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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 were independent predictors of CV. HF had less robust associations with LBGI in multivariable models.
Conclusions: HF is not associated with increased GV or hypoglycemia risk during initial titration of insulin. Further research is needed to determine prognostic implications.

1. 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 (Kannel, Wilson, D'Agostino, & Cobb, 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 2013). However, other data support a paradoxical (Aguilar, Bozkurt, Ramasubbu, & Deswal, 2009; Tomova, Nimbal, & Horwich, 2012) or J-shaped relationship (Eshaghian, Horwich, & Fonarow, 2006) between HbA1c and outcomes, indicating that hypoglycemia may mitigate possible benefits of lower HbA1c. Unfortunately, it cannot 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, Taherzadeh, Schultz, & Abu-Hanna, 2011) and possibly HF exacerbation (Dungan, Binkley, Nagaraja, Schuster, & Osei, 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

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hypoglycemia (Alghothani & Dungan, 2011; Murata, Duckworth, Shah, Wendel, & Hoffman, 2004). 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; Burger & Aronson, 2001; Jankowska et al., 2006; Niskanen, Virkamäki, Hansen, & Saukkonen, 2009). Assessing measures of GV may be useful for assessing hypoglycemia risk (Monnier, Wojtusciszyn, Colette, & Owens, 2011; Niskanen et al., 2009) 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. 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, Graessle, & Sagrilla, 2013; Dungan, Osei, Gaillard, Moore, & Binkley, 2014; Dungan, Osei, et al., 2013). Inclusion criteria for both studies included significant insulin use (>20 U/day) or hyperglycemia (BG >180 mg/dl [10 mmol/l] on at least 2 occasions separated by at least 4 h 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 h, 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, Osei, et al., 2013). 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 h using CGMS solutions software. Capillary glucose values (Accu-Chek Inform®, Roche) were measured every 4–6 h (before meals and bedtime when eating) in the SQ group. Calibrations were performed at 4 pre-determined time points each day (closest to 7 AM, 11 AM, 4 PM and 9 PM) 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, Graessle, & Sagrilla, 2013).

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, Heise, Nosek, Heinemann, & Heckermann, 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 h of enrollment. QT interval was corrected for heart rate, gender, and QRS interval as previously reported (Rautaharju et al., 2009; Rautaharju, Zhang, Prineas, & Heiss, 2004). Change in plasma volume was calculated with the hemoglobin and hematocrit from successive days as published previously (Kalra, Anagnostopoulos, Bolger, Coats, & Anker, 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. 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,