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

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Team

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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

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**Incident rate ratio [95% CI]**

- Complex VPB: 0.52 [0.32; 0.86]
- VPB: 1.11 [0.90; 1.36]
- AF: 1.54 [1.30; 1.83]
- Atrial ectopic: 2.07 [1.70; 2.52]
- Bradycardia: 8.98 [7.16; 11.26]

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 \(11 \pm 7\) 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 60 min
  - **Hypoglycaemic** clamp (HYPO): glucose at 2.5 mmol/L, for 60 min
Recordings

• 12 lead ECG @ 1000 Hz
  • 5 min stable resting ECG segments at timepoints: 0, 30, 60, 120 min and recovery after clamp

• Blood pressure: SBP, DBP, respiration

• Plasma electrolytes (Na, K), catecolamines (adrenaline, noradrenaline) at 0 and 120 min

• Glucose sample taken every 5 min
  – 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

T wave symmetry: \( TS = \frac{A}{B} \)

- \( TS \approx 1.5 \): normal non-symmetric T wave
- \( TS \approx 1 \): symmetrical T wave - abnormal repolarization

QT interval: duration of ventricular depolarisation and repolarisation

T wave amplitude
Methods: Principal component analysis

Parameters of repolarisation variation (heterogeneity) calculated from principal components

First 3 principal components: ‘compressed ECG leads’
- PC1 – PC3 ~ 98 % energy
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 baseline
- 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, noradrenalin)
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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