Efficacy of Pulsatile Versus Continuous Insulin Administration on Hepatic Glucose Production and Glucose Utilization in Type I Diabetic Humans

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SUMMARY

To evaluate the role of pulsatile insulin administration, hepatic glucose production (HGP) and utilization were studied in type I diabetic patients in the fasting state and during a euglycemic insulin (1 mU · kg^{-1} · min^{-1} i.v.) clamp with continuous and pulsatile insulin administration. In the latter study, insulin was infused at twice the continuous rate with 3-min-on/7-min-off intervals, thereby reducing total insulin delivery by 40%. The restraining effect of pulsatile insulin on basal HGP (1.91 ± 0.35 mg · kg^{-1} · min^{-1}) was equipotent to continuous insulin exposure (1.80 ± 0.17 mg · kg^{-1} · min^{-1}). During the insulin-clamp studies, HGP was equally suppressed by pulsed (0.62 ± 0.12 mg · kg^{-1} · min^{-1}) as by continuous insulin infusion (0.63 ± 0.12 mg · kg^{-1} · min^{-1}). Insulin-stimulated glucose utilization was not significantly altered in either study (2.55 ± 0.27 vs. 2.92 ± 0.23 mg · kg^{-1} · min^{-1}). When in further studies the total insulin dose given during the pulsatile study was infused continuously (0.6 mU · kg^{-1} · min^{-1}), HGP in the basal state and residual HGP during the insulin-clamp study were 25–30% higher than in the pulsatile experiments, whereas glucose utilization was not significantly different.

In conclusion, by reducing total hormone delivery by up to 40%, but given in a pulsatile fashion, insulin is equally potent in controlling HGP as continuous insulin administration. This greater efficacy of pulsatile exposure in suppressing HGP is accompanied by an equipotent effect on glucose utilization. Application of pulsatile insulin substitution in intravenous-pump users may reduce systemic hyperinsulinemia and, in the long run, insulin resistance by reversing downregulation of insulin receptors. DIABETES 1986; 35:922–26.

In humans, various hormones, e.g., insulin, glucagon,[1–3] growth hormone,[4] and luteinizing hormone,[5] are secreted in pulsatile fashion. The resulting oscillating plasma hormone concentrations are thought to be of biologic importance in that downregulation of receptors is avoided and hormone action is thus enhanced. As for growth hormone[6] and luteinizing hormone,[7] their intermittent administration has been successfully applied to substitutional therapy in the respective hormone deficiency syndromes. Komjati et al.[8] have recently provided in vitro evidence that the effect of insulin and glucagon on hepatic glucose production during pulsatile administration is equipotent to that of the respective hormones' continuous infusion, even though the hormone load was significantly reduced.

To test the hypothesis that the cyclic mode of insulin secretion has a biologic advantage in regulating glucose metabolism in humans, our study was designed to elucidate the efficacy of continuous versus intermittent exposure to insulin in type I diabetic humans lacking poststimulatory C-peptide release on hepatic and peripheral glucose disposal. Studies were performed under basal and hyperinsulinemic conditions.

PATIENTS AND METHODS

Patients. Thirteen insulin-dependent diabetic (type I) patients, whose clinical data are given in Table 1, participated in the study. Their mean body weight was 65 ± 2 kg (100 ± 3% of ideal body weight based on medium-frame individuals from the Metropolitan Life Insurance Tables, 1959). The duration of their diabetes was 1–25 yr (mean 11.5 yr). The mean morning postprandial blood glucose concentration obtained during the last three outpatient visits within the preceding 3 mo was 9.0 ± 1.0 mmol/L, and HbA_{1c} was 7.2 ± 0.5% (normal <5.8%). All patients were devoid of any endogenous insulin secretory capacity as determined by the failure of plasma C-peptide concentrations to increase after a 30-g arginine load. Apart from their diabetes, all patients were healthy, and none had a history of any other endocrine disease. They were asked to continue their usual weight-maintaining diet containing 150–240 g carbohydrate/day.

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TABLE 1
Clinical data of insulin-dependent diabetic patients

Patient	Sex	Age (yr)	Duration of diabetes (yr)	HbA_{1c} (%)	Insulin requirements (IU/day)
1	M	62	19	6.5	68
2	F	20	5	8.2	67
3	M	24	16	6.9	40
4	M	39	25	5.2	55
5	M	38	14	4.5	42
6	M	27	12	8.8	34
7	M	38	1	9.0	48
8	M	22	3	11.4	50
9	M	42	2	8.0	50
10	M	39	14	6.0	52
11	M	30	20	5.6	54
12	M	41	5	8.3	40
13	F	32	13	5.8	42

No patient was on medication except for insulin. The purpose and potential risks of the study were explained to all patients before obtaining their free consent to participate.

Protocol. In all patients, subcutaneous insulin therapy was switched from long-acting to regular insulin preparations 48 h before the study. On the evening before the test, intravenous administration of regular semisynthetic human insulin (Actrapid HM, Novo, Copenhagen, Denmark) was begun and continued overnight via a polyethylene catheter inserted into an antecubital vein. The insulin infusion rate was adjusted on the basis of multiple blood glucose measurements to achieve intraindividually comparable glycemic control at 5–8 mmol/L before the study. All tests were started at 0700 with the patients fasted overnight for 12–14 h. While the catheter for insulin infusion was also used for cold and tritiated glucose administration, a second polyethylene catheter was inserted in a retrograde direction in a wrist vein for blood sampling, and that hand was kept in a heated box at 70°C to ensure arterialization of venous blood.

Studies of glucose turnover were preceded by a 3-h equilibration period for the infusion of [^{3}H-3]glucose, followed by a 60-min basal period, during which the basal insulin infusion was maintained. Thereafter, a 2-h euglycemic insulin-clamp study was performed. The study design is depicted in Fig. 1. Each patient participated in two studies with either continuous (CII) or pulsatile (PII) insulin infusion. CII or PII were maintained during the basal and clamp periods. In the 10-min cycles of PII, insulin was administered during "on" periods of 3 min followed by "off" periods of 7 min. In eight patients (study A) the rate of insulin administered in the CII study was doubled during the 3-min-on periods of PII, thereby reducing total insulin delivery by 40%. In another five patients (study B), time-averaged insulin doses administered during CII and PII were kept identical. To this end, the rate of insulin administration during PII was increased by 40% in the basal state but kept identical to that of study A in the clamp study. It was reduced by 40% in the intraindividual CII clamp study.

Euglycemic insulin clamp. After a 60-min basal period, a primed continuous (study A, 1.0 $mU \cdot kg^{-1} \cdot min^{-1}$; study B, 0.6 $mU \cdot kg^{-1} \cdot min^{-1}$) infusion of regular insulin (Actrapid HM, Novo) was administered to acutely raise and maintain free plasma insulin concentration at ~60 and 30 mU/L, respectively. In the PII experiments, time-averaged dose was 0.6 $mU \cdot kg^{-1} \cdot min^{-1}$ in both studies. Plasma glucose was maintained at the fasting level during the clamp study by determination of plasma glucose every 5 min and appropriate adjustment of the infusion rate of a 20% dextrose solution.[9,10] Hepatic glucose production (HGP) was estimated by a primed continuous infusion of tritiated glucose ([^{3}H-3]glucose; Amersham, Amersham, UK), which was administered in a 55-uCi bolus followed by a continuous infusion at a rate of 0.40 uCi/min. Plasma [^{3}H]glucose-specific activity was determined at 5- to 10-min intervals throughout the study. Plasma concentrations of free insulin were determined in 10-min intervals in the CII studies and at the end of the off periods of each 10-min insulin cycle in the PII studies. Furthermore, plasma insulin was also measured every 2 min for the last 10 min of the basal as well as of the clamp period to document stability in the CII studies and oscillation in plasma insulin concentrations.

Calculations. During the clamp studies, the glucose infusion rate was determined by calculating the mean value from 20 to 120 min. The total amount of glucose metabolized by the entire body (commonly referred to as glucose utilization or glucose uptake) was calculated by adding the rate of endogenous glucose production to the exogenous glucose infusion rate required to maintain the desired glucose level. The rate of glucose turnover was calculated by Steele's[11] equations in their derivative form, with a total volume of distribution of 280 ml/kg body wt and a pool fraction of 0.65.[12] The rate of endogenous glucose production was determined by subtracting the glucose infusion rate from the rate of glucose appearance as determined by the isotopic tracer technique. Mean insulin levels achieved during pulsatile administration were calculated by averaging plasma insulin concentrations taken at 2-min intervals from $t = -10$–0 min and $t = 110$–120 min.

Analytical procedures. Glucose was analyzed in duplicate in arterialized venous samples by the glucose oxidase

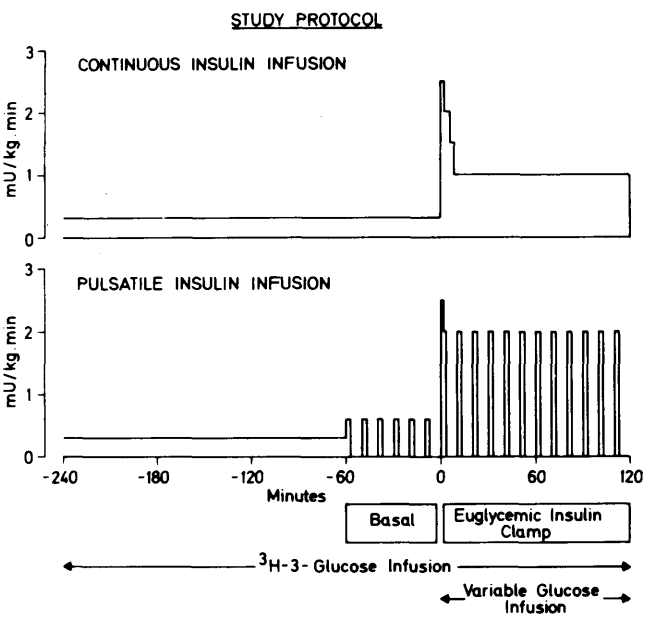

FIG. 1. Design of studies with continuous (*upper panel*) and pulsatile (*lower panel*) insulin infusion in basal state and during euglycemic insulin clamp in type I diabetic patients.

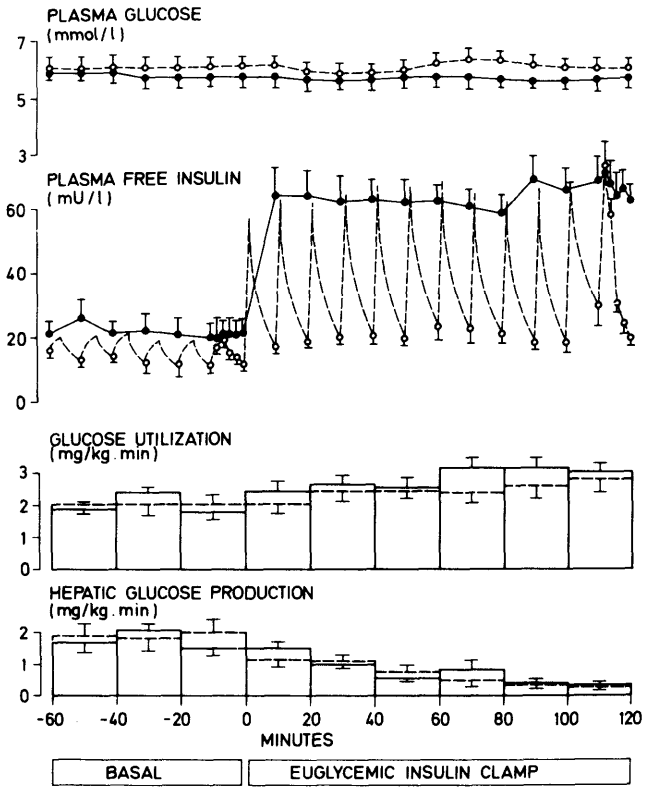

FIG. 2. Arterial plasma concentrations of glucose and insulin as well as glucose utilization and hepatic glucose production in basal state and during euglycemic insulin clamp in type I diabetic patients with continuous (●) or pulsatile (○) insulin administration. Results are expressed as mean ± SE (*N* = 8).

method (glucose analyzer II, Beckman, Fullerton, CA). [^{3}H]glucose-specific activity was determined by the procedure of Somogyi,[13] with glucose concentration in the Somogyi filtrates analyzed by the hexokinase reaction (Boehringer, Mannheim, FRG). Plasma free insulin was measured by radioimmunoassay after precipitation with polyethylene glycol.[14]

Statistics. Data in the text, table, and figures are presented as the mean ± SE. The paired two-tailed Student's *t* test was employed for statistical analysis.

RESULTS

STUDY A

In this study, a time-averaged dose of insulin was reduced by 40% during PII compared with CII (Fig. 2).

Arterial concentrations of plasma glucose and free insulin. The rates of continuous insulin infusion necessary to maintain near normoglycemia on the mornings of the CII and PII test days were identical, 1.14 ± 0.24 and 1.16 ± 0.23 U/h, respectively. The obtained mean plasma free-insulin concentration was 22 ± 4 mU/L during CII. In the pulsatile studies, plasma insulin peaked at almost the same level at the end of the on period (21 ± 2) but fell to a nadir of 14 ± 2 mU/L by the end of the off phase. Mean insulin concentration (15 ± 4 mU/L) was thus reduced by 30 ± 5%. Plasma glucose concentrations were constant and similar during CII (5.7 ± 0.4 mmol/L) and PII (6.1 ± 0.3 mmol/L; $P > .4$).

During the euglycemic insulin (1.0 mU · kg^{-1} · min^{-1})–clamp study with CII, steady-state insulin concentration was increased to 64 ± 6 mU/L, while plasma glucose (5.7 ± 0.4 mmol/L) was held constant at the basal level as demonstrated by a small coefficient of variation (3.6 ± 0.4%). In the clamp study with PII, peak levels of insulin were also in the range achieved with CII (74 ± 6) but fell to a nadir of 20 ± 2 mU/L at the end of the off periods. Thereby, mean insulin concentration was reduced by 36 ± 6% to 39 ± 7 mU/L. Glucose concentration was again held constant at 6.1 ± 0.3 mmol/L.

Hepatic production and utilization of glucose. In the basal state, HGP averaged 1.80 ± 0.17 mg · kg^{-1} · min^{-1} in the CII study and was almost identical in the PII experiments (1.91 ± 0.35 mg · kg^{-1} · min^{-1}; $P > .6$). During the hyperinsulinemic clamp study, the time course and degree of suppression of HGP were almost identical in both studies. Note that HGP suppressed incompletely during the 2nd h of both studies (CII 0.52 ± 0.14; PII, 0.42 ± 0.15 mg · kg^{-1} · min^{-1}).

Glucose uptake by the entire body during CII was 2.03 ± 0.12 mg · kg^{-1} · min^{-1} in the basal state, increasing only slightly to 2.92 ± 0.23 mg · kg^{-1} · min^{-1} during the 20 to 120-min^{-1} period of the clamp study. These uptake data were not different from those during the PII experiments,

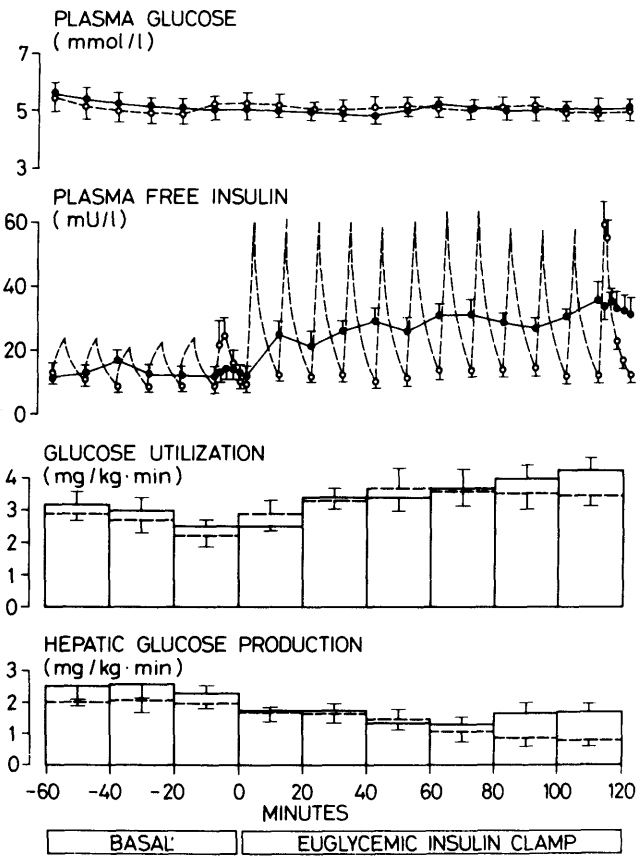

FIG. 3. Arterial plasma concentrations of glucose and insulin as well as glucose turnover in basal state and during euglycemic insulin clamp in type I diabetic patients with equal time-averaged insulin doses administered either in continuous (0.6 mU · kg^{-1} · min^{-1}; ●) or pulsatile (○) fashion. Mean ± SE (*N* = 5).

2.02 ± 0.20 and 2.55 ± 0.27 mg · kg^{-1} · min^{-1} for the basal and hyperinsulinemic periods, respectively. When the total amount of glucose taken up was expressed per unit of mean plasma insulin concentration, the index of insulin sensitivity metabolism-to-insulin increased by 30–40% from 0.050 ± 0.008 during CII to 0.068 ± 0.009 mg · kg^{-1} · min^{-1} per mU/L on PII ($P < .025$).

STUDY B

In this study the time-averaged insulin dose was identical during the pulsatile and continuous experiments (Fig. 3).

Mean plasma free-insulin concentrations in the basal period were 13 ± 2 and 15 ± 1 mU/L in the CII and PII studies, respectively. Plasma glucose concentration was 5.1 ± 0.3 mmol/L under both experimental conditions. During the insulin (0.6 mU · kg^{-1} · min^{-1})-clamp studies, mean free-insulin concentrations were increased to 29 ± 3 (CII) and 30 ± 3 (PII) mU/L, whereas plasma glucose was maintained constant at 5.0 ± 0.3 mmol/L (coefficient of variation 3.4 ± 0.7%).

In the basal state, HGP averaged 1.99 ± 0.25 mg · kg^{-1} · min^{-1} during pulsatile insulin exposure but increased to 2.48 ± 0.25 mg · kg^{-1} · min^{-1} ($P < .02$) when the same insulin dose was given continuously. During the 2-h hyperinsulinemic clamp study, residual HGP during CII (1.52 ± 0.19) was 30% higher than during PII (1.18 ± 0.24 mg · kg^{-1} · min^{-1}; $P < .05$). Whereas suppression of HGP was similar in the first 60 min, reduced suppressibility of HGP during CII compared with PII became apparent in the 2nd h of the clamp (CII, 1.52 ± 0.25; PII, 0.93 ± 0.22 mg · kg^{-1} · min^{-1}; $P < .05$). Glucose uptake in the basal state was similar during CII (2.89 ± 0.25) and PII (2.60 ± 0.25 mg · kg^{-1} · min^{-1}). It increased during the clamp to 3.76 ± 0.40 and 3.50 ± 0.30 mg · kg^{-1} · min^{-1}, respectively. These rates of glucose utilization were not statistically different ($P > .4$).

DISCUSSION

Even though there is ample in vitro and in vivo evidence for the pulsatile release of insulin from the β-cell, the physiologic role and metabolic effectiveness of this secretory mode compared with continuous hormone exposure in intact humans has not yet been convincingly demonstrated. In vitro data on the oscillatory pattern of insulin secretion were obtained by experiments with the isolated perfused pancreas[15] and individual islet cell preparations,[16] whereas in vivo evidence is based on experiments in humans,[1-3] monkeys,[17] and dogs.[18] Under therapeutic conditions this secretory pattern of insulin might be of benefit in that unphysiologic hyperinsulinemia achieved by conventional insulin treatment in insulin-dependent diabetic patients appears to contribute to insulin resistance characteristic for these patients.[19] Thus, oscillatory insulin replacement would not only help to maintain receptor integrity but also to avoid constant hyperinsulinemia with its possible deleterious effects in regard to the development of late diabetic complications.[20] Evidence for the biologic advantage of cyclic operations over stationary steady-state reaction systems has also been provided on theoretical grounds as to efficacy and flexibility of metabolic responses.[21]

The findings of our study demonstrate that, despite a significant reduction in total hormone supply by up to 40%, but given in a more physiologic, i.e., pulsatile, fashion, insulin is equally effective in restraining HGP and stimulating glucose utilization (study A; Fig. 2). If the same dose of insulin given intermittently is provided continuously, the insulin's suppressive effect on HGP becomes diminished (study B; Fig. 3). The potential role of such cyclic insulin delivery regulating hepatic and peripheral glucose metabolism has so far been discussed in a few studies.[22,23] The two in vivo studies, however, which exposed healthy subjects to an identical amount of insulin given in a pulsatile or continuous fashion, came up with different conclusions.

In the first study by Matthews et al.,[22] in which endogenous insulin secretion was suppressed by somatostatin, intravenous insulin pulses for 2 min with an insulin-free interval of 11 min lowered plasma glucose concentration more strongly than when the same total insulin dose was given continuously. This greater hypoglycemic effect, however, did not become significant before 7 h of pulsatile insulin administration. Simultaneously, insulin binding to monocytes was augmented after pulsatile hormone infusion. No glucose kinetic analysis, i.e., endogenous production and utilization of glucose, was performed in this study. In contrast, in the second study, Verdin et al.,[23] using the euglycemic hyperinsulinemic (0.4 mU · kg^{-1} · min^{-1}) glucose-clamp technique combined with glucose kinetic analysis, provided evidence that pulsatile versus continuous insulin infusion was equipotent rather than superior in regard to suppression of endogenous production and metabolic clearance rate of glucose. However, the findings of our study could be explained by the fact that the liver was still exposed to ongoing endogenous insulin secretion as demonstrated by unchanged arterial plasma C-peptide concentrations in these healthy subjects, which may have added to insulin action. Because HGP was completely suppressed under both conditions, no difference in the efficacy of pulsatile compared with continuous insulin administration was demonstrable.

Glucose clearance was described in the latter study to be unchanged in healthy humans at mean insulin concentrations of ~30 mU/L achieved in both continuous and pulsed insulin infusion studies.[23] This finding was confirmed by our study with the same insulin concentration (study B). However, insulin sensitivity appeared to be increased in study A, in which similar glucose utilization rates were achieved during continuous and pulsed insulin administration, even though mean insulin levels were 40% lower under the latter condition (39 vs. 64 mU/L). However, it cannot be excluded that the only slight stimulation of glucose utilization by insulin in our diabetic, insulin-resistant patients compared with that achieved under the same conditions in normal humans[24] could have rendered some reduction in glucose utilization by pulsing undetectable. However, the 7.5-min insulin pulses followed by a gap of 7.5 min without insulin as employed by Verdin et al.[23] might have been long enough to obscure any benefit of pulsatile hormone administration. Not surprisingly, pulsed insulin administered subcutaneously is not superior to continuous infusion, because no oscillations in plasma insulin concentration are achieved.[25]

As to the importance of oscillatory exposure of the liver to hormonal action, the findings of our study are supported by

recent in vitro experiments.[8,26] Using freshly isolated rat hepatocytes, Weigle et al.[26] demonstrated that glucose production in response to a fixed total dose of glucagon was enhanced if glucagon was delivered as a series of brief pulses. In our studies,[8] isolated perfused rat liver was exposed continuously or intermittently to glucagon and insulin. We showed that glucagon-stimulated glucose production was identical despite reduction of the total glucagon dose by 50%, when given intermittently. As for insulin, reduction in total hormone dose to 33%, but given at timed intervals, did not diminish insulin's suppressive effect on glucagon-stimulated hepatic glucose release.

In summary, our results indicate that by reducing hormone delivery by up to 40%, but given in a pulsatile fashion, insulin is equally potent in controlling HGP when compared with continuous insulin administration. Possible alterations in insulin action by pulsed hormone exposure on glucose utilization by peripheral tissues may be masked by the insulin-resistant state of diabetic patients. Chronically, application of pulsatile insulin substitution in intravenous pump users may reduce systemic hyperinsulinemia and, in the long run, insulin resistance by reversing downregulation of insulin receptors.

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