Ultradian Variation of Blood Glucose in Intensive Care Unit Patients Receiving Insulin Infusions

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Treatment of hyperglycemia with an insulin infusion protocol (IIP) has improved outcomes in intensive care unit (ICU) patients (1,2). While morning glucose has been reported, little is known about variation of blood glucose for patients on IIP, causing uncertainty about the optimal treatment of ICU patients (3–5). Our objectives were to test whether morning glucose represented whole-day glucose and to determine whether glucose varied over the course of the day. In ICU patients receiving IIP, glucose was lower in the early morning, correlated poorly with average glucose, and varied with an ultradian pattern.

RESEARCH DESIGN AND METHODS

— In this prospective, single-center, observational study in the ICUs of a university tertiary care hospital, we recorded all glucose measurements in two cohorts of ICU patients receiving an IIP targeting blood glucose 80–110 mg/dl. Supplementary details are available in an online appendix (available at http://dx.doi.org/10.2337/dc07-0865.).

RESULTS

— Between 20 May 2006 and 6 August 2006, 141 ICU patients were treated with IIP, 8 of whom received insulin for two periods, resulting in 149 patient episodes. The average duration of insulin use for an episode was 115 ± 9 h (range 5–604). Forty-one percent (n = 11,670) of glucose measurements during this period were in the target range (80–110 mg/dl) (Fig. 1*A*). In preliminary data acquired between May 2004 and June 2005, the proportion of measurements in the target range increased initially and then stabilized (Fig. 1). Twenty-six percent of patients experienced at least one glucose value <60 mg/dl, and 2.7% had a glucose value <40 mg/dl.

The IIP was designed to control glucose within 8 h (1), and slightly more glucose measurements beyond 8 h (42%, n = 10,766) were in range (P = 0.014) (Fig. 1*B*). The mean and median of this positively skewed, non-Gaussian distribution ($P < 0.0001$, Kolmogorov-Smirnov test) were 118.5 and 112 mg/dl, respectively. The 0600-h measurements were also positively skewed (Fig. 1*B*) ($P < 0.0001$, Kolmogorov-Smirnov test). At 0600 h, glucose was lower than at the remaining times (112 ± 1.4 [n = 477] vs. 119 ± 0.3 [n = 10,364] mg/dl; $P < 0.0001$), and more of the 0600-h values were in the target range (47%). The correlation between 0600-h glucose measurement and average glucose for the consecutive 23 h was weak (Fig. 1*C*) ($r^2 = 0.07$; $P < 0.0001$; n = 472).

A plot of average glucose with time of day from the 149 patient episodes revealed an ultradian pattern (Fig. 1*D*). Mean glucose was steady overnight with an 0700-h nadir after which glucose values rose, peaking at 1100 and again at 2200 h. Mean blood glucose values were described after 0800 h by a sine wave with a period of 10.6 h and amplitude of 3 mg/dl. A second independent cohort of glucose measurements (n = 12,922) made from 201 patient episodes between 30 August and 31 October 2006 confirmed the ultradian pattern (Fig. 1*D*). Insulin infusion rates were collected, with the second cohort showing a similar partially sinusoidal ultradian pattern (Fig. 1*D*) (hourly n = 647–731) that was phase shifted by 1.2 h. Median and mean blood glucose values of the combined data varied similarly (Fig. 1*E*).

CONCLUSIONS

— Interest in blood glucose control in the critically ill increased following the demonstration that targeting normoglycemia in a surgical ICU improves outcome (1). However, debate continues over the optimal target glucose and how to best achieve it using IIP. Our major findings are that glucose is the lowest in the morning, glucose at 0600 h correlates poorly with daily glucose, and glucose fluctuates with an ultradian pattern in ICU patients on IIP. Furthermore, we report that only a minority of glucose values were in the target range despite established IIP use, that glucose values were not normally distributed, and that insulin use was also ultradian.

Our data illustrate complex variability in blood glucose, which may complicate achievement of optimal control. The single randomized trial in which IIP improved mortality only reported 0600-h glucose values (mean ± SD 103 ± 19 mg/dl) (1). Assuming a normal distribution, we calculate that 55% of all glucose values in that study would have been in the target range (1). We found 47% of glucose values in range at 0600 h but only

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Abbreviations: IIP, insulin infusion protocol; ICU, intensive care unit.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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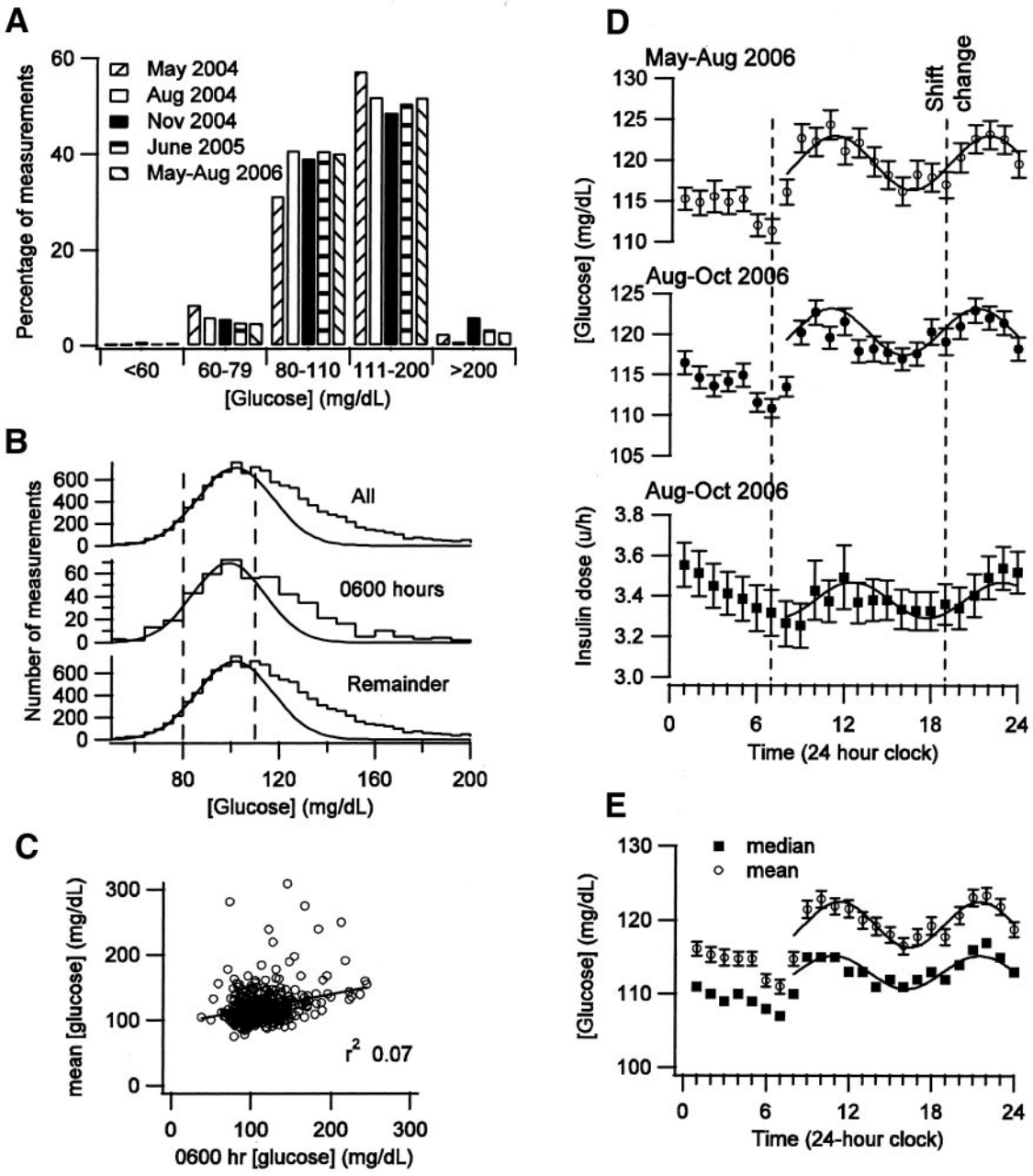

Figure 1—*Blood glucose variation in ICU patients receiving IIP.* A*: Category plot of the percentage of measurements in described blood glucose ranges in ICU patients receiving IIP for hyperglycemia. The measurements* (n = *655, 1,374, 2,508, 1,547, and 11,707) were collected over 2-week periods in May 2004, August 2004, November 2004, June 2005, and between 20 May and 6 August 2006 from 19, 38, 57, 31, and 141 patients, respectively.* B*: The histograms show blood glucose values after 8 h of IIP in 141 patients pooled (top trace), at 0600 h (bottom trace), and pooled data excluding those from 0600 h (middle trace). All data are positively skewed. The target range is described by vertical broken lines, and the Gaussian functions fit to all data up to modal value are given by the unbroken curves. The fitted Gaussian curves have means ± SD of 100 ± 16, 95 ± 15, and 100 ± 16 mg/dl for upper, middle, and lower histograms, respectively.* C*: Plot of 0600-h glucose* (n = *472) vs. average measured glucose for consecutive 23 h showing low correlation* (r^2 = *0.07).* D*: Time-averaged data from the 149 patient episodes show an ultradian variation in the mean glucose* (upper plot, ○) *(hourly* n = *407–493) against time. Glucose peaked at 1100 and 2200 h and was described from 0800 h by a sine wave with a mean value of 120 mg/dl, an amplitude of 3 mg/dl, and a period of 10.6 h. The mean glucose of the second cohort of measurements plotted against time also displayed an ultradian pattern (●) (hourly* n = *482–624) and was described from 0800 h by a sine wave with a mean value of 120 mg/dl, an amplitude of 3 mg/dl, and a period of 10.1 h. Insulin infusion rates, collected contemporaneously with the second cohort, were also ultradian and fitted to a sine wave from 0800 h, which had a mean value of 3.4 IU/h, an amplitude of 0.09 IU/h, a period of 10.4 h, and a phase delay of 1.2 h (■) (hourly* n = *647–731).* E*: Plots of median and mean blood glucose vs. time of the pooled data from the two cohorts showed similar ultradian variation. This graph shows combined data from 350 patient episodes, and each point represents between 889 and 1,092 measurements. The sine waves fitted to median and mean data have mean values of 113 and 120 mg/dl, amplitudes of 2.3 and 3.0 mg/dl, and periods of 10.7 and 10.3 h, respectively.*

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42% if all values were considered, similar to the 22–52% reported previously (6–8). Since glucose is lowest at ~0600 h (Fig. 1*B* and *C*), it remains unclear what proportion of the day glucose must be in the target range to improve outcome (9,10).

Difficulty in achieving tight glucose control has been attributed to patient instability and variability of glucose intake (11); however, the ultradian pattern of blood glucose demonstrated here may also explain some of the difficulty. Because a mean glucose rise of 20 mg/dl increases mortality by 30% (12), even the modest peak-to-trough ultradian variation (~12 mg/dl) (Fig. 1*D*) that we observed may significantly impact mortality and morbidity.

This study cannot determine the mechanism of the ultradian variation. The falls in glucose from peaks at ~1100 and 2300 h despite no increase in insulin indicate a decreased insulin requirement, possibly reflecting increasing insulin sensitivity or decreased glucose load. Likewise, the rise in glucose at 0900 and 2100 h occurred with little change in insulin. Nursing shift changes (Fig. 1*D*), changes in nutritional support, and medication administration are factors that may influence these observations. Interestingly, patients with type 2 diabetes have a similar ultradian pattern of blood glucose (13). Recently, a circadian pattern of glucose values was observed in Australian ICU patients when glucose values were pooled over 4-h periods. The apparently lower frequency of glucose variation may reflect the lower sampling rate or the impact of low use of IIP in Australian ICUs (14).

While we included medical, cardiac, neurosurgical, trauma, and general surgical ICU patients, further studies are required to determine if the findings may be extended to other patient populations at other institutions.

In conclusion, glucose is lower in the morning than during the remainder of the day. Blood glucose varies during the day in ICU patients receiving insulin. Consideration of this ultradian variation when treating hyperglycemia may help reduce the frequency of hypo- and hyperglycemic episodes.

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