

# THE IMPACT OF INSULIN LEVELS ON QTc INTERVAL IN THOROUGH QT STUDIES CONDUCTED IN HEALTHY SUBJECTS

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## Introduction

Food might alter the T-wave and the QTc. This was first described by Widerlöv in 1999<sup>1</sup>. This was recently re-examined by us<sup>4</sup> showing that food shortens the QTcF significantly and reproducibly for up to 4 hours. This is incongruent with claims that insulin prolongs the QTc interval (Gastaldelli<sup>2</sup>) as a meal will lead to a physiological insulin release. C-peptide has been associated with QTc interval shortening in type 1 diabetic patients (Wahren<sup>3</sup>). Reliable data on the effects of a meal on QTc are very limited.

**QTc shortening after a meal was incongruent with the claim that insulin prolongs QTc**

Meals may be given in different compositions during clinical trials and may be a confounding factor when analyzing ECG obtained during a clinical trial. Wrong comparisons may be drawn between different study days where meal effects may not be quantifiable yet may lessen or mask a QTc prolonging effect.

## Aims

One aim of the present TQT study (NCT01642485) was to show that insulin does not prolong QTc during a hyperinsulinic euglycaemic clamp experiment and to correlate the plasma concentrations of insulin, glucose and C-peptide to the observed changes in QTcF. Assay sensitivity was to be confirmed by the use of 400mg moxifloxacin as a positive control.

## Methods

32 healthy Caucasian and Japanese subjects were randomised to receive the following treatments over two periods:

- |  |   |
|--|---|
| <b>P</b> placebo                             | <b>F</b> calorie reduced FDA breakfast <sup>†</sup> |
| <b>I</b> hyperinsulinic euglycaemic clamp    | <b>M</b> moxifloxacin                               |
| <b>B</b> high carbohydrate content breakfast | <b>M+B</b> combined <sup>†</sup>                    |
- (<sup>†</sup> Data presented elsewhere)

The clamp was run over two hours during which insulin was infused at a constant rate following a loading dose. The glucose infusion was continued until 2.5 hours, i.e. 30 minutes longer.

Measurements of QT intervals were performed automatically with subsequent manual adjudication in accordance with ICH E14. Fredericia's formula was used to calculate QTc.

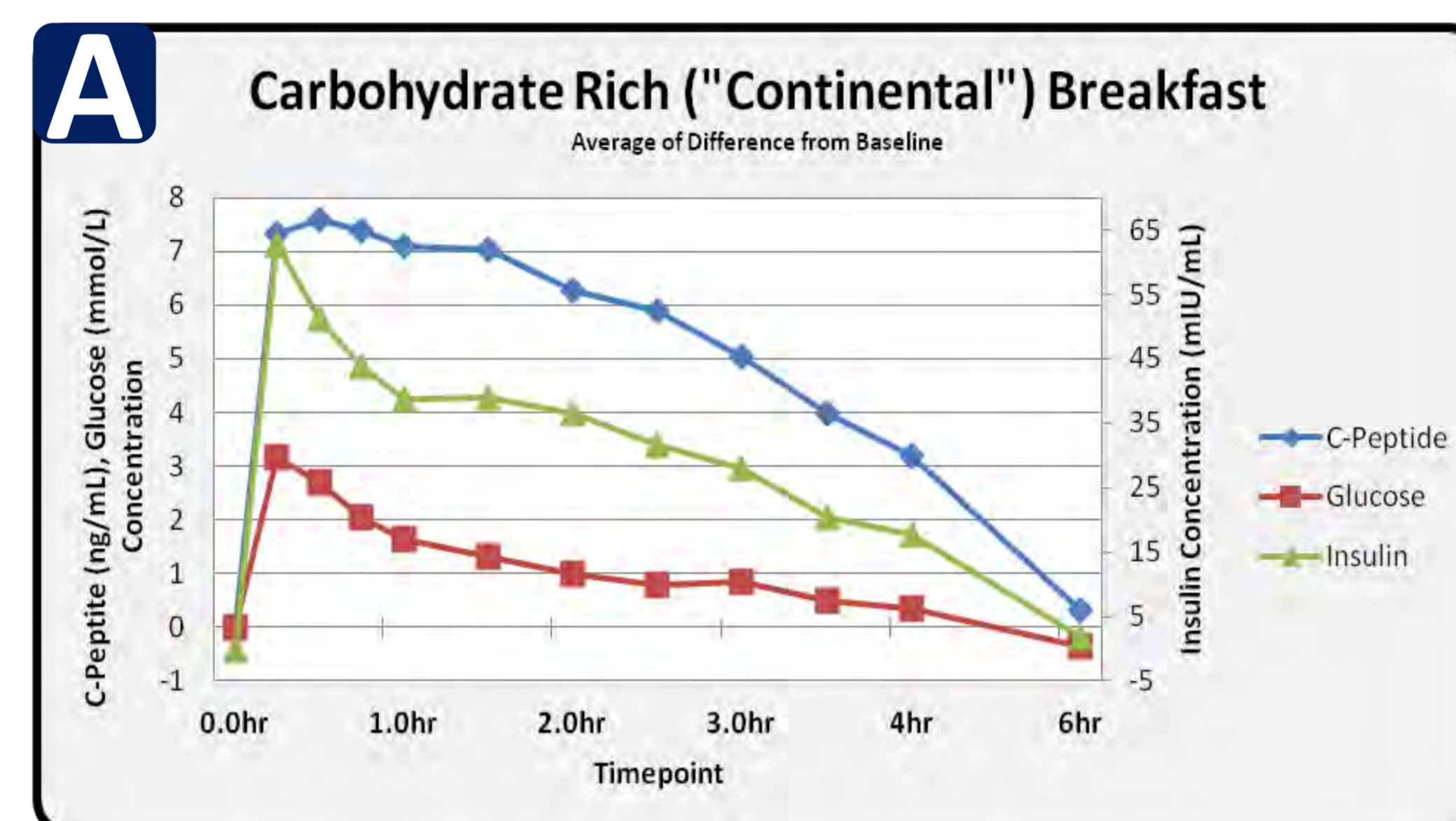
Day	Period 1			Washout <sup>†</sup>	Period 2			
	Day 1	Day 2	Day 3		Day 1	Day 2	Day 3	
P	P	I	M	Minimum of 3 days	P	B	F	M+B
	I	B	M			F	P	M+B
	B	F	M			P	I	M+B
	F	P	M			I	B	M+B
	P	I	M+B			B	F	M
	I	B	M+B			F	P	M
	B	F	M+B			P	I	M
	F	P	M+B			I	B	M

## Results

Panel A shows the physiological plasma levels in healthy volunteers for insulin, glucose and C-Peptide after a carbohydrate rich meal.

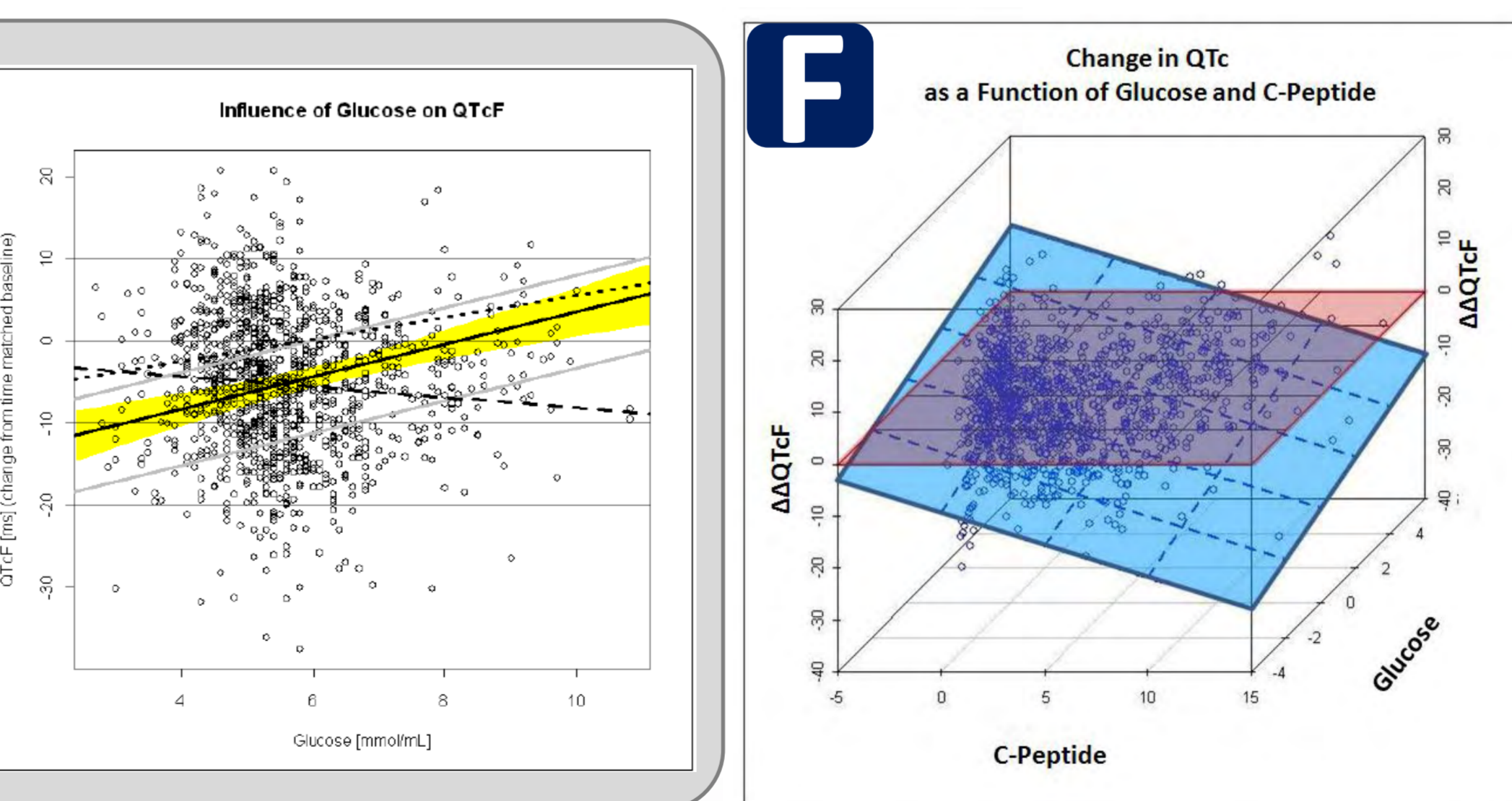
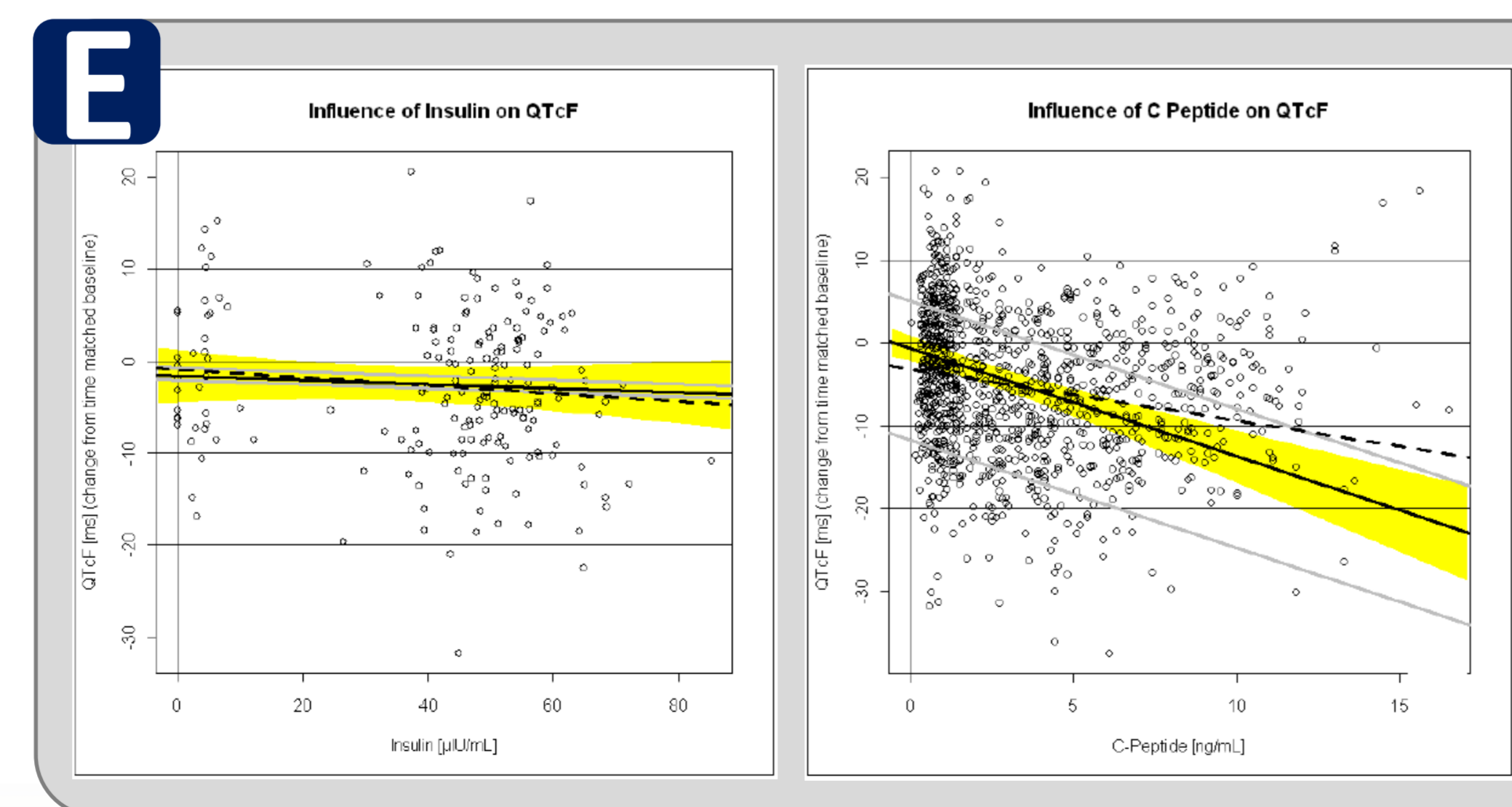
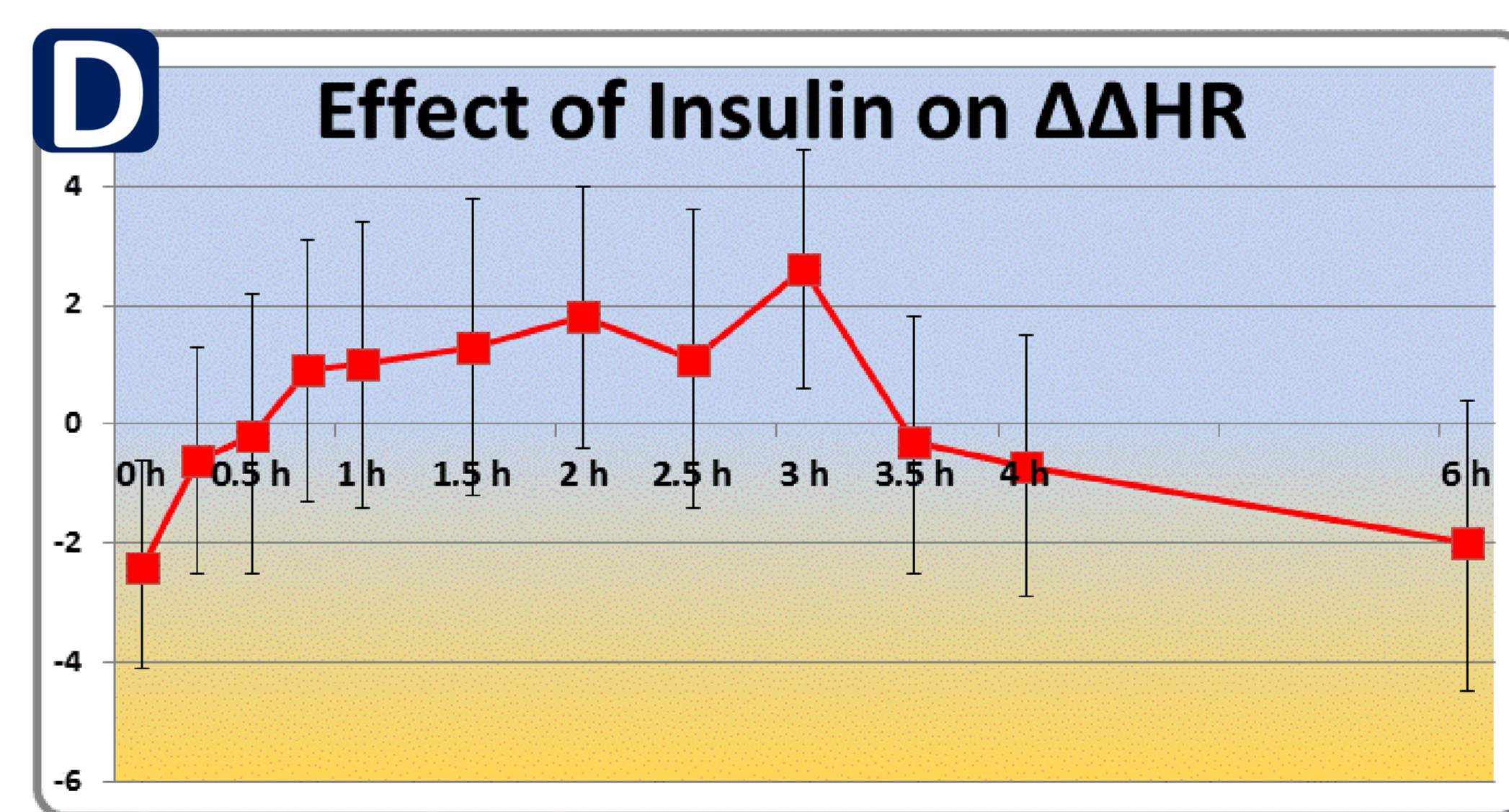
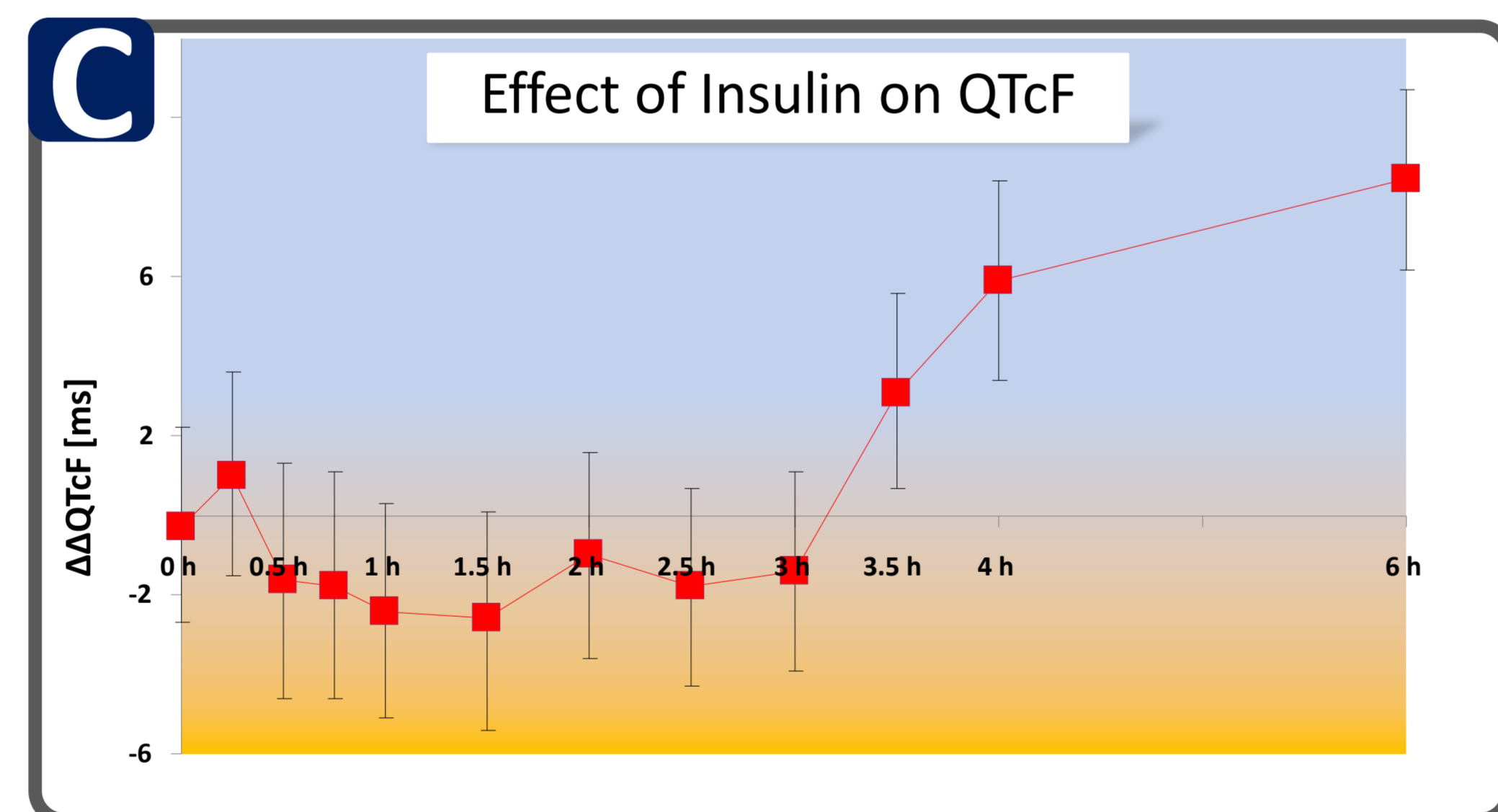
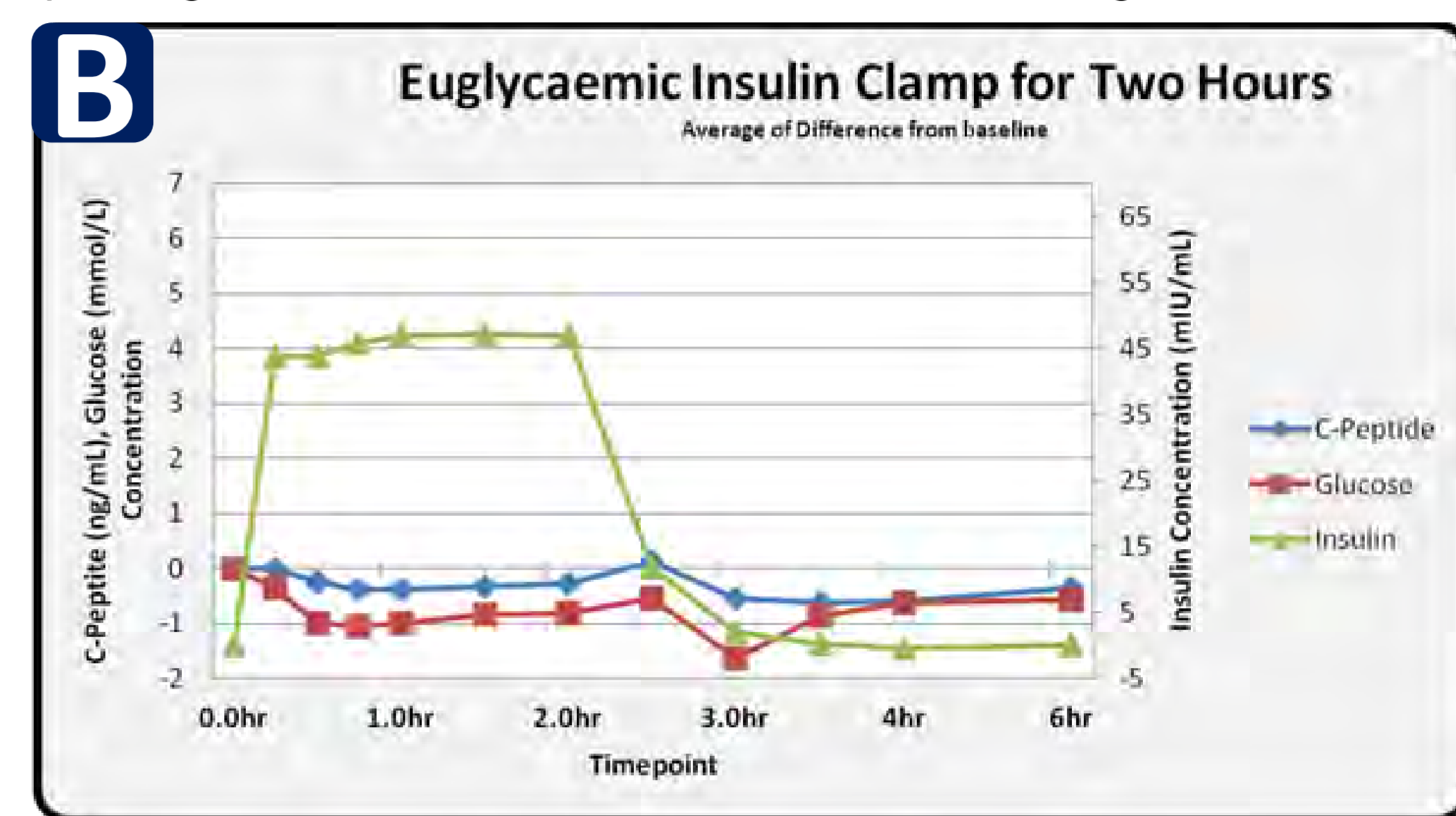
Panel B shows that there was no change in C-peptide levels during the hyperinsulinic euglycaemic insulin clamp, indicating that C-peptide release was successfully suppressed, leaving only insulin as a variable.

Panel C shows QTcF which remains unchanged until the 3.5 hour time point, i.e. until 1.5 hours after the end of the clamp.



During the clamp insulin in blood was raised to physiological levels comparable to those seen after a meal. At the same time the endogenous release of C-peptide was suppressed; this indicates that insulin by itself has no effect on the QTc interval in either direction. Panel D shows that there is no discernible heart rate effect.

Panel E shows the PK-PD relationship for the three analytes. Panel F shows the net effect of the QTc shortening effect of C-Peptide and the antagonistic effect of glucose which appears to prolong QTc. The net effect is a 10msec shortening of QTcF.



## Discussion

A clamp experiment was used to investigate the effects of insulin on the QTc interval. Food alters the heart rate and we have chosen QTcF as the most appropriate HR correction method<sup>4, 5</sup>.

**The data shows that insulin has no direct effect on the QTc interval in any direction**

The QTcB prolongation reported by Gastaldelli<sup>2</sup> in a similar clamp experiment was comparable to QTcB changes we have shown in our previous work<sup>4</sup>. Bazzetti's correction formula is inappropriate when the heart rate is increased significantly<sup>5</sup>; in her study the uncorrected QT interval was unchanged by insulin and the transient QTcB changes she observed traced the increase in heart rate of 5 b.p.m during the clamp. In our study, plasma levels of glucose, insulin and C-Peptide were measured in a GLP certified laboratory and clearly show that during the clamp experiment glucose and C-Peptide were held at baseline levels, making insulin the only variable. Raising insulin levels did not affect QTc. By contrast when correlating QTcF changes to the three analytes (Panel E) a clear concentration response relationship was seen between glucose, C-peptide and QTcF; not for insulin (Panel E).

**The data suggests that C-peptide shortens QTcF and that glucose prolongs QTcF. The net effect of these antagonistic effects is the shortening of QTcF we observe at physiological insulin levels following a meal.**

The three dimensional model (Panel F) shows the relationship between C-peptide, glucose and QTcF. The mechanism by which C-Peptide shortens QTcF is unknown. It has been proposed by Wahren<sup>3</sup> that C-peptide may interact with the Na<sup>+</sup>/K<sup>+</sup> ATPase which exchanges intra-cellular sodium for extra-cellular potassium thereby maintaining the membrane potential.

More research is needed to better understand the direct effects of glucose on QTc.

## References

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