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Glycemic Variability During Algorithmic Titration of Insulin Among Hospitalized Patients with Type 2 Diabetes and Heart Failure

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Abstract

AIMS—The objective of this study is to assess hypoglycemia and glycemic variability (GV) in hospitalized patients with and without heart failure (HF) exacerbation.

METHODS—Hospitalized patients with type 2 diabetes (T2D) with (N=35) or without (N=16) HF who had hyperglycemia or significant insulin use were included. Subjects underwent continuous glucose monitoring during algorithmic titration of basal bolus insulin.

RESULTS—HF subjects had lower glucose coefficient of variation ([CV], 31+/−12 vs. 22+/−8.2, p=0.02), lower Low Blood Glucose Index (LBGI) and less hypoglycemia (25 vs. 2.6%, p=0.02), but similar mean glucose and glycemic lability index as non-HF subjects on day 1, but not on day 2. Sensor CV was correlated with hypoglycemia (ρ 0.32, p=0.02), HF status (ρ −0.35, p=0.013), T2D duration (ρ 0.29, p=0.04), insulin use prior to admission (ρ 0.42, p=0.002) and catecholamine levels. After controlling for differences in age, HbA1c, hypoglycemia, catecholamine levels, QT interval, and beta blocker use, only HF and diabetes duration or insulin use prior to admission

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CONTRIBUTOR STATEMENTS

K.D. performed study design, researched the data, and wrote the manuscript, P.B. and K.O. assisted with study design, reviewed/ edited the manuscript and contributed to the discussion.

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were independent predictors of CV. HF had less robust associations with LBGI in multivariable models.

CONCLUSIONS—HF is not associated increased GV or hypoglycemia risk during initial titration of insulin. Further research is needed to determine prognostic implications.

Keywords

heart failure; hypoglycemia; glycemic variability; insulin; hospital

1.0 INTRODUCTION

Heart failure (HF) is a frequent comorbidity of diabetes that poses an enormous medical, societal and financial burden, affecting 5 million Americans, and leading to $27.9 billion in costs annually.[American Heart Association 2005] Diabetes is an independent predictor of mortality in patients with HF. [De Groote et al. 2004. Gustafsson et al. 2004] Experts recommend relaxed glucose targets among patients with significant comorbidities and an individualized approach based upon the perceived risk of hypoglycemia as well as the potential for adverse sequelae related to hypoglycemia.[Inzucchi et al. 2012, Ismail-Beigi et al. 2011] Hypoglycemia may be particularly concerning in HF patients, due to the predisposition for arrhythmias and ischemic events.[Kennel et al. 1998, Uretsky et al. 2000] However, glucose control has not been well characterized in patients with HF.

In patients with heart failure (HF), higher HbA1c has been associated with increased mortality in some studies, [Gerstein et al. 2008, Romero et al. 2013]. However, other data support a paradoxical [Auilar et al. 2009, Tomova et al. 2012] or J-shaped relationship [Eshaghian et al. 2006] between HbA1c and outcomes, indicating that hypoglycemia may mitigate possible benefits of lower HbA1c. Unfortunately, it can not be determined from these studies whether the low HbA1c per se is harmful, or even whether hypoglycemia plays a role. Furthermore, observations are confounded by non-glycemic factors, which may disproportionately affect the measurement of HbA1c in sicker patients.

Continuous glucose monitoring has the potential to uncover patterns in glucose control which are not captured by HbA1c. Measures of glycemic variability (GV) have garnered interest since numerous studies have demonstrated that increasing measures of GV are associated with higher mortality during critical illness, [Eslami et al. 2011] and possibly HF exacerbation.[Dungan et al. 2011] Patients with long-standing diabetes have increasing GV with both beta cell and counterregulatory hormone failure, and GV is a predictor of counterregulatory failure in response to hypoglycemia.[Murata et al. 2004, Alghothani and Dungan 2011] However, HF itself is characterized by profound neuroendocrine disturbances, and thus it is unclear if this may play a role in the development of hypoglycemia or GV.[Braunwald 2008, Jankowska et al. 2006, Niskanen et al. 2009] Assessing measures of GV may be useful for assessing hypoglycemia risk[Niskanen et al. 2009, Monnier et al 2011] which may limit the titration of therapies.

The objective of this study is to assess whether hypoglycemia or GV differs among hospitalized patients with or without HF exacerbation.

2.0 MATERIAL AND METHODS

2.1 Patients

Study subjects were enrolled as part of separate studies of hospitalized patients with type 2 diabetes, one in patients admitted with HF as the primary diagnosis and the other in subjects without a history of HF.[Dungan et al. 2014, Dungan et al. 2013a] Inclusion criteria for both studies included significant insulin use (>20 units/day) or hyperglycemia (BG >180 mg/dl [10 mmol/l] on at least 2 occasions separated by at least 4 hours apart). Exclusion criteria for both studies included type 1 diabetes, hyperglycemic emergency, critical illness (such as the need for mechanical ventilation and hypotension requiring vasopressors), corticosteroid use, end stage renal or liver disease, hospital stay expected to be less than 48 hr, inability to consent, prisoners and pregnancy. The HF study also excluded patients with acute myocardial infarction within the previous 3 months or predominantly right-sided heart failure. The non-HF group also excluded patients with arrhythmia or autonomic neuropathy. All studies were approved by the Institutional Review Board at the study institution and all patients signed informed consent.

2.2 Intervention

Patients were randomly assigned to intravenous (IV) or subcutaneous (SQ) insulin. However, due to differences in the IV insulin protocols, only subjects receiving SQ insulin could be analyzed for the current study. The SQ insulin algorithm was identical for both studies. All oral or non-insulin agents were discontinued. In insulin naïve patients the total daily dose of SQ insulin was 0.4 or 0.5 times the body weight in kg for an enrollment glucose of <180 mg/dl or >180 mg/dl respectively. In patients admitted on insulin, the total daily dose of SQ insulin was estimated as 100 or 120% of the total home dose of insulin in patients with an enrollment glucose of <180 mg/dl or >180 mg/dl respectively. Basal insulin was administered as approximately half of the estimated total daily dose of insulin. Prandial insulin was delivered according to carbohydrate intake as described previously.[Dungan et al. 2014, Dungan et al. 2013a] The target glucose range was 100–150 mg/dl and adjustments were made in the total daily insulin dose of +/−10–20% per day.

A continuous glucose monitor (CGMS Ipro®, Medtronic) was used in accordance with manufacturer instructions. The sensor was inserted on the abdomen and downloaded after at least 48 hours using CGMS solutions software. Capillary glucose values (Accu-Chek Inform®, Roche) were measured every 4–6 hours (before meals and bedtime when eating) in the SQ group. Calibrations were performed at 4 pre-determined time points each day (closest to 7AM, 11AM, 4PM and 9PM) within the allowable glucose limits (40–400 mg/dl) of the software. CGM data had a correlation of 0.88 (p-value <0.0001) and a mean absolute difference of 9.6% compared to capillary blood glucose assessments.[Dungan et al. 2013b]

2.3 Analysis

Glycemic variability was measured with the coefficient of variation (CV, standard deviation/mean glucose) and glycemic lability index (GLI, which is calculated by first finding the square of the difference between successive glucose measurements, dividing this value by the difference in time between measurements, and then calculating the sum of the quotients).

[Ryan et al. 2004] Hypoglycemia was defined as a *blood* glucose 70 mg/dl (<3.9 mmol/l) due to the concern for low accuracy of continuous glucose monitoring in the hypoglycemic range.[Zijlstra et al. 2013] Due to the relatively low number of hypoglycemic events, a hypoglycemic risk score, the Low Blood Glucose Index (LBGI), was also calculated as reported previously using a transformed scale to correct the skewness of the glucose range. [Kovatchev et al. 1998]

The QT interval was obtained from patients who had a 12-lead electrocardiogram within 24 hours of enrollment. QT interval was corrected for heart rate, gender, and QRS interval as previously reported.[Rautaharju et al. 2004, Rautaharju et al. 2009] Change in plasma volume was calculated with the hemoglobin and hematocrit from successive days as published previously.[Kalra et al. 2002]

Continuous variables were reported as mean (standard deviation) or median (interquartile range) for normal and non-normal distributions respectively. Unpaired t-tests or Wilcoxon rank-sum tests were used to compare groups as appropriate. Dichotomous variables were reported as number (percentage) and between group comparisons were made using Fisher's exact test. Statistical significance was determined at a p-value <0.05. Spearman's correlation coefficients were calculated. Multiple linear regression analyses were performed for CV using least squares linear regression and backward stepwise methodology. Variables were chosen for entry into the model based upon univariable effect estimates (cut-off p-value of 0.1). Age and beta blockade were added to models due to baseline differences between groups. Statistical analyses were performed using JMP 10.0 software.

3.0 RESULTS

A total of 35 patients with HF and 16 patients without HF met the inclusion and exclusion criteria. Baseline characteristics, stratified by HF status, are presented in Table 1. Patients with HF were older (63 +/−12 vs. 55 +/−10.4 years, p=0.02), more likely to be on a beta blocker (90 vs. 44%, p=0.0007), and had lower HbA1c (7.7 +/−1.4 vs. 9.2 +/−2.5, p=0.04) than patients without HF. Patients with HF had higher norepinephrine (1167 +/−698 vs. 389 +/−264 pg/ml, p<0.0001), epinephrine (69 +−51 vs. 20 +/−14 pg/ml, p<0.0001), and corrected QT interval (342 +/− 10.2 vs. 360 +/− 27.5, p=0.008) compared to those without HF. Otherwise, baseline characteristics were similar.

HF subjects had lower glucose CV, (31+/−12 vs. 22+/−8.2, p=0.02), less hypoglycemia (25 vs. 2.6%, p=0.02), and tended to have lower LBGI compared to non-HF subjects overall (Table 1). Mean glucose and GLI were similar between CH and non-HF subjects. Daily differences were evident for CV, LBGI, and hypoglycemia on day 1 but not day 2.

Sensor CV was correlated with hypoglycemia (ρ 0.32, p=0.02), HF status (ρ −0.35, p=0.013), duration of diabetes (ρ 0.29, p=0.04), corrected QT interval (ρ −0.38, p=0.03) and catecholamine levels, but was not correlated with age, beta blocker use, body mass index, renal function or other variables (Table 2). GLI was not correlated with any of the variables analyzed (Table 2).

LBGI was correlated with T2D duration (ρ 0.35, p=0.01), admission on insulin (ρ 0.28, p=0.042), epinephrine (ρ −0.35, p=0.01), renal function (ρ −0.33, p=0.02)), and QT_c (ρ −0.40, p=0.02) (Table 2). LBGI showed only a trend for correlation with HF status (ρ −0.24, p=0.08).

Multivariable models were created using CV as the dependent variable and HF status as well as potential confounders or mediators as independent variables (Table 3). In model 1, HF status was the only significant independent variable (p=0.008) after controlling for diabetes duration, beta blockade, epinephrine level, and hypoglycemia. Following backward linear regression, both HF status and diabetes duration were independent predictors in the final model, such that HF was associated with 5.18% lower CV compared to non-HF status (p=0.001), and each year of diabetes duration was associated with a 0.35% increase in CV (p=0.01). After log-transformation of diabetes duration, only HF was a significant predictor (data not shown). In model 2, HF status (p=0.004) and insulin use prior to hospitalization (p=0.04) were independent predictors of CV, independent of age, beta blockade, and HbA1c. Following backward linear regression, both HF and insulin use prior to admission were independent predictors in the final model, such that HF was associated with a 4.36% lower CV compared to no HF (p=0.003), and insulin use was associated with 4.46% increase in CV compared to non-use (p=0.01). Finally, in model 3, corrected QT interval was not a significant predictor of CV after controlling for HF, beta blockade, and insulin use prior to admission.

Multivariable models were also conducted using LBGI as the dependent variable and HF status and other variables as independent variables (Table 4). In initial models adjusting for HF status, age, diabetes duration, insulin use prior to admission, epinephrine level, beta blockade, renal function, and QTc interval, HF was not a significant predictor. However, HF was a significant predictor of LBGI in final models following backward linear regression.

4.0 DISCUSSION

In this study, hospitalized patients with HF had lower GV, assessed as CV, on day 1 of titration of insulin compared to those without HF, even after controlling for other differences between groups. In addition, the crude frequency of hypoglycemia and LBGI, a measure of hypoglycemia risk, was lower in HF patients compared to non-HF patients. HF was a predictor of LBGI in final models but was not a significant predictor of LBGI in fully adjusted models.

Patients with HF have more risk factors for hypoglycemia, including renal failure; thus the results are somewhat unexpected. However, HF like many illness states, is marked by “decomplexification”, or increased regularity of physiologic rhythms such as heart rate and respiratory rate”.[Seely and Macklem 2004] Thus, there could be important interactions between physiologic parameters in various disease states that are not very well understood. For example, it is known that changes in glucose in controlled settings may alter autonomic tone, measured with heart rate variability and QT interval.[Takei et al 2007, Santini et al. 2007, Koivikko et al. 2005] In HF, these autonomic measures are abnormal at baseline and are blunted to outside stimuli.[Guzzetti et al 2001] In previous studies, IV insulin resulted in

higher GV (measured with GLI) and greater sympathetic tone (measured with pre-ejection period) compared to SQ insulin in non-HF patients[Dungan et al 2013a], but the effect was very weak in a study of HF patients.[Dungan et al 2014] Thus, susceptibility of effects of autonomic perturbations on glucose fluctuations could be dampened in HF. In this study, increasing catecholamine levels were inversely correlated with CV, but there was no association after controlling for other variables, suggesting that other factors are more important for explaining differences in glycemic variability between HF and non-HF patients. However, tissue specific differences in autonomic reactivity may still play a role and are not completely assessed by circulating catecholamine levels.

It is possible that HF patients may have had less awareness of hypoglycemia, but the use of CGM should have identified asymptomatic hypoglycemia. CGM does have limitations in accuracy, particularly at low glucose values, [Choudhary et al. 2001] but the LBGI is reported to be a strong predictor of future severe hypoglycemia.[Kovatchev et al. 1998] Other studies have shown that GV is a predictor of hypoglycemia and may be a useful tool for hypoglycemia risk stratification.[Niskanen et al 2009] While cardiac autonomic neuropathy may increase the risk of severe hypoglycemia through impaired sympathoadrenal responses to hypoglycemia, [Cryer 2001] the autonomic responses to hypoglycemia in the setting of HF are unknown.

Hyperglycemia related treatment factors are expected to play a minimal role in explaining differences between HF and non-HF patients, as all patients were managed using a consistent insulin dosing algorithm and titration scale. While the use of beta blockers differed between groups, it was not significantly associated with GV or hypoglycemia. These findings are in agreement with literature supporting the general safety of beta blockade in patients with diabetes, [Murad et al 2009, Kerr et al. 1990] and additionally, provide reassurance of the safety of their use in insulin-requiring patients with T2D and HF. In fact, beta blockade has been shown to prevent the impaired autonomic response to hypoglycemia known to follow an antecedent hypoglycemic event.[Ramanathan and Cryer 2011] Several factors, including age, HbA1c, catecholamine levels, and QT interval differed by HF status, but none were significant predictors of CV or LBGI after controlling for HF and diabetes duration or insulin use. Unfortunately, QT interval was only available in a subset of patients. Thus, a larger sample size is needed to further evaluate this issue. Of note, the differences in hypoglycemia and GV dissipated after study day 1, suggesting that they are modified by other factors, such as changes in acuity of illness or active insulin titration. Thus, these findings warrant confirmation with other treatment regimens and in other settings.

Although these results are reassuring, it does not automatically follow that lower GV or hypoglycemia risk translates to improvement in outcomes in HF patients. In fact, it could be a sign of more advanced HF and portend worse outcomes. Nor can we conclude from this data that hypoglycemia, when it occurs, is more or less harmful in HF patients compared to those without HF. This will require future investigation, though our preliminary studies suggest possibly blunted autonomic responses in HF patients. In the meantime, providers should continue to individualize treatment goals based upon known factors that increase the

risk related to hypoglycemia and the potential benefits of glucose control in a given individual.

Several limitations are worthy of mention. The sample size was small, the observation period was short, and titration was performed in an unblinded manner. Residual confounding by unmeasured factors is therefore still possible and these findings should be confirmed in larger studies of greater duration. Strengths include a novel patient population at high risk for potential adverse effects of hypoglycemia, the use of CGM measures for a more complete picture of glucose patterns, and consistent hyperglycemia therapy.

In conclusion, HF was not associated with increased GV or hypoglycemia risk in hospitalized patients with type 2 diabetes during algorithmic titration of basal bolus insulin. Further study is needed to verify these findings, identify mechanisms, and assess glucose targets.

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Table 1

Baseline Characteristics by Heart Failure Status

	No Heart Failure	Heart Failure	P-value
Age	55 (10.4)	63 (12.4)	**0.02**
Male	12 (75%)	26 (70%)	0.75
Caucasian	14 (88%)	27 (74%)	0.47
Diabetes duration (years)	12 (7–17)	11 (9–20)	0.66
Coronary artery disease	6 (38%)	25 (64%)	0.08
Beta Blockade	7 (44%)	35 (90%)	0.0007
CHF treatment			
Dobutamine - N (%)	-	6 (15%)	-
Milrinone - N (%)	-	5 (13%)	-
Nesiratide - N (%)	-	6 (15%)	-
Intravenous diuretic - days (IQR)	-	4 (2–7)	-
BNP^			
day 1	-	431 (224–976)	-
day 4	-	299 (135–713)	-
Insulin prior to admission	13 (81%)	33 (85%)	0.71
Insulin total dose day 1 (units)	58 (19–85)	35 (18–58)	0.19
Insulin total dose day 2 (units)	43 (15–74)	38 (24–72)	0.49
Body mass index (kg/m^2)	35 (7.4)	39 (8.8)	0.08
HbA1c (%)	9.2 (2.5)	7.7 (1.4)	
HbA1c (mmol/mol)	77 (27.3)	61 (15.3)	0.04
Admit serum glucose (mg/dl)	212 (64)	175 (61)	0.06
Estimated GFR (mg/dl)*	57 (27)	50 (20)	0.35
Hemoglobin (gm/dl)			
day 1	11.6 (2.55)	11.3 (1.85)	0.65
day 2	10.9 (2.17)	11.3 (1.78)	0.62
%change plasma volume	2.45 (−3.73– 14.8)	0.59 (−0.61– 7.97)	0.31
Norepinephrine (pg/ml)	389 (264)	1167 (698)	<0.0001
Epinephrine (pg/ml)	20 (14)	69 (51)	<0.0001
QT interval†	342 (10.2)	360 (28)	0.008
Hospital length of stay (days)	7.5 (5.3–12.3)	8 (5–12)	0.55

^P-value within group over time =0.0003.

*Estimated GFR is assessed using the Modified Diet in Renal Disorders equation.

†QT interval corrected for heart rate, gender, and QRS; N=10 without HF and N=24 with HF.

HF=heart failure, GFR=glomerular filtration rate.

Table 2

Glucose Measures by Heart Failure Status

Sensor glucose			
Mean (mg/dl)	156 (36)	166 (40)	0.37
Mean day 1	155 (36)	169 (49)	0.27
Mean day 2	156 (70)	164 (41)	0.68
GLI ([mg/dl]^2/hr*day^{-1})	0.94 (0.45–2.02)	0.75 (0.37–2.62)	0.37
GLI day 1	0.88 (0.74–2.74)	0.66 (0.29–2.01)	0.15
GLI day 2	0.32 (0.19–0.92)	0.51 (0.30–1.51)	0.30
Coefficient of Variation (%)	31 (12)	22 (8.2)	0.019
CV day 1	29 (13)	19 (8.5)	0.008
CV day 2	16 (6.6)	19 (8.0)	0.13
Low Blood Glucose Index (LBGI)	7.73 (1.2–12.2)	2.44 (1.05–5.93)	0.08
LBGI day 1	8.42 (1.09–18.2)	2.29 (0.52–6.89)	0.04
LBGI day 2	1.35 (0.51–11.4)	0.99 (0.58–3.30)	0.60
Hypoglycemia day 1–2	4 (25%)	1 (2.6%)	0.02
Day 1 hypoglycemia	4 (25%)	1 (2.6%)	0.02
Day 2 hypoglycemia	0 (0%)	1 (2.6%)	>0.99

GLI=glycemic lability index. Hypoglycemia is defined as blood or interstitial fluid glucose <70 mg/dl.

Table 3

Correlations with Glucose Variability

	Coefficient of Variation		Glycemic Lability Index		Low Blood Glucose Index	
Variable	**Spearman ρ**	**P-value**	**Spearman ρ**	**P-value**	**Spearman ρ**	**P-value**
Sensor Mean	0.18	0.19	0.36	0.0006	−0.16	0.28
Hypoglycemia day1–2	0.32	0.024	0.03	0.83	0.32	0.020
Heart failure	−0.35	0.013	−0.13	0.37	−0.24	0.08
Age	−0.03	0.85	−0.15	0.28	−0.08	0.59
Male	−0.17	0.23	−0.20	0.15	−0.16	0.25
Caucasian	0.13	0.36	−0.05	0.74	−0.07	0.62
Diabetes duration	0.29	0.04	0.06	0.69	0.35	0.013
Beta blocker	0.02	0.90	−0.04	0.77	−0.10	0.47
Insulin prior to admission	0.42	0.002	−0.11	0.45	0.28	0.04
Body mass index	−0.14	0.32	0.05	0.70	−0.04	0.78
HbA1c	0.19	0.18	−0.02	0.90	−0.07	0.63
Admission glucose	0.26	0.067	0.21	0.14	0.15	0.27
Norepinephrine	−0.29	0.046	0.08	0.61	−0.11	0.44
Epinephrine	−0.52	0.0002	−0.21	0.16	−0.35	0.01
Estimated GFR	−0.09	0.52	0.04	0.81	−0.33	0.02
$QT_{c\text{-}RR,QRS}$*	−0.38	0.03	0.018	0.92	−0.40	0.02

*QT interval was corrected for gender, heart rate, QRS interval.

GFR=glomerular filtration rate

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Table 4

Multivariable Models for Coefficient of Variation

Final Model 1			
Term	Estimate	SE	P-value
Heart failure	−5.18	1.44	0.001
Diabetes duration	0.35	0.14	0.01
Final Model 2			
Term	Estimate	SE	P-value
Heart failure	−4.36	1.38	0.003
Insulin prior to admission	4.46	1.67	0.01
Final Model 3			
Term	Estimate	SE	P-value
Heart failure	−4.36	1.38	0.003
Insulin prior to admission	4.46	1.67	0.01

Model 1 initially included heart failure, diabetes duration, beta blockade, epinephrine and hypoglycemia. Model 2 initally included age, heart failure, beta blockade, insulin prior to admission, and HbA1c. Model 3 initially included heart failure, insulin prior to admission, QTc (corrected for gender, heart rate, QRS interval) and beta blockade.

Table 5

Multivariable Models for Low Blood Glucose Index

Final Model 1			
Term	Estimate	SE	P-value
Heart failure	−2.88	0.88	0.002
Insulin prior to admission	2.346	1.05	0.031
Final Model 2			
Term	Estimate	SE	P-value
Heart failure	−2.88	0.88	0.002
Insulin prior to admission	2.34	1.05	0.031
Final Model 3			
Term	Estimate	SE	P-value
Heart failure	−2.79	0.90	0.003

Model 1 initially included heart failure, insulin prior to admission, estimated glomerular filtration rate, epinephrine, and QT interval corrected for gender, heart rate, and QRS interval. Model 2 initially included age, heart failure, beta blocker, insulin prior to admission, and epinephrine. Model 3 initially included heart failure, diabetes duration, estimated glomerular filtration rate, epinephrine, and QT interval corrected for gender, heart rate, and QRS interval.