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Effect of the Approach to Insulin Therapy on Glycemic Fluctuations and Autonomic Tone in Hospitalized Patients with Diabetes

Kathleen Dungan, MD, MPH¹, Kwame Osei, MD¹, Colleen Sagrilla, BS², and Philip Binkley, MD, MPH^{2,3}

¹The Ohio State University Division of Endocrinology, Diabetes & Metabolism

²The Ohio State University Dorothy M. Davis Heart and Lung Research Institute

³The Ohio State University Division of Cardiovascular Medicine

Abstract

AIMS—Glycemic variability (GV) is associated with mortality in acutely ill patients, but the mechanism is unknown. The objective of this study is to determine whether common approaches to insulin therapy have distinct effects on GV and autonomic tone.

MATERIALS & METHODS—Hospitalized patients with diabetes were randomized to short-term intravenous (IV) or physiologic subcutaneous (SQ) insulin. Heart rate variability (HRV) and cardiac impedance (pre-ejection period, PEP) were used to estimate parasympathetic and sympathetic tone respectively. GV was measured using a continuous glucose monitor.

RESULTS—Mean glucose tended to be lower initially in the SQ group (N=16) compared to the IV group (N=17) on day 1 (10.5 vs. 8.6mmol/l, p=0.05), but became nonsignificant during the transition off of the infusion. There was no difference in glycemic lability index (GLI), continuous overlapping net glycemic action (CONGA) or coefficient of variation (CV) on day 1, but by day 2, these measures were higher in the IV group (p<0.05 for all). PEP was higher in the SQ group during (110 vs. 123 ms, p=0.02) and after the intervention (104 vs. 126 ms, p=0.004). Hypoglycemia was similar in both groups. There were only small differences in HRV. Post-treatment PEP was inversely correlated with log GLI (r= -0.41, p=0.03) but not other measures.

CONCLUSIONS—Short-term IV insulin is associated with an increase in multiple GV measures compared to optimal SQ insulin. However, GLI was the only predictor of PEP. Further research is needed to determine if interventions that minimize GV improve outcomes in the hospital.

Keywords

glycemic variability; autonomic tone; intravenous insulin; inpatient

Corresponding author: Kathleen M. Dungan, MD, MPH, The Ohio State University, Division of Endocrinology, Diabetes, and Metabolism, 5th Floor McCampbell Hall, 1581 Dodd Drive, Columbus, OH 43210-1296, Phone (614) 685-3333, Fax (614) 366-0345, Kathleen.dungan@osumc.edu.

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KD performed study design, patient procedures, analysis of data, and preparation of the manuscript. KO assisted with study design and reviewed the manuscript. CS performed patient enrollment and procedures, and assisted with analysis of data. PB assisted with study design, analysis of data and preparation of manuscript.

INTRODUCTION

Large epidemiologic studies have demonstrated that glycemic variability (GV) is associated with increased mortality, independently of mean glucose or hypoglycemia in hospitalized patients, but the mechanism for harm is unclear [1–4]. In an outpatient, euinsulinemic clamp study, oscillating glucose levels between 5 and 15 mmol/l resulted in increased endothelial dysfunction and oxidative stress that exceeded the effects of sustained hyperglycemia [5]. GV is also a predictor of hypoglycemia, which may itself be related to mortality [6].

Stress hyperglycemia may mediate much of the GV during acute illness [7]. However, patients with well-controlled diabetes (defined by HbA1c) who develop hyperglycemia in the intensive care unit (ICU) have higher mortality than those with poor chronic control suggesting that GV plays a role in patients with diabetes as well [8]. In addition, GV is a function of patient specific factors that may be difficult to manipulate. Patients with glycemic lability often have long-standing diabetes with both beta cell and counterregulatory hormone failure [9]. It is unclear therefore how different therapeutic approaches will affect GV in the hospital. The frequent practice of interrupting outpatient regimens in favor of “sliding scale” insulin may have the effect of inducing GV. The current guidelines recommend basal bolus subcutaneous insulin in hospitalized patients [10,11], but there are as yet few data to support one approach over another. It is possible that intravenous (IV) insulin may provide a smoother transition than traditional SQ insulin.

We were interested in determining whether treatment-associated changes in GV in acutely ill patients may affect autonomic tone. Power spectral analysis of heart rate variability (HRV) allows for a simple way to measure parasympathetic (high frequency [HF] power) and a combination of parasympathetic and sympathetic (low frequency [LF] power) tone [12]. The LF/HF ratio has been proposed as an index of “sympathovagal balance” [12]. HRV aberrations appear early in the course of diabetes and are associated with mortality, in part due to increased risk of ventricular arrhythmias [13,14]. Both acute hyperglycemia and hypoglycemia increase the LF/HF ratio [15,16]. Transthoracic cardiac impedance may be used to derive the pre-ejection period (PEP), the time between the onset of electrical depolarization of the ventricle and opening of the aortic valve, which estimates sympathetic tone more exclusively than HRV [12,17,18]. Increased sympathetic cardiac activity is a risk factor for cardiovascular disease and sudden cardiac death [19]. In a recent study, PEP was associated with the metabolic syndrome independently of HF HRV [20]. However, it is unknown whether PEP is associated with glycemic control.

The objective of this pilot study is to determine whether interruption of outpatient therapy for short-term intravenous (IV) insulin differentially affects GV compared to traditional physiologic subcutaneous (SQ) basal bolus insulin, and whether this results in changes in autonomic tone.

MATERIALS AND METHODS

Subjects

Inclusion criteria included age over 18 years, type 2 diabetes, and admission to a medical or surgical ward service with significant insulin use (>20 units/day) or hyperglycemia (BG >10 mmol/l on at least 2 occasions separated by at least 4 hours apart). Exclusion criteria included type 1 diabetes, hyperglycemic emergency, hospital stay expected to be less than 48 hr, inability to consent, pregnancy, prisoners, known autonomic neuropathy, conditions that preclude accurate HRV monitoring such as atrial fibrillation, heart failure, or frequent ectopy, or end stage renal or liver disease. This study was approved by the Ohio State

University Institutional Review Board. All patients provided written informed consent prior to any study procedures.

Intervention

Patients were randomized to IV insulin or continuation of physiologic basal-bolus insulin. All oral agents were discontinued. Prandial insulin was delivered subcutaneously according to carbohydrate intake based upon total daily dose (as opposed to fixed meal doses) in both groups. Among patients receiving subcutaneous insulin, basal and prandial insulin were administered in approximately equal total daily doses with correction dosing and adjustments based upon a published algorithm [21]. The target glucose range was 5.6–8.3 mmol/l.

In patients assigned to IV insulin, basal insulin was discontinued and IV insulin was started at 0500 hours the morning following consent in order to (1) allow time for continuous glucose monitoring (CGM) initiation, (2) to minimize sleep disruption, and (3) to better understand any role of interruptions and transitions in glucose lowering therapies. Patients continued to receive prandial and correction insulin until the IV insulin was started, after which only the prandial component was continued. All patients receiving IV insulin were managed using our hospital's universal nursing run guideline, which was adapted from a published protocol [22] and has a target glucose of 6.1–8.3 mmol/l. All floor nurses are trained in its use. Subjects treated with IV insulin also received 5% dextrose in half-normal saline at 10 ml/hour according to hospital guidelines. Patients were transitioned from the infusion at 1700 hours using approximately 70% of the estimated basal insulin infusion requirement with 4 hours of overlap.

Assessments

The Michigan Neuropathy Screening Instrument was assessed at baseline [23]. Electrocardiographic and impedance measures were obtained using a Bionex system (Mindware, Gahanna, OH). Impedance and HRV were performed with the subject lying supine with the head of the bed raised 45 degrees. The electrocardiogram was performed in the standard lead II configuration and impedance cardiography was performed using a standard tetrapolar arrangement as described previously [24,25]. Measures were performed at baseline (1600 hr, day 0), during (1100 hr, day 1), and following (0800 hr, day 2) the intervention for 7 minutes each.

The middle five minutes of the recordings were scored minute by minute and then collapsed over the five minute period. Software (Mindware, Gahanna, OH) was used to derive PEP, HF, LF, and LF/HF HRV. PEP is measured in milliseconds and lower values reflect higher sympathetic tone. HF HRV was calculated using power spectral analysis of the interbeat interval with fast Fourier transformation and integration over the respiratory band (0.12–0.40 Hz) as reported previously [26]. HF HRV is reported as the natural log of the heart period variance in the respiratory band (ms^2). All patients had respiratory rates within the respiratory band.

Continuous subcutaneous glucose monitoring (CGM) was performed using an Ipro CGM (Medtronic, Minneapolis, MN) for 72 hours. CGM was activated using the quick-start feature in order to avoid interference from devices on the wards. It was otherwise inserted on the abdomen and downloaded using CGMS solutions software according to manufacturer guidelines. Capillary glucoses were analyzed with the Accu-Chek Inform® system (Roche, Indianapolis, IN), which were used to calibrate the sensor according to manufacturer guidelines. Capillary glucoses were collected hourly during insulin infusions and every 4–6 hour otherwise. However, only glucoses at four predetermined time points per day (pre-meal

and at bedtime closest to 0700 hr, 1200 hr, 1700 hr, and 2100 hr) within the allowable glucose limits of the software (2.2–22.2 mmol/l) were used to calibrate the CGM device. Glucose values were presented in 24 hour periods (starting from the time of the baseline cardiac assessment on day 0 at 1600 hr to 1600 the following day). Thus day 1 incorporates the initiation of IV insulin and day 2 incorporates the transition period off of IV insulin). GV was assessed through the coefficient of variation (CV, standard deviation/mean glucose), glycemic lability index (GLI, sum of the square of the difference between successive glucose measurements divided by the difference in time between measurements) [27], and continuous overlapping net glycemic action (CONGA) [28]. Hypoglycemia was defined as a *blood* glucose <3.9 mmol/l due to the concern for low accuracy of CGM in the hypoglycemic range [29].

Morning blood draws were performed on day 1 and day 2 for epinephrine, and norepinephrine. Plasma samples were collected on ice and immediately processed and frozen. Samples were analyzed using high performance liquid chromatography.

Statistical analyses

Continuous variables were reported as mean (standard deviation) for normal distributions or median (interquartile range) for non-normal distributions. Differences between groups were determined with the unpaired student's t-test or Wilcoxon rank-sum as appropriate. Dichotomous variables were reported as number (percentage) and differences between groups were determined using Fisher's exact test. P-values less than 0.05 were considered statistically significant. Correlations were performed using Spearman's correlation coefficients with log transformation of non-normally distributed variables. Analyses were performed using JMP 9.0 software.

RESULTS

Of the 42 subjects who signed consent, 9 subjects were removed prior to initiation of study intervention due to new arrhythmia (2), early discharge (2), new altered mental status (1), initiation of IV insulin (2) and CGM issues (2). An additional 2 subjects were found to have weak or unstable electrocardiographic or impedance signal at the time of analysis and were excluded from those measures only. Therefore, the final sample was 33 subjects.

Baseline characteristics are similar in both groups and are shown in Table 1. The majority of subjects (65 and 81% in IV and SQ groups respectively) were on insulin therapy prior to admission. The admission glucose was similar between groups (14.3 vs. 11.8 mmol/l in IV vs. SQ groups, $p=0.17$) and most patients were hyperglycemic on admission (76 vs. 75% in IV vs. SQ groups). Two patients were admitted in part due to hyperglycemia but both patients also had infections as additional indications. No patient had severe hyperglycemia (>22 mmol/l) at enrollment. Many patients were admitted for a new infection (41% and 31% in the IV and SQ groups), of which 2 patients met systemic inflammatory response syndrome (SIRS) criteria.

Insulin, glucose, and laboratory assessments are shown in Table 2. The SQ group had borderline lower glucose on day 1 (8.6 vs. 10.5 mmol/l, $p=0.05$) but not by day 2. A similar number of patients (1 in the IV group and 3 in the SQ group) experienced hypoglycemia. There were no events less than 2.2 mmol/l in either group. GLI, CV, and CONGA were significantly higher in the IV group by day 2. There was no difference in catecholamines between groups.

Cardiac and autonomic measures are shown in Table 3. PEP was significantly higher (indicating lower sympathetic tone) in the SQ group during ($p=0.02$) and after ($p=0.004$) the

intervention. RSA was borderline higher at baseline in the SQ group ($p=0.05$), and this reached statistical significance during the infusion ($p=0.04$). There was no difference in blood pressure, LF HRV or LF/HF HRV.

The association between route of insulin and PEP after the infusion remained significant after adjusting for baseline PEP and mean glucose ($p=0.02$). After adjusting for baseline, there was no association between insulin route and HF HRV or LF/HF HRV at after the infusion.

In pooled analysis, day 1 PEP was correlated with log GLI ($r = -0.38$, $p=0.04$) and mean glucose ($r = -0.38$, $p=0.04$), but not CV ($r = 0.05$, $p=0.80$), admission glucose ($r = 0.09$, $p=0.62$), or CONGA ($r = -0.31$, $p=0.10$). We further analyzed relationships between relevant baseline and study characteristics and day 2 PEP since this was the time at which differences in PEP between groups peaked (Table 4). Higher log GLI at day 1 ($r = -0.41$, $p=0.03$) was significantly correlated with lower PEP (higher cardiac sympathetic activity). There was a trend for correlation with mean glucose at day 1 ($r = -0.33$, $p=0.08$). Day 2 log GLI and mean glucose were not significantly associated with day 2 PEP. Admission glucose, CV, CONGA, and hypoglycemia did not correlate with PEP. PEP was not associated with other variables, such as age, gender, race, infection, coronary artery disease, beta blockade, insulin dose, body mass index, or neuropathy scores. Furthermore, exclusion of the two patients with SIRS did not significantly affect the results.

DISCUSSION

The results demonstrate that short-term IV insulin may lead to increased GV, measured by CV, CONGA, and GLI, and greater cardiac sympathetic activity, as determined by shorter PEP, in acutely ill patients. In pooled analysis, GLI was significantly correlated with PEP, but mean glucose tended to be correlated as well, making it difficult to determine the individual role of each. However, the per protocol analysis suggests that emergent differences in GV may be important. Hypoglycemia is known to evoke sympathetic responses [30,31], but it was infrequent in this study and did not clearly explain the differences in PEP.

Importantly, the association of GLI but not CV or CONGA with PEP suggests that multiple measures of dispersion may be necessary for assessing effects of GV on outcomes. One explanation for the disparate findings is that GLI more explicitly reflects rate of change than CONGA, or CV. In addition, CONGA is a measure of the *variability* of the rate of change, and is therefore essentially a derivative function. From the view of pattern recognition, taking a derivative of a sample is known to introduce high frequency “noise” in the measure [32], and this might also explain the smaller association between CONGA and PEP compared to GLI. These findings require further study. The best measure of GV has not been established, but measures that are associated with outcomes are desirable as opposed to measures that are validated solely by expert clinical opinion of the ability to detect variability [33]. GLI was of interest because, compared to SD or mean amplitude of glycemic excursion (MAGE), it had the best discrimination for mortality in patients with sepsis in a previous study from our institution [34]. At the time of the study design, this was one of few studies that compared multiple methods of GV. GLI was also associated with mortality in other studies [35,36], but not in a more recent large study [37]. CONGA has been advocated as an alternative measure of GV for use with CGM, but to the best knowledge of the authors, it has not been reported in hospitalized patients to date.

This is the first study to report the relationship between measures of glycemic control and PEP. It has important ramifications as it provides a potential novel mechanism for harm

related to GV in acutely ill patients. Increased cardiac sympathetic activity is a known risk factor for mortality and sudden cardiac death [38]. Although these patients were not necessarily admitted to the hospital for cardiac diagnoses, cardiovascular disease still serves as the major cause of mortality among patients with diabetes [39]. Other measures, such as microneurography and regional sampling of radiotracer labeled catecholamines, are also used for measuring sympathetic activity, but are more invasive and less suitable for a hospitalized patient population [40].

Trends for HF HRV also favor SQ insulin, but are more likely explained by baseline differences. LF HRV is known to be influenced by both sympathetic and parasympathetic input [12,40]. Therefore, the lack of association of glucose measures with LF HRV or LF:HF ratio may be due to the lack of specificity of these measures for measuring sympathetic tone.

It is worth noting that patients with cardiac arrhythmias or devices which preclude accurate HRV or cardiac impedance measures were excluded from this study. Baseline factors, such as coronary artery disease, neuropathy scores, infection, and beta blockade did not appear to affect the results. However, various illness and treatment related factors may affect cardiac autonomic activity and larger studies will be needed to investigate these factors. Of some reassurance is the observation that beta blockade has not been shown to eliminate the predictive capability of HRV following myocardial infarction [41].

The observation that GLI, CONGA and CV were increased on day 2 indicates that the transition from IV to SQ insulin may have resulted in higher GV than the infusion itself. Data from our institution suggest that 12 hours was a reasonable time to reach target glucose levels, but perhaps it is not long enough to accurately calculate basal insulin requirements [42]. This possibility requires further study. Hsia and colleagues report that administering glargine during insulin infusion may prevent rebound hyperglycemia, which probably contributes to GV in the transitional period. However, rebound hyperglycemia was minimized by the overlap of 4 hours between the infusion and the SQ basal insulin in this study. A higher conversion factor for dose calculation could have been considered, but the trade-off is an increase in the risk of hypoglycemia [43]. Careful consideration for smooth transitions in therapy in general, such as at the time of admission and at discharge, would be of interest for further study.

The study is limited by small sample size, owing to the effort to establish proof of concept. It is unclear whether a computerized insulin algorithm, particularly one that would provide IV insulin boluses over a timeframe that is useful for prandial coverage, would have minimized GV compared to the algorithm used in this study. In addition, consideration for the time required to initiate CGM necessitated a delay in the start of IV insulin in the study design. This delay and the short duration of IV infusion likely explain the slightly higher glucose in the IV compared to the SQ group. However, the conditions created by the delay are not unusual in the inpatient setting, where patients on stable outpatient regimens may be admitted and placed directly on sliding scale insulin with subsequent loss of glycemic control [44]. Finally, while the majority of published mortality data relate to the intensive care unit (ICU) with respect to GV [1–4], we studied non-ICU patients, where measures of autonomic tone can be obtained more readily (without the interference of mechanical ventilators for example). This may limit external validity. However, acute fluctuations in glucose are not limited to the use of IV insulin or to ICU patients. The data support the need to avoid abrupt transitions in therapy in general. Furthermore, new hyperglycemia is associated with adverse outcomes outside of the ICU, and GV is associated with mortality for CHF exacerbation outside of the ICU [45], suggesting that potential outcomes are not limited to the ICU.

The data indicate that treatment-associated changes in glycemic control and glycemic lability contribute to increased cardiac sympathetic activity in acutely ill patients. Further study is warranted to determine the optimal means of lowering glucose while minimizing GV, and whether this impacts outcomes.

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Abbreviations

GV	glycemic variability
ICU	intensive care unit
IV	intravenous
HRV	heart rate variability
HF	high frequency
LF	low frequency
PEP	pre-ejection period
SQ	subcutaneous
CGM	continuous glucose monitor
CV	coefficient of variation of glucose
GLI	glycemic lability index

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Table 1

Baseline Characteristics

	IV (N=17)	SQ (N=16)	p-value
Age (years)	53.8 (10.7)	55.1 (10.5)	0.71
Male	9 (53%)	12 (75%)	0.28
Caucasian	15 (88%)	14 (88%)	>0.99
Duration of DM (years)	12 (5.5–16)	12 (7–27)	0.90
Body mass index (kg/m ²)	36 (10)	35 (7)	0.68
Hypertension	15 (88%)	13 (81%)	0.66
Coronary Artery Disease	6 (35%)	6 (38%)	>0.99
Retinopathy	4 (24%)	3 (19%)	>0.99
Nephropathy	5 (29%)	5 (31%)	>0.99
Neuropathy history	6 (35%)	8 (50%)	0.49
Neuropathy symptom score (points)	3.9 (2.7)	4.1 (2.7)	0.90
Neuropathy exam score (points)	3.8 (2.7)	5.0 (2.1)	0.17
Current tobacco use	4 (24%)	7 (44%)	0.28
Admit for Hyperglycemia*	2 (12%)	0 (0%)	0.48
Admit for Infection*	7 (41%)	5 (31%)	0.72
Insulin use prior to admission	11 (65%)	13 (81%)	0.28
Beta Blocker	9 (53%)	7 (44%)	0.73
Admission Glucose (mmol/l)	14.3 (6.6)	11.8 (3.6)	0.17
HbA1c (%)	10.1 (2.8)	9.2 (2.5)	0.33

Data are presented as mean (SD), median (IQR, 25%–75%), or number (%).

Table 2

Insulin and Laboratory Measures

	IV		SQ		p-value
	N		N		
Insulin (units)					
Day 1	17	40 (17–57)	16	58 (19–85)	0.11
Day 2	17	49 (30–149)	16	43 (15–74)	0.11
Mean Glucose (mmol/l)					
Day 1	15	10.5 (3.0)	16	8.6 (2.0)	0.05
Day 2	13	10.4 (2.7)	15	8.7 (3.9)	0.17
CV Glucose (%)					
Day 1	15	22 (8.3)	16	29 (13)	0.08
Day 2	13	22 (5.8)	15	16 (6.6)	0.02
GLI ^a					
Day 1	14	1.69 (0.66–2.2)	16	0.88 (0.74–2.7)	0.56
Day 2	14	0.99 (0.64–1.75)	15	0.32 (0.19–0.92)	0.01
CONGA					
Day 1	14	33 (25–45)	16	33 (21–48)	0.63
Day 2	13	31 (24–36)	15	20 (14–29)	0.03
Blood glucose <3.9 mmol/l Day 1	17	1 (5.9%)	16	1 (6.3%)	>0.99
Blood glucose <3.9 mmol/l Day 2	17	0 (0%)	16	2 (12.5%)	0.23
Norepinephrine (pg/ml)					
Baseline	17	408 (260–535)	15	330 (139–660)	0.76
Follow-up	17	343 (167–552)	15	368 (118–500)	0.65
Epinephrine (pg/ml)					
Baseline	16	21 (9.9–40)	16	11 (9.9–29)	0.45
Follow-up	16	17 (9.9–46)	16	15 (9.9–30)	0.53

Day 1 is defined as the 24 hour period starting at 1600 hr on the day of consent. Day 2 is defined as the subsequent 24 hours (the transitional period). For epinephrine and norepinephrine, baseline is defined as the 4AM blood draw (prior to IV insulin) following consent and follow-up is defined as the 4AM blood draw the following day (after cessation of IV insulin). CV=coefficient of variation, GLI=glycemic lability index, CONGA=continuous overlapping net glycemic action.

^aunits in (mg/dl)²/hr*day⁻¹.

Cardiac Measures

Baseline is defined as 1600 hrs the day of consent (prior to IV insulin), 6 hour refers to 1100 hrs (following initiation of IV insulin), and 24 hour refers to 0800 hrs the following morning (following cessation of IV insulin). SBP=systolic blood pressure, DBP=diastolic blood pressure, PEP=pre-ejection period, RSA=respiratory sinus arrhythmia, LF=low frequency, HRV=heart rate variability, HF=high frequency.

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Table 4

Correlations with 24 Hour PEP*

by Variable	Correlation	P-value
Age	−0.06	0.77
Male	0.08	0.68
Non-Caucasian	−0.30	0.10
Coronary artery disease	−0.03	0.87
Beta blocker	−0.06	0.76
Total daily insulin day 1 ^a	0.19	0.32
BMI	−0.16	0.41
Neuro symptom score	−0.19	0.33
Neuro exam score	−0.04	0.84
Hba1c	−0.04	0.82
Admission Glucose	0.12	0.53
GLI day 1 ^a	−0.41	0.03
GLI day 2 ^a	−0.29	0.15
Mean glucose day 1	−0.33	0.08
Mean glucose day 2	−0.14	0.48
CV day 1	0.04	0.83
CV day 2	−0.04	0.86
CONGA day 1 ^a	−0.28	0.15
CONGA day 2 ^a	−0.22	0.27
Blood glucose <70 mg/dl	−0.02	0.91

Correlations were calculated using Spearman's correlation coefficients.

^aLog-transformed values