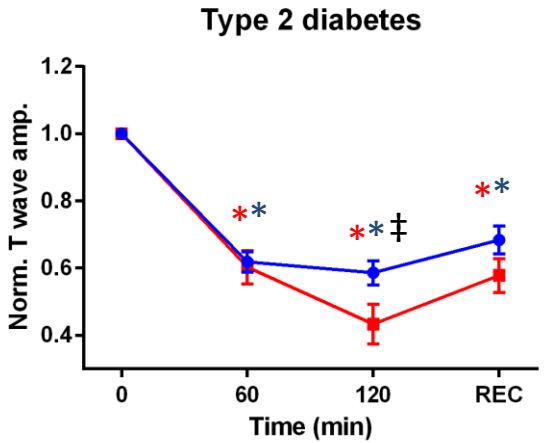
The last data point is recovery (REC) – stable normal blood sugar level in all cases!

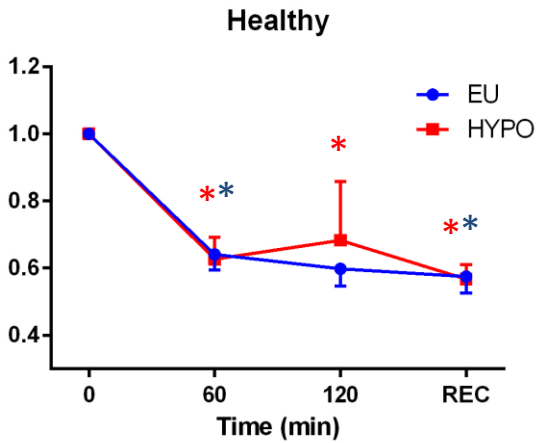


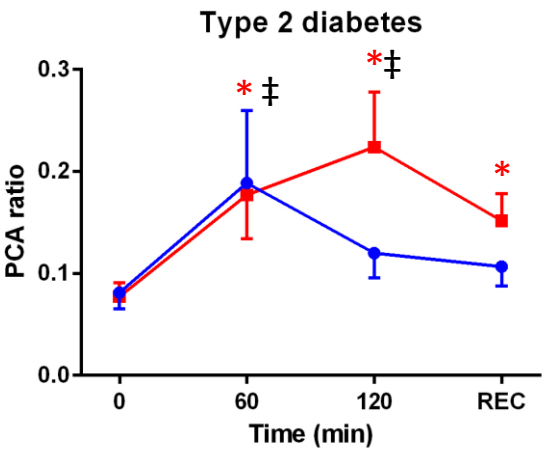
- QTc prolonged in both clamps and both groups
- Bigger prolongation during HYPO
- Does not fully recover to basline
- T symmetry index decreased
- Decrease in diabetes bigger during HYPO vs EU

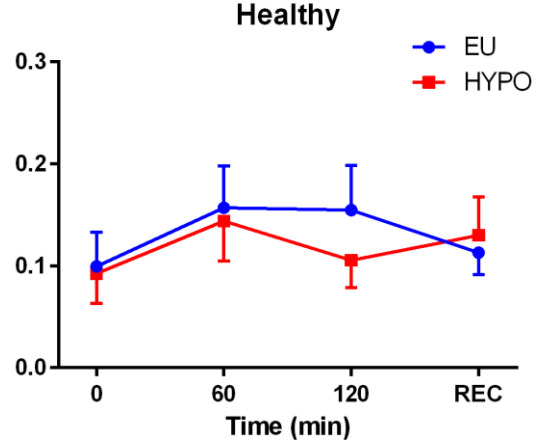
* P<0.05 vs baseline
‡ p<0.05 HYPO vs EU

Results









- T wave amplitude decreased during clamps by ~50%
- In diabetes the decrease bigger during HYPO vs EU
- PCA ratio (heterogeneity of repol.) increased only in diabetes
- Larger increase during HYPO vs EU in diabetes, no changes in healthy

* P<0.05 vs baseline
‡ p<0.05 HYPO vs EU

Results: Summary

- HR and HRV responses during hypoglycaemia are time dependent and different between patients with type 2 diabetes and healthy controls
- Hypoglycaemia is associated with abnormal cardiac repolarisation, affecting both T wave morphology and heterogeneity of repolarisation
- Individuals with type 2 diabetes show greater repolarisation abnormalities
- Comparable sympathetic response (adrenaline, noradrenaline)

Conclusions

- The presented mechanisms could contribute to arrhythmias that have been reported in clinical hypoglycaemia
- Further evidence to explain the possible relationship between hypoglycaemia and increased CV mortality in type 2 diabetes.

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