Impact of hybrid closed-loop insulin delivery on cardiac rhythm in older adults with type 1 diabetes

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DOI:
10.1111/dom.15366

Received: 6 July 2023 | Revised: 20 October 2023 | Accepted: 30 October 2023

DOI: 10.1111/dom.15366

RESEARCH LETTER

WILEY

Impact of hybrid closed-loop insulin delivery on cardiac rhythm in older adults with type 1 diabetes: A post hoc analysis of trial data

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Funding information
Medical Research Council, Grant/Award Number: MR/T023899/1; National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award Number: 1DP3DK112176-01

1 | BACKGROUND

People with type 1 diabetes (T1D) are at higher risk from cardiovascular disease and cardiac arrhythmia when compared with people without diabetes, and these risks increase with age.[1] T1D is also associated with higher risks from sudden cardiac death, which may be up to 10-fold higher than the background population.[2] Growing evidence indicates that glycaemic excursions, specifically hypoglycaemia, have a causal role in precipitating cardiovascular events, arrythmias and increasing mortality risk.[3,4] The higher vulnerability of people with T1D to hypoglycaemia-induced arrythmia appears to persist, even following recovery from hypoglycaemia.[5] Observational and experimental studies have found that dysglycaemia increases the risk of ventricular arrythmias and pro-arrhythmic repolarization abnormalities such as QTc-interval prolongation.[5]

Hybrid closed-loop (HCL) devices or automated insulin delivery systems provide modulated insulin delivery to address constantly changing insulin requirements and reduce the burden of daily self-management. Randomised controlled trials (RCT) and real-world observational studies of HCL in T1D have shown improved time in range and glycated haemoglobin, while reducing the risk and burden of hypoglycaemia.[6]

To our knowledge, no study has evaluated the impact of HCL on cardiac rhythm. Therefore, our objective was to assess the impact of an adaptive HCL system on cardiac rhythm, assessed from Holter monitoring, in a post hoc analysis of RCT data in a group of older adults with T1D.

2 | METHODS

In a previously reported crossover RCT, glucose control with the CamAPS FX HCL system was compared with sensor-augmented pump therapy (SAP) in older adults aged ≥60 years with T1D.[7] The CamAPS FX HCL comprises an unlocked android smartphone (Samsung Galaxy S8) hosting the CamAPS FX app (CamDiab) running the Cambridge adaptive model predictive control algorithm (version 0.3.71), which receives sensor data from the Dexcom G6 continuous glucose monitor (Dexcom) and directs insulin delivery on a Dana Diabecare RS insulin pump (Sooil). Following randomization, participants initially assigned to the CamAPS FX HCL device were appropriately trained and then used it for 16 weeks. During the SAP period, participants used the same devices but with the auto mode (closed loop) function disabled. There was no low glucose suspend or predictive low glucose suspend functionality during the SAP period. For those assigned to SAP therapy first, this sequence was reversed. There was no blinding of participants from continuous glucose monitor data during either the HCL or SAP periods.

Twenty-four-hour Holter monitoring with the use of Lifecard CF (Reynolds Medical) was carried out on two occasions in study participants; each 7-day monitoring period started within 13-14 weeks of initiating the HCL and SAP study periods. During the study, participants underwent normal everyday activities without restriction or supervision.

Holter recordings were analysed retrospectively by a single cardiac physiologist at the end of the study period using the SpaceLab Sentinel system (Spacelabs Healthcare Ltd). When analysing the Holter data, the cardiac physiologist was blinded to clinical status, study arm and glucose sensor data of participants. Holter outcomes were defined as any of the following arrythmias: bradycardia defined as 60 bpm, tachycardia as 100 bpm and pause as >1.5 s (3 s significant). Ventricular/supraventricular tachycardias were defined as >3 consecutive ventricular complexes at a rate >100 bpm, and sustained as >30 s.

2.1 | Statistical analysis

Analyses were on an intention-to-treat basis. Daily sensor glucose and 24-h Holter monitoring parameters were aggregated across individual intervention periods. Continuous variables were assessed for normality using the Shapiro-Wilk test and quantile-quantile plots. Differences in normally distributed variables between study periods were assessed using mixed-effects regression models, while for non-normal variables, the Wilcoxon signed rank test was applied.

As a post-hoc exploratory study, no a priori power calculation was performed, and no adjustments were made for multiple comparisons. Regression analyses were used to explore relationships between variables. Results at the level of $p < .05$ were assumed to be statistically significant.

Sensor-based glucose outcomes were calculated using GStat software, version 2.3 (University of Cambridge). Holter monitor parameters were analysed using Spacelabs Sentinel software (Spacelabs Healthcare Ltd). Statistical analyses were conducted using SPSS (version 25; IBM software).

3 | RESULTS

Thirty-seven participants were randomized in the original study.[7] A subgroup of 29 participants who had Holter monitoring during both intervention periods were selected for the current study [median (IQR) age 68 (64-70) years, 55% men, 97% White ethnicity, mean (SD) baseline glycated haemoglobin 57 (10) mmol/mol]. Severe hypoglycaemia occurring during the preceding 6 months was an exclusion criterion. Data on prevalent hypoglycaemia unawareness were not collected. Four participants had a history of macrovascular disease. Prescribed medication at enrolment is listed in Table S1.

Time in range during the 7-day period of Holter monitor wear was 5.3 percentage points higher ($p = .018$) in the HCL period compared with SAP period (Table 1). Time spent >10.0 mmol/L was lower using HCL versus SAP with no significant difference in mean glucose and glucose variability (Table 1). Within both treatment periods, time spent hypoglycaemic (<3.9 mmol/L and <3.0 mmol/L) were comparable ($p = .231$ and $p = .224$, respectively).

The cardiac rhythm parameters are presented in Table 1. No statistically significant differences were found between HCL and SAP groups in mean heart rate, QTc-interval or the number of bradycardia and tachycardia events. No significant between-group differences were observed in the number of ventricular or supraventricular arrhythmias, including single ectopic beats.

Across the whole group, longer time spent within a normoglycaemic range (3.9-10.0 mmol/L) moderately correlated with having fewer dropped beats ($r = -0.446$, $p = .033$) and fewer single supraventricular ectopic beats ($r = -0.411$, $p = .002$). In comparison, longer time spent in the hyperglycaemia range (>10.0 mmol/L) was associated with higher numbers of dropped beats ($r = 0.471$, $p = .023$) and higher numbers of single supraventricular ectopic beats ($r = 0.394$, $p = .004$).

Longer time spent hypoglycaemic <3.0 mmol/L across the whole group was found associated with an increased number of supraventricular ectopic runs ($r = 0.308$, $p = .025$) and supraventricular couplets ($r = 0.321$, $p = .019$).

TABLE 1 Between-group differences in glucose sensor outcomes and 24-h Holter monitoring parameters during the intervention periods.

Glucose sensor outcomes	HCL (N = 29)	SAP (N = 29)	Paired mean difference[a]	*p*-Value
Time spent at glucose level, %				
3.9-10.0 mmol/L	76.3 (12.6)	71.5 (13.4)	5.3 (95% CI 1.0, 9.6)	.018
>10.0 mmol/L	21.7 (12.9)	26.0 (13.9)	−5.0 (95% CI −9.2, −0.8)	.023
<3.9 mmol/L	1.6 (0.70, 2.4)	1.8 (1.3, 3.2)	NA	.231
<3.0 mmol/L	0.2 (0.1, 0.5)	0.2 (0.0, 0.4)	NA	.224
Mean glucose, mmol/L	8.2 (1.2)	8.4 (1.2)	−0.3 (95% CI −0.7, 0.0)	.057
Glucose coefficient of variation, %	33.2 (5.0)	33.3 (5.6)	−0.1 (95% CI −2.6, 2.4	.944
Holter monitoring parameters				
Mean heart rate, bpm	71.3 (9.7)	71.3 (11.4)	0.44 (95% CI −1.04, 1.93)	.543
Min heart rate, bpm	52.7 (8.5)	52.7 (9.3)	0.41 (95% CI −1.1, 1.9)	.590
Max heart rate, bpm	124.3 (13.1)	124.2 (20.8)	1.1 (95% CI −5.9, 8.1)	.747
QTc-interval, ms	412.3 (20.8)	415.3 (18.9)	−0.83 (95% CI −5.5, 3.8)	.717
Rate-dependent events, n				
Pause	0 (0, 0)	0 (0, 0)	NA	.465
Bradycardia	0 (0, 3)	0 (0, 3)	NA	.666
Tachycardia	0 (0, 0)	0 (0, 0)	NA	1.0
Dropped beat	5 (2, 18)	5.5 (4, 12)	NA	.779
Ventricular arrythmias, n				
Broad complex tachycardia	0 (0, 0)	0 (0, 0)	NA	1.0
V-Run/AIVR	0 (0, 0)	0 (0, 0)	NA	.785
IVR	0 (0, 0)	0 (0, 0)	NA	1.0
Triplet	0 (0, 1)	0 (0, 0)	NA	.236
Couplet	0 (0, 3)	0 (0, 2)	NA	.969
Bigeminy	0 (0, 0)	0 (0, 1)	NA	.574
Trigeminy	0 (0, 1)	0 (0, 1)	NA	.285
Single VE events	59 (13, 702)	90 (11, 502)	NA	.301
Supraventricular arrhythmias, n				
SVT	0 (0, 0)	0 (0, 0)	NA	.317
SVE run	3 (0, 8)	3 (0, 7)	NA	.407
SVE couplet	6 (0, 15)	4 (1, 14)	NA	.278
Single SVE events	226 (47, 1040)	165 (65, 1298)	NA	.156

Note: Data expressed as mean (SD) or median (IQR).

Abbreviations: AIVR, accelerated idioventricular rhythm; bpm, beats per minute; HCL, hybrid closed-loop; IVR, idioventricular rhythm; NA, not applicable; SAP, sensor augmented pump; SVE, supraventricular ectopic beat; SVT, supraventricular tachycardia rhythm; VE, ventricular ectopic beat.

[a]Normally distributed data are presented as mean differences (HCL intervention minus SAP control phase). A positive difference indicates that the measurement was higher during the HCL period than during the SAP period. Mean differences were not calculated for skewed data (denoted by NA).

4 | DISCUSSION

In this post hoc analysis, we observed no significant differences in the frequency of cardiac arrhythmias during HCL use when compared with during SAP use. This was in the context of low baseline levels of cardiac disease and arrhythmia, high levels of time in range and low levels of time spent hyperglycaemic during both HCL and SAP use, although the HCL intervention led to significant between-group differences in these glycaemic parameters in favour of HCL. However, time spent hypoglycaemic was low and was comparable during both study periods.

We showed that higher time in range and lower time in hyperglycaemic excursions were found to correlate moderately with lower numbers of dropped beats and isolated supraventricular ectopic beats. We also found across the whole group that time spent hypoglycaemic (<3.0 mmol/L) was associated with higher numbers of supraventricular ectopic beats, a known risk factor for atrial fibrillation.[8]

To our knowledge, the relationships between changes in glucose control with HCL and their impacts on cardiac rhythm have not been reported to date. Our data are important because experimental hypoglycaemia studies show that when compared with people without

diabetes, individuals with diabetes had more markers of arrhythmia risk and myocardial ischaemia.[9] These differences occurred despite both groups having comparable sympathoadrenal responses to hypoglycaemia. Observational studies involving cardiac and glucose monitoring in young people with T1D also indicate that hypoglycaemia is pro-arrhythmogenic.[10] What makes our data more relevant clinically is the substantial evidence showing that hypoglycaemia unawareness and severe hypoglycaemia, which are risk factors for fatal cardiac arrythmia, are more commonly observed in older rather than in younger people with T1D.[4,11]

The burden of hypoglycaemia in our cohort was relatively low. Time in range in the SAP group during the Holter monitoring periods was also relatively high (>70%), and therefore the between-group improvement in glucose control was small in our study than in others.[12,13] This relatively small treatment effect may have therefore attenuated any cardiac rhythm improvement. Animal studies have shown that acute hyperglycaemia can enhance cellular pro-arrhythmic mechanisms.[14,15] Meta-analysis of patients admitted with myocardial infarction has suggested that hyperglycaemia is associated with higher risks of arrhythmia.[16] These findings may be relevant to our population, as older people with T1D have higher risks of arrhythmia and myocardial infarction than the general population.[1,4] HCL use in our study reduced time spent in the hyperglycaemic range without increasing hypoglycaemia burden, and while we observed that shorter time spent hyperglycaemic was associated with fewer supraventricular ectopic and dropped beats, its clinical significance remains uncertain.

Our study has several strengths. First, its randomized crossover study design, using participants as their own control, has maximized treatment-effect signals and has limited bias from potential confounding factors. Second, HCL efficacy and safety were assessed in older adults with T1D, a cohort at high risk from arrhythmias who are usually excluded from studies of diabetes technology. Third, the relationships between glycaemia outcomes and cardiac rhythms were assessed using 7-day duration Holter monitoring and glucose sensor data that were reported using internationally recommended standards.

Our study had some limitations. First, participants had relatively good glycaemic control and low hypoglycaemic burden during both study periods, which may have limited both treatment-related differences and the generalizability of results. Second, as this was a post hoc analysis with a relatively short duration of continuous glucose monitor sensor and Holter recording, it may have been underpowered to identify small treatment-related differences. However, these data provide valuable information that will inform the design of future similar studies. Third, as 97% of participants were white and ethnicity is a known cardiac risk factor, this may have attenuated cardiac event risk and limit generalizability. Fourth, we did not have access to data on physical activity, but there is no reason to expect differences in physical activity between the two monitoring periods that were large enough to influence rates of incident arrhythmia. Finally, echocardiographic data were not available. However, our study's crossover design limits any bias because of the presence of any pre-existing cardiac disease.

In conclusion, improved glycaemia with HCL in older people with T1D, low levels of cardiac disease and good baseline glycaemia was associated with no overall change in cardiac arrhythmia. The association between glucose levels and cardiac rhythm is of interest; however, its clinical relevance is uncertain and warrants further investigation. Future studies in T1D are called for that assess the impact of HCL on arrhythmia risk in individuals with higher levels of cardiac disease, arrhythmia risk and hypoglycaemia burden/unawareness.

ACKNOWLEDGMENTS

We are grateful to study volunteers for their participation. We like to thank Sara Hartnell, Katharine Draxlbauer and Tina Poettler for their involvement and contribution to the study. We thank Josephine Hayes (University of Cambridge, UK) for administrative support. This work was funded by the National Institute of Diabetes and Digestive and Kidney Diseases under the grant number 1DP3DK112176-01 and the UK MRC Clinical Academic Research Partnership (MR/T023899/1). The work was supported by the NIHR Manchester Biomedical Research Centre. Additional support for the artificial pancreas work was from National Institute for Health Research Cambridge Biomedical Research Centre, and JDRF. Dexcom supplied discounted continuous glucose monitoring devices. The University of Cambridge has received salary support for MLE through the National Health Service in the East of England through the Clinical Academic Reserve. The views expressed are those of the author(s) and not necessarily those of the funders.

CONFLICT OF INTEREST STATEMENT

HT receives consulting fees and speaker honoraria from Eli Lilly, and reports having received research support from Dexcom Inc. CKB has received consulting fees from CamDiab and speaker honoraria from Ypsomed. JKM is a member on the advisory board of Abbott Diabetes Care, Boehringer Ingelheim, Becton-Dickinson, Eli Lilly, Medtronic, Novo Nordisk A/S, Prediktor A/S, Roche Diabetes Care, Sanofi-Aventis, Viatris and received speaker honoraria from Abbott Diabetes Care, Becton-Dickinson, Dexcom, Eli Lilly, Medtrust, MSD, Novo Nordisk A/S, Roche Diabetes Care, Sanofi, Servier, Viatris and Ypsomed. MLE is a clinical triallist with and/or has served on advisory boards and/or received speakers/ writers fees from Medtronic, Dexcom, Abbott Diabetes Care, Roche, Astra Zeneca, Novo Nordisk, Eli Lilly, Zucara, Pila Pharma, Imcyse Pharma. LL has received personal fees from Abbott Diabetes Care, Dexcom, Insulet, Medtronic, Novo Nordisk and Sanofi. MEW reports patents related to closed-loop and being a consultant at CamDiab. RH reports receiving speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving licence and/or consultancy fees from B. Braun and Abbott Diabetes Care; patents related to closed-loop, and being director at CamDiab. SA, RH, WM, JR, CF, CG and MKR have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15366.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Thabit H, Boughton C, Mubita W, et al. Impact of hybrid closed-loop insulin delivery on cardiac rhythm in older adults with type 1 diabetes: A post hoc analysis of trial data. *Diabetes Obes Metab*. 2023;1-5. doi:10.1111/dom.15366