Predicting Insulin Requirements for a Portable Insulin Pump Using the Biostator

Evidence for Reversible Insulin Resistance in Poorly Controlled Type I Diabetics

RONALD K. MAYFIELD, FRANCIS M. SULLIVAN, JOHN A. COLWELL, AND HULDA J. WOHLTMANN

SUMMARY

Glycemic control was achieved in 14 patients with insulin-dependent diabetes mellitus (IDDM) by 36–48-h treatment with a recently marketed clinical model, Biostator glucose controller (Life Science Instruments, Miles Laboratories, Elkhart, Indiana). Control was maintained by continuous subcutaneous insulin infusion with a portable pump, programmed using infusion profiles from the Biostator. Control of glycemic excursion with the Biostator was variable among patients. This control, reflected by the M-value or a blood glucose index (mean of pre-, peak, and 2-h postmeal levels for four meals) of each patient, correlated directly with their prior glycemic control, as assessed by hemoglobin A_{1c} (HbA_{1c}) level ($r = 0.66$, $P < 0.01$ and $r = 0.82$, $P < 0.005$, for M-value and blood glucose index, respectively).

Total insulin infused by the Biostator/24 h overpredicted the subcutaneous infusion dose required on day 2 of pump treatment (183 ± 11%, $P < 0.001$). Therefore, these data were not used to program the portable pump. Instead, total insulin dose was estimated using a dietary glucose/insulin (G/I) ratio. This ratio, derived from dietary total available glucose, urine glucose, and insulin dose/24 h during depot insulin treatment, accurately estimated total insulin for pump infusion (97 ± 4%). The basal infusion rate of the Biostator between 2400 and 0600 h also exceeded the subcutaneous infusion requirement and was reduced to 40% for the initial pump basal rate. The remainder of the insulin (total minus basal) was distributed as premeal boluses according to the Biostator infusion profile for meals. This initial distribution (%) of premeal insulin correlated well with that eventually needed for optimal control with infusion pump treatment ($r = 0.88$, $P < 0.001$). The insulin regimens derived resulted in average premeal plasma glucose levels of 113 ± 5.9 mg/dl on day 2 of pump treatment.

During 5–10 days of continued infusion pump treatment, the insulin dose needed to maintain blood glucose control decreased in the group as a whole. This decrease was primarily due to the dose reductions seen in patients who were in poor glycemic control before study. The decrease (%) in insulin dose in patients with $HbA_{1c} > 11\%$ was 31.3 ± 4.1% ($P < 0.001$) compared with 8.6 ± 4.9% in patients with $HbA_{1c} < 11\%$ (P = NS). In all patients, the change in insulin requirements (%) correlated with their initial HbA_{1c} level ($r = 0.72$, $P < 0.05$). Glycemic control did not change significantly during this period.

Our study supports the coordinated use of closed- and open-loop insulin delivery systems. The Biostator infusion profiles are helpful in programming meal insulin distribution for the portable infusion pump. However, with the algorithms we used, the Biostator significantly overestimates total and basal insulin needs for subcutaneous infusion. The correlation between initial HbA_{1c} levels and glycemic control on the Biostator as well as the relationship of HbA_{1c} to the subsequent decrease in insulin requirements during pump treatment suggest that patients with poorly controlled IDDM are insulin resistant, and that this improves with strict glycemic control. DIABETES 32:908–914, October 1983.

Normal blood glucose excursion is the goal of new intensive treatment regimens for insulin-dependent diabetic patients. Insulin replacement, balanced caloric intake, and exercise are recognized as major determinants of glucose control. Recently, new modes of insulin delivery have been employed to provide more physiologic insulin replacement. Near-normalization of blood glucose excursion is possible with closed-loop glucose-controlled insulin delivery systems.[1,2] Marked improvement in control has been achieved with fixed schedules of continuous insulin infusion by portable pump.[3] Since individual insulin regimens vary considerably among patients, and differences in diurnal insulin requirements are

From the Departments of Medicine and Pediatrics, Medical University of South Carolina, Charleston, South Carolina.
Address reprint requests to Ronald K. Mayfield, M.D., Medical University of South Carolina, Department of Medicine, 171 Ashley Avenue, Charleston, South Carolina 29425.
Received for publication 12 April 1982 and in revised form 28 March 1983.

recognized in many, closed-loop systems have been used to define insulin distribution for portable pump infusion.[4-8]

In this article we report our experience using the recently marketed, clinical model, closed-loop glucose controller (Biostator, Life Science Instruments) to control glycemia in insulin-dependent diabetic patients and to program a portable insulin infusion pump. We found that insulin requirements for subcutaneous infusion were significantly overestimated by the Biostator. However, insulin infusion profiles from the closed-loop system were useful for distributing meal-related insulin for portable pump infusion. Our data also suggest that the patient's prior glycemic control influences both the effectiveness of this closed-loop system to normalize plasma glucose and the stabilization of insulin dose during the early phase of portable infusion pump treatment.

MATERIALS AND METHODS

Subjects. Fourteen insulin-dependent diabetic patients were studied in the General Clinical Research Center of the Medical University of South Carolina Hospital. There were eight female and six male subjects. Nine patients were between 10 and 20 yr of age. Four were 20–30 yr old and one patient was a 61-yr-old labile diabetic. All patients were ketosis prone, by history, and were within 15% of ideal body weight. Duration of diabetes ranged from 4 to 24 yr and averaged 11.4 ± 1.2 yr (mean ± SE). Seven of the patients had retinopathy, proliferative in four, and two had clinically apparent nephropathy. All patients were being treated with one or two doses of mixed, intermediate- and short-acting, insulin before study.

Protocol. The protocol was approved by the Institutional Review Board for Human Research and informed consent was obtained from all patients or guardians before study. Patients were admitted to the General Clinical Research Center of the Medical University Hospital and maintained on their prestudy insulin regimen for 4 days, while baseline studies were obtained. They were fed a constant isocaloric diet containing 45% of total calories as carbohydrate, 35% as fat, and 20% as protein. This distribution was identical for all meals. Weight did not change significantly during the study. Daily dietary total available glucose (TAG) was determined for each patient.[9] One hundred percent of the grams of dietary carbohydrate, 58% of protein, and 10% of fat were totaled to obtain dietary TAG. Thirty percent of TAG was given at each of three meals and 10% at an evening snack, with the exception of one patient who received morning and afternoon snacks as well.

Beginning on the fifth day all patients were treated for 36–48 h with the Biostator glucose controller. This clinical model, closed-loop system contains preset algorithms for insulin and dextrose infusion rates. Programmable constants were set as follows: BI 90 mg/dl, BD 70 mg/dl, RD 50 mg/min, FI 300 mU/min, FD 250 mg/min, VAR 100%. Basal insulin infusion rate (RI) is maintained at 0.15 mU/kg/min when VAR is 100%. Other preset constants, which are not programmable, for insulin and dextrose infusion rates include: KR 166, KF 44, QI 30, and QD 25. Although a dextrose infusion is provided, in almost all cases dextrose was not given during the course of Biostator monitoring. Biostator treatment was initiated in the p.m. hours. After overnight control, data obtained during the next 24–36-h period were used. Interruptions of monitoring and insulin administration were minimal during the periods used for data analysis. Intermediate-acting insulin had been discontinued for 36 h, and subcutaneous regular insulin for at least 18 h before data collection.

Immediately upon completion of closed-loop control, continuous subcutaneous insulin infusion was begun with the Autosyringe AS2C infusion pump (Autosyringe Incorporated, Hooksett, New Hampshire). The initial total insulin dose to be given by the infusion pump was calculated for each patient from their TAG intake and dietary glucose:insulin (G/I) ratio.[10] The G/I ratio was calculated from data obtained on the fourth day. This was the last day of subcutaneous insulin treatment before closed-loop monitoring. The G/I ratio is derived from dividing the utilized TAG (dietary TAG minus grams of urinary glucose/24 h) by total insulin dose on that day. The ratio is an index of dietary available glucose metabolized for each unit of insulin given. (For example, a patient receiving 30 U insulin and a dietary TAG of 200 g has urinary glucose excretion of 50 g/24 h. The G/I ratio is (200 − 50)/30 = 5. Total insulin needed to eliminate glycosuria for the 200-g TAG diet would be: 200 g TAG divided by 5 g TAG utilized/unit of insulin = 40 U.)

The insulin delivery rate by the Biostator between 2400 and 0600 h was used to calculate the basal infusion rate for the portable pump. The remainder of the insulin (total minus basal) was distributed as premeal boluses given 30 min before meals. Meal insulin was distributed according to the percent of total meal-related insulin given by the Biostator for each meal and snack. Biostator meal-related insulin was defined as the amount delivered from the beginning of a meal until the blood glucose returned to the premeal level. Subcutaneous insulin infusion was continued for 5–10 days, with adjustments of basal and meal insulin made to maintain optimal glycemic control.

Laboratory methods. Hourly blood glucose profiles during subcutaneous insulin infusion were performed on venous blood sampled from an indwelling catheter. Capillary blood was used for all other glucose measurements during pump therapy. Blood glucose levels were measured with the Ames Dextrometer (Miles Laboratories, Elkhart, Indiana), the accuracy of which was verified daily by autoanalyzer. Hemoglobin A_{1c} (HbA_{1c}) was measured in fasting blood samples by isoelectric focusing of erythrocyte hemolysates over a pH gradient of 6–8, according to the method of Spicer et al.[11]

Data analysis. Data are expressed as mean ± SE. Mean amplitude of glycemic excursion (MAGE) and M-value were calculated as previously described.[12,13] The M-value was modified using a standard glucose level of 90 mg/dl. Differences in glucose levels, insulin doses, and HbA_{1c} levels were analyzed by Student's *t* test for paired or unpaired data. Correlations were determined by linear regression analysis. Differences and correlations were considered significant at $P < 0.05$.

RESULTS

Blood glucose control during closed-loop insulin delivery. The mean 24-h blood glucose profile during closed-loop control is shown in Figure 1A for 13 patients (the profile of one patient receiving six feedings is excluded). The blood glucose excursion was greatest after breakfast, despite a greater rate of insulin infusion at that time (Figure 1B). The

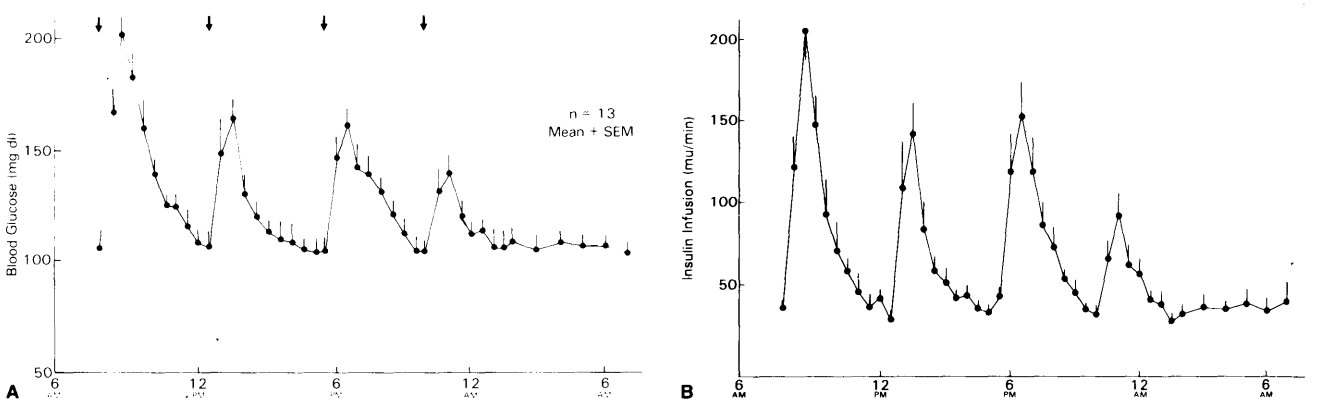

FIGURE 1. (A) Mean blood glucose profile during closed-loop (Biostator) control. Glucose level (mean ± SEM) is plotted at 30-min intervals from 0730 to 0200 h and at 60-min intervals from 0200 to 0700 h. Arrows represent meals. (One patient receiving between-meal snacks is excluded.) (B) Mean insulin infusion profile from Biostator for 13 patients. Time points are the same as for the glucose profile above.

proportion of total meal insulin given for each meal was: breakfast, 36 ± 1.8%; lunch, 23 ± 1.6%; supper, 30 ± 1.2%; snack, 11 ± 1.2%. Mean amplitude of glycemic excursion (MAGE) and M-value were 74 ± 4 mg/dl and 7.2 ± 0.9, respectively.

Since the Biostator-controlled glycemic excursion was better in some subjects than others, we analyzed our data to see whether Biostator control of glycemia had any relationship to the patient's previous control. A blood glucose index, reflecting glucose excursion during Biostator control, was calculated as the mean of 12 blood glucose levels for each patient (premeal, peak postmeal, and 2-h postmeal levels for four meals during a 24-h period). This index was directly correlated with the HbA_{1c} level of each patient at entry into the study ($r = 0.82$, $P < 0.001$; Figure 2). Another index of treatment efficacy, the M-value, calculated for the same period, was also correlated with the HbA_{1c} level ($r = 0.66$, $P < 0.01$). Since the Biostator responds to higher glucose levels with increased insulin delivery, as might be expected, a correlation was also found between the M-value and insulin dose delivered by the Biostator ($r = 0.63$, $P < 0.05$). However, a significant correlation did not exist between the blood glucose index and insulin delivered. Although the patient's M-value during Biostator control correlated with insulin delivered, and was predicted by their HbA_{1c} level (above correlation), the HbA_{1c} level did not correlate with insulin delivered by the Biostator.

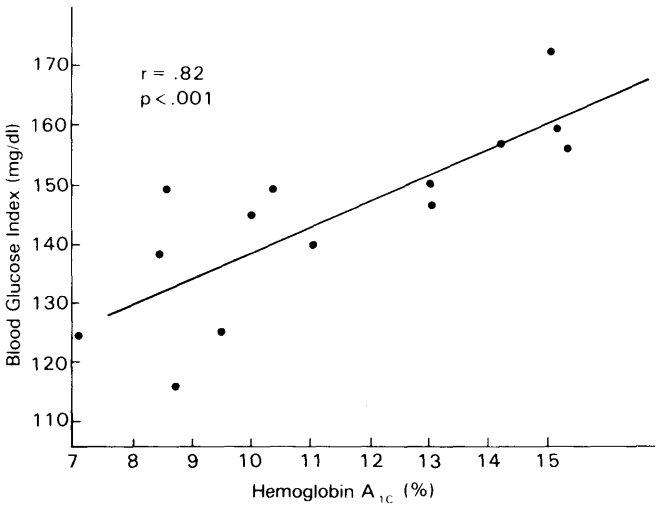

FIGURE 2. Correlation of blood glucose index during Biostator control with hemoglobin A_{1c} obtained at entry to the study ($y = 96.7 + 4.2x$). Blood glucose index is the mean of premeal, peak postmeal, and 2-h postmeal blood glucose levels for four meals during a 24-h period in each patient ($N = 14$). The M-value, calculated from the same period, also correlated with hemoglobin A_{1c} ($y = 6.1 \pm 1.9x$, $r = 0.66$, $P < 0.01$). The ability of the closed-loop system to control glycemic excursion was not as good in previously uncontrolled patients.

Programming of insulin infusion pump. We observed that total insulin delivered during closed-loop control with the Biostator was significantly greater than requirements during continuous subcutaneous infusion or depot insulin therapy. Since it overpredicts subcutaneous insulin requirements, we were unable to use the Biostator to determine total insulin dose for subcutaneous infusion. Total insulin dose was derived from the dietary G/I ratio of each patient (see METHODS). The G/I ratio was calculated from the dietary TAG, insulin dose, and urinary glucose excretion/24 h on the fourth day. These parameters were 284 ± 19 g, 44 ± 4.0 U, and 32 ± 5.9 g, respectively. The dietary G/I ratios calculated averaged 6.5 ± 0.9 g TAG/unit insulin, with a range of 3.1–13.9. Using each patient's G/I ratio as an index of dietary carbohydrate equivalents metabolized per unit of insulin, the estimated total dose of insulin required for their TAG intake was calculated. The insulin pump infusion was begun with this estimated total dose and adjustments were made on the second day. A comparison of the total doses predicted by the Biostator and by the G/I ratio, with the dose required on the second day of infusion pump treatment, is shown in Table 1. The average total insulin infused by the Biostator in 24 h for all patients was 90 ± 7 U. This was significantly greater ($P < 0.001$) than the dose predicted by the G/I ratio (50 ± 5 U), or required to maintain plasma glucose control on the second day of subcutaneous insulin infusion (51 ± 4 U). The average premeal plasma glucose level in the patients of 113 ± 6 mg/dl is proof that insulin given on day 2 was indeed the required dose. Because there were an equal frequency and magnitude of increases and decreases from the dose predicted by the G/I ratio to the required dose, average predicted and required doses were nearly equal (Table 1).

TABLE 1
Comparison of total insulin dose predicted by the Biostator and glucose/insulin (G/I) ratio (N = 14)

	Insulin dose predicted		Insulin required*
	Biostator	G/I	
U/day	90 ± 7†	50 ± 5	51 ± 4
% Required dose	183 ± 11†	97 ± 4	100

*Dose required on day 2 of infusion pump treatment, when premeal plasma glucose averaged 113 ± 6 mg/dl.
†P < 0.001 compared with G/I predicted or required dose.

However, the absolute dose change on day 2, from the predicted dose, was 5.4 ± 1.2 U, an average adjustment of 11 ± 2.7%.

Basal infusion rates for the portable infusion pump were also overestimated by the Biostator. A uniform reduction from the closed-loop basal rate was made and portable pump basal rates were initiated at 40% of the closed-loop rate between 2400 and 0600 h. The initial portable infusion pump basal rate ranged from 0.39 to 1.56 U/h (13.8 ± 1.4 mU/kg/h; range: 7–22). This rate was subsequently adjusted to maintain the fasting glucose level below 130 mg/dl. Only four patients required basal rate adjustments. In each case an increase in basal rate between 0500 and 0800 h was required to control the fasting glucose level.

Remaining insulin (total minus basal) was distributed as premeal boluses. Insulin infusion profiles from the Biostator were used to determine distribution of the premeal insulin for subcutaneous infusion. The percentage of total meal-related insulin (insulin infused from the beginning of meal until glucose level returned to baseline) given by the Biostator for each meal was used in the initial distribution of meal insulin for a portable pump infusion. Subsequent changes were made if necessary. Figure 3 shows that the percentage of meal insulin given for each meal by the Biostator correlated well with the percentage given at the end of portable infusion pump treatment ($r = 0.88$, $P < 0.001$). The final distribution remained nearly that predicted by the Biostator, despite a necessary reduction in total insulin dose during portable pump treatment (see below). The usefulness of the Biostator in predicting meal insulin distribution is also supported by the glucose control that was achieved on the second day of subcutaneous insulin infusion (above).

Blood glucose control during portable insulin infusion pump treatment. Plasma glucose profiles were obtained in 11 of 14 patients at the end of continuous subcutaneous insulin infusion, and the mean profile is shown in Figure 4. Although glycemic control was good with both Biostator and portable pump treatment, mean glucose levels were lower at several comparable times during pump treatment. As with closed-loop delivery, glucose excursion was greatest after breakfast. There was a trend for plasma glucose levels to fall from the postbreakfast peak to a nadir in later afternoon, with this decline temporarily interrupted by the glucose rise from the noon meal. MAGE during pump treatment was 79 ± 7 mg/dl and the M-value was 8.2 ± 1.3. These are not different from values obtained during closed-loop control.

Insulin requirements during portable insulin infusion pump treatment. During the period of subcutaneous insulin infusion, insulin requirements decreased in all but two patients. Comparing total insulin dose on the second day of portable pump treatment to the final day's requirement, the decrease in insulin dose was 18.8 ± 4.5% for the entire group ($P < 0.01$). The decrease in requirements ranged from 5% to 45%, with two subjects requiring small increases. To determine if the observed fall in insulin requirements was related to the degree of previous glycemic control, subjects were categorized by HbA_{1c} levels. Patients were considered in good to moderate control ($HbA_{1c} < 11\%$) or poor control ($HbA_{1c} > 11\%$). HbA_{1c} in the former group, group 1 (N = 8), was 9.2 ± 0.4% compared with that of the poor control group, group 2 (N = 6), which averaged 13.1 ± 0.6% ($P < 0.001$). The insulin dose required to maintain glycemic control during pump treatment did not decrease significantly in group 1 (8.6 ± 4.9%, Table 2). Group 2 patients had a 31.3 ± 4.1% decrease in insulin dose during the same period ($P < 0.001$). The decrease in insulin requirements in group 2 was significantly greater than that observed in group 1 ($P < 0.01$). The length of pump treatment did not differ in the two groups: 6.8 ± 0.9 days in group 1 and 9.2 ± 0.7 days in group 2.

Premeal blood glucose levels, measured four times daily, did not differ between the two groups at the beginning or the end of portable pump infusion, nor did the glucose levels change within either group during the course of treatment (Table 1). Group 1 had mean premeal glucose levels of 118 ± 9 mg/dl on the second day and 102 ± 5 mg/dl on the final day of subcutaneous insulin infusion. Average initial and final premeal glucose levels for group 2 were 105 ± 7 and 99 ± 8 mg/dl, respectively. Therefore, the fall in insulin requirements during this period could not be attributed to any differences in glycemic control. Also, weight did not change significantly during the study in the entire group or either subgroup of patients.

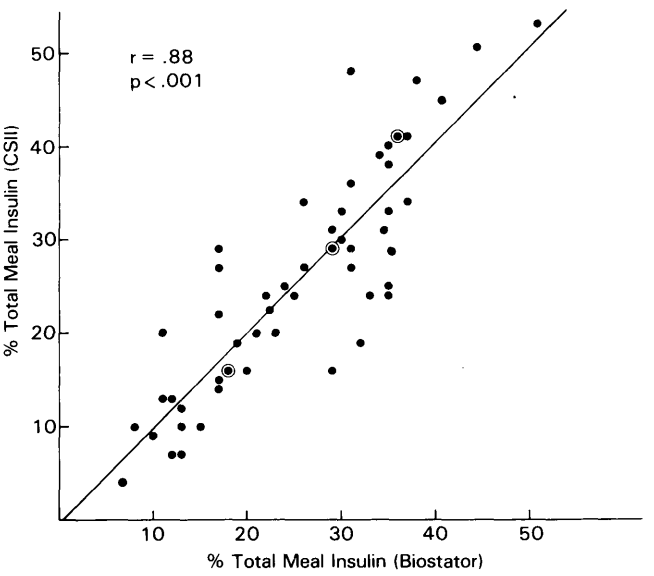

FIGURE 3. Correlation of meal-related insulin distribution (%) during Biostator and final day of continuous subcutaneous insulin infusion (CSII). Each point is the insulin dose for each meal, represented as the % of total meal insulin during Biostator and CSII (y = −0.45 + 1.02x). Meal insulin during Biostator treatment is considered as insulin delivered from the beginning of each meal until glucose level returns to premeal level. (N = 56 for 14 patients; ◉ = 2 points).

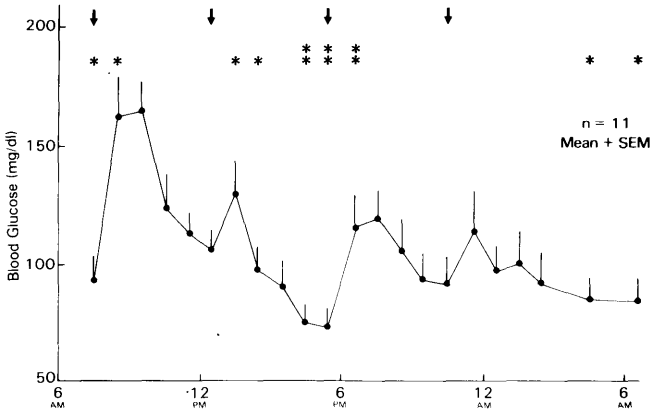

FIGURE 4. Blood glucose profile during continuous subcutaneous insulin infusion in 11 patients in whom full profiles were obtained. Arrows represent meals. At several points blood glucose levels were lower than comparable times during closed-loop control. *P < 0.05; **P < 0.001.

In the 12 patients demonstrating a fall in insulin requirements during portable infusion pump treatment, the percent decrease was directly correlated with the HbA_{1c} level ($r = 0.69$, $P < 0.05$; Figure 5). Two patients who demonstrated increases (7% and 17%) in insulin requirement during this period had HbA_{1c} levels below 10%. Including these patients, a similar relationship was observed between HbA_{1c} level and percent change in insulin requirement ($r = 0.72$, $P < 0.05$; Figure 5, legend).

DISCUSSION

Using the recently available Biostator glucose controller (clinical model), the present study supports the coordinated application of closed- and open-loop insulin delivery systems. As reported by others comparing closed- and open-loop systems, we achieved quite acceptable control of glycemic excursion with both methods.[5-8,14] Comparison of the glucose profile obtained with the clinical model Biostator glucose controller to that reported with the Biostator glucose-controlled insulin infusion system (GCIIS) and similar systems, reveals minor differences. Control of postprandial glucose excursion, particularly after breakfast, was not as good in our study.[6,14,15] This may be related to the distribution of calories in our study, with a larger percentage of total calories given at breakfast,[6,14] less frequent and larger meals,[6,14] as well as a greater proportion of carbohydrate.[15] Postabsorptive glucose levels were also approximately 10 mg/dl higher in our study. This is likely a result of using a BI level of 90 mg/dl (glucose level at which basal insulin infusion is given) rather than a level of 80 mg/dl.[14]

When insulin is administered peripherally, hyperinsulinemia is required to normalize levels of gluconeogenic precursors and achieve glycemic normalization. Hanna et al.[16] observed that a reduction in insulin infusion rate of only 5–10% increased postabsorptive glucose levels significantly during closed-loop delivery. Although we did not measure free insulin levels, the high basal infusion rates given with the Biostator (Figure 1B) should have achieved high peripheral insulin levels, since infusion rate correlates well with free immunoreactive insulin.[17] Measurement of insulin levels in the infusion solution confirmed our calculated level (data not shown), and therefore loss of insulin in the reservoir did not occur.

Glucose excursion tended to be somewhat more normalized during subcutaneous insulin infusion, although MAGE and M-values were similar for the two systems. There was a trend, with pump treatment, for the glucose level to fall during the day from a postbreakfast peak to a nadir in late afternoon, with the decline temporarily interrupted by the glucose rise after lunch. This pattern is apparent in data from other studies.[8] The smaller postprandial glucose excursion with subcutaneous infusion that we observed has also been observed by others.[6] Kølendorf et al.[6] have suggested that this weakness of the closed-loop system might be overcome with preprogrammed increases in insulin infusion rates at the start of meals. Bolus injection of insulin subcutaneously, 30 min before meals, results in an earlier increase in plasma free insulin levels compared with that of the Biostator, responding to the rising glucose level after a meal.[8]

The absence of this early postprandial increase in insulin levels, along with higher postprandial plasma glucose levels, may partially explain our finding that total insulin required by the Biostator to control glycemia is greater than with preprogrammed open-loop insulin delivery. This difference is consistent with previous reports.[4,7,18,19] Mirouze has suggested that true insulin requirements can only be determined during optimal glucose control.[7] It seems likely that higher glucose levels during closed-loop control in our study partly account for the greater insulin delivery observed. However, it also appears that the Biostator programmed with insulin delivery constants (KR and QI) at the level preset in the system we used may give unphysiologically high amounts of insulin when the blood glucose level is rapidly rising postprandially.[18] Christiansen et al.[20] have found that revision of

TABLE 2
Decrease in insulin requirements during continuous subcutaneous insulin infusion

	HbA_{1c} (%)	Initial glucose† (mg/dl)	Final glucose† (mg/dl)	Decrease in insulin dose (%)
Group 1* (N = 8)	9.2 ± 0.4	118 ± 9	102 ± 5	8.6 ± 4.9
Group 2* (N = 6)	13.1 ± 0.6§	105 ± 7	99 ± 8	32.3 ± 4.1‡

*Group 1 patients defined by $HbA_{1c} < 11\%$ and group 2 by $HbA_{1c} > 11\%$.
†Mean of four premeal blood glucose levels on initial (second) and final days of subcutaneous insulin infusion.
‡$P < 0.01$ compared with group 1 and $P < 0.001$ for the decrease within group 2; the decrease in group 1 was not significant.
§$P < 0.001$ compared with group 1.

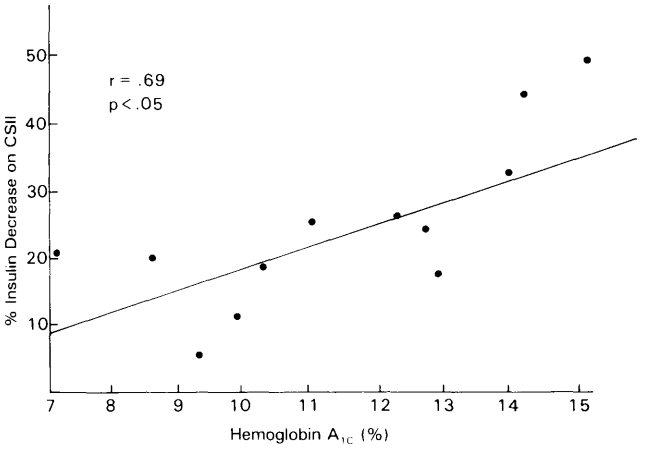

FIGURE 5. Correlation of decrease in insulin requirement (%) during continuous subcutaneous insulin infusion (CSII), with hemoglobin A_{1c} level obtained at entry to the study, in the 12 patients demonstrating a decrease in dose ($y = -14.2 + 3.3x$). Including two patients who did not have a decrease in insulin requirement, a similar correlation is obtained ($y = -37.3 + 5.2x$, $r = 0.72$, $P < 0.01$). Patients with previously poor glycemic control, assessed by hemoglobin A_{1c}, had a greater reduction in insulin dose needed to maintain control during CSII.

these constants decreased the amounts of insulin infused without affecting glucose excursion.

Although the Biostator overpredicted subcutaneous requirements, the dietary glucose/insulin ratio, introduced by Hartman shortly after the introduction of insulin,[10] provided an accurate method of estimating total insulin dose for pump infusion. Irsigler employed a similar ratio (insulin required during normoglycemia per gram of carbohydrate intake) for adjusting insulin to meal size.[4] In establishing an optimal insulin regimen for portable pump infusion, the equally important aspect of distributing meal insulin was predicted well by the Biostator. The meal distribution of insulin remained stable despite a needed reduction in total insulin dose during the course of subcutaneous infusion.

Our data suggest that the prior glycemic control of patients studied, a factor not previously considered, is important when evaluating and comparing closed- and open-loop insulin delivery systems. We observed a relationship between the patient's prior glycemic control, assessed by HbA_{1c} level, and glucose excursion during closed-loop insulin delivery. The prestudy HbA_{1c} levels also correlated directly with the decrease in insulin requirements that occurred during open-loop insulin delivery. Thus, in patients with relatively good control before study, glycemic control with the Biostator was better and there was no significant decrease in insulin requirement during insulin pump treatment. However, in patients with high HbA_{1c} levels, M-value and blood glucose index were higher during closed-loop treatment, and significant reductions in insulin requirements occurred during subsequent subcutaneous insulin infusion. In the absence of any change in plasma glucose control, the reduction in insulin needs suggests improved insulin responsiveness. Together these findings suggest that insulin resistance is present in previously uncontrolled insulin-dependent diabetics and improves with tight glucose control. Although commonly invoked in the pathogenesis of non-insulin-dependent diabetes, insulin resistance is not usually considered characteristic of the insulinopenic diabetic. Some early studies in type I diabetics have been conflicting, reporting normal insulin sensitivity,[21] resistance in a portion of patients studied,[22,23] or in all subjects.[24] The present study suggests that these differences may relate to the previous metabolic control of patients studied.

Reaven et al.[25] made similar observations in dogs treated with variable doses of alloxan. During infusion of epinephrine, propranolol, glucose, and insulin, steady-state glucose levels indicated insulin resistance in animals with fasting glucose levels above 150 mg/dl, but not in those with fasting glucose below 150 mg/dl. DeFronzo et al.,[26] employing the insulin clamp technique, found a marked reduction in insulin-stimulated glucose metabolism in insulin-dependent diabetics. Although HbA_{1c} levels were not reported, the fasting glucose level correlated directly with hepatic glucose production and inversely with glucose clearance.

Our study provides no direct information on the mechanisms by which insulin resistance might develop. Insulin receptors in IDDM have been reported to be both increased or decreased;[27] however, it has been suggested that hyperinsulinemia might lead to receptor-mediated insulin resistance.[16] We found no correlation between insulin dose before study and the glycemic control achieved during closed-loop monitoring or subsequent decrease in insulin requirement (data not shown). Marked insulin deficiency in rats is associated with a postreceptor defect in insulin-stimulated glucose transport and metabolism, in both adipocytes[28] and muscle.[29,30] Peripheral tissues, rather than liver, have been implicated as a site of insulin resistance in human diabetics as well.[26] Another recent study has demonstrated that the capacity to oxidize and store exogenous carbohydrate is markedly impaired in type I diabetics, and that these functions are restored to normal after several days of Biostator insulin delivery.[31] Documented increases of counterregulatory hormones, such as glucagon, growth hormone, and catecholamines, in uncontrolled IDDM are normalized with 1–2 wk of strict glucose control and may contribute to reversible insulin resistance.[32,33]

In conclusion we suggest that the coordinated use of closed- and open-loop insulin delivery systems provides an excellent means of achieving initial strict glucose control in an overall program of intensified diabetic management. Our findings suggest that an insulin-resistant state exists in the uncontrolled insulin-dependent diabetic, which may influence the ability of closed-loop insulin delivery systems to achieve normalization of blood glucose excursion. Because of this, the effectiveness of closed-loop system algorithms for maintaining normoglycemia may not be adequately assessed in previously uncontrolled patients. Possibly related to resolution of insulin resistance, strict glycemic control in previously uncontrolled diabetic patients is followed by a significant reduction, over several days, of insulin required to maintain that control. This may influence the time required to reach a stable insulin regimen and should be considered when beginning continuous insulin infusion.

ACKNOWLEDGMENTS

The authors thank the nursing and laboratory staffs of the General Clinical Research Center for their excellent assist-

ance in carrying out this study and Julia Brandon for preparation of the manuscript.

This study was supported in part by National Institutes of Health grants AM 00892 and RR 01070, and South Carolina Biomedical Research Appropriations. Dr. Mayfield is the recipient of a Special Emphasis Research Career Award from the NIADDK and NHLBI.

REFERENCES

[1] Kerner, W., Thum, C., Tamas jun, G., Beischer, W., Clemens, A. H., and Pfeiffer, E. F.: Attempts at perfect normalization of glucose tolerance test of severe diabetics by artificial beta cell. Horm. Metab. Res. 1976; 8:256–61.

[2] Clarke, W. L., Thomas, L., and Santiago, J. V.: Clinical evaluation and preliminary studies on the use of an artificial pancreatic beta cell in juvenile diabetes mellitus. J. Pediatr. 1977; 91:590–96.

[3] Tamborlane, W. V., Sherwin, R. S., Genel, M., and Felig, P.: Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable pump. N. Engl. J. Med. 1979; 300:573–78.

[4] Irsigler, K., Kritz, H., Kasper, L., Brandle, J., Koller, W., and Franetzki, M.: Preprogrammed infusion with a portable pump system. Horm. Metab. Res. (Suppl.) 1979; 8:193–97.

[5] Stavljenić, A., Granić, M., Topić, B., and Skrabalo, Z.: Comparison of a perfusion syringe (Mill Hill infusor) and a glucose-controlled insulin infusion system in the regulation of diabetes mellitus. Horm. Metab. Res. (Suppl.) 1979; 8:207–11.

[6] Kølendorf, K., Christiansen, J. S., Bojsen, J., Svendsen, P. A., and Teglbjaerg, L. L. S.: Determination of 24-hour insulin infusion pattern by an artificial endocrine pancreas for intravenous insulin infusion with a miniature pump. Horm. Metab. Res. 1981; 13:245–49.

[7] Mirouze, J., Selam, J. L., Pham, T. C., and Chenon, D.: Programming of an open-loop system for i.v. insulin infusion in insulin-dependent diabetes. Acta Diabetol. Lat. 1980; 17:103–109.

[8] Service, F. J., Rizza, R. A., Westland, R. E., Hall, L. D., Nelson, R. L., Haymond, M. W., Clemens, A. H., and Gerich, J. E.: Considerations for the programming of an open-loop insulin infusion device from the Biostator glucose controller. Diabetes Care 1980; 3:278–84.

[9] Woodyatt, R. T.: Objects and method of diet adjustment in diabetes. Arch. Intern. Med. 1921; 28:125–41.

[10] Hartmann, A. F., Sr.: The natural course of diabetes mellitus in infants and children. *In* Diabetes Mellitus in Infants and Children. M and R Pediatric Research Conference. Columbus, Ohio, M and R Laboratories, 1954:19–28.

[11] Spicer, K. M., Allen, R. C., and Buse, M. G.: A simplified assay of hemoglobin A_{1c} in diabetic patients using isoelectric focusing and quantitative microdensitometry. Diabetes 1978; 27:384–88.

[12] Service, F. J., Molnar, G. D., Rosevear, J. W., Ackerman, E., Gatewood, L. C., and Taylor, W. F.: Mean amplitude of glycemic excusions, a measure of diabetic instability. Diabetes 1970; 19:644–55.

[13] Schlichtkrull, J., Munck, O., and Jersild, M.: The M-value, an index of blood sugar control in diabetics. Acta Med. Scand. 1965; 177:95–102.

[14] Rizza, R. A., Gerich, J. E., Haymond, M. W., Westland, R. E., Hall, L. D., Clemens, A. H., and Service, F. J.: Control of blood sugar in insulin-dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion, and intensified conventional insulin therapy. N. Engl. J. Med. 1980; 303:1313–18.

[15] Zinman, B., Stokes, E. F., Albisser, A. M., Hanna, A. K., Minuk, H. L., Stein, A. N., Leibel, B. S., and Marliss, E. B.: The metabolic response to glycemic control by the artificial pancreas in diabetic man. Metabolism 1979; 28:511–18.

[16] Hanna, A. K., Zinman, B., Nakhooda, A. F., Minuk, H. L., Stokes, E. F., Albisser, A. M., Leibel, B. S., and Marliss, E. B.: Insulin, glucagon, and amino acids during glycemic control by the artificial pancreas in diabetic man. Metabolism 1980; 29:321–32.

[17] Perlman, K., Ehrlick, R. M., Filler, R. M., and Albisser, A. M.: Waveform requirements for metabolic normalization with continuous intravenous insulin delivery. Diabetes 1981; 30:710–17.

[18] Christiansen, J. S., Svendsen, P. A., and Deckert, T.: Insulin treatment and state of control before, during, and after connection to a glucose controlled insulin infusion system (Biostator). Horm. Metab. Res. (Suppl.) 1979; 8:131–34.

[19] Irsigler, K., Kritz, H., Kaspar, L., Brändle, J., and Franetzki, M.: Use of glucose-controlled insulin infusion system for improvement of subcutaneous insulin regimen. Horm. Metab. Res. (Suppl.) 1979; 8:134–40.

[20] Christiansen, J. S., Svendsen, P. A., Søegaard, U., Frandsen, M., Mathiesen, E., Winther, K., and Deckert, T.: An artificial beta cell: assessment of the glucose analyser, infusion system and optimization of constants for the algorithms. Scand. J. Clin. Lab. Invest. 1981; 41:647–54.

[21] Ginsberg, H. N.: Investigation of insulin sensitivity in treated subjects with ketosis prone diabetes mellitus. Diabetes 1977; 26:278–83.

[22] Himsworth, H. P., and Kerr, R. B.: Insulin sensitive and insulin-insensitive types of diabetes mellitus. Clin. Sci. 1939; 4:119–52.

[23] Martin, F. I. R., and Stocks, A. E.: Insulin sensitivity and ^{131}I-insulin metabolism in juvenile-type diabetics. Aust. Ann. Med. 1961; 16:289–96.

[24] Harano, Y., Ohgaku, S., Hidaka, H., Haneda, K., Kikkawa, R., Shigeta, Y., and Abe, H.: Glucose, insulin and somatostatin infusion for the determination of insulin sensitivity. J. Clin. Endocrinol. Metab. 1977; 45:1124–27.

[25] Reaven, G. M., Sageman, W. S., and Swenson, R. S.: Development of insulin resistance in normal dogs following alloxan-induced insulin deficiency. Diabetologia 1977; 13:459–62.

[26] DeFronzo, R. A., Hendler, R., and Simonson, D.: Insulin resistance is a prominent feature of insulin-dependent diabetes. Diabetes 1982; 31:795–801.

[27] Pedersen, O., Beck-Nielsen, H., and Heding, L.: Insulin receptor on monocytes from patients with ketosis-prone diabetes mellitus. Diabetes 1978; 27:1098–104.

[28] Kobayshi, M., and Olefsky, J. M.: Effects of streptozotocin-induced diabetes on insulin binding, glucose transport, and intracellular glucose metabolism in isolated rat adipocytes. Diabetes 1979; 28:87–95.

[29] Kipnis, D. M., and Cori, C. F.: Studies of tissue permeability. V. The penetration and phosphorylation of 2-deoxyglucose in the rat diaphragm. J. Biol. Chem. 1959; 234:171–77.

[30] Morgan, H. E., Cadenas, E., Regen, D. M., and Park, C. R.: Regulation of glucose uptake in muscle. II. Rate-limiting steps and effects of insulin and anoxia in heart muscle from diabetic rats. J. Biol. Chem. 1961; 236:262–68.

[31] Foss, M. C., Vlachokosta, F. V., Cunningham, L. N., and Aoki, T. T.: Restoration of glucose homeostasis in insulin-dependent diabetic subjects: an inducible process. Diabetes 1982; 31:46–52.

[32] Raskin, P., Pietri, A., and Unger, R.: Changes in glucagon levels after four to five weeks of glycoregulation by portable insulin infusion pumps. Diabetes 1979; 28:1033–35.

[33] Sherwin, R. S., Tamborlane, W. V., Genel, M., and Felig, P.: Treatment of juvenile-onset diabetes by subcutaneous infusion of insulin with a portable pump. Diabetes Care 1980; 3:301–308.