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Chronic Intermittent Intravenous Insulin Therapy: A New Frontier in Diabetes Therapy

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ABSTRACT

The limited success achieved in controlling diabetes and its complications with conventional insulin therapy suggests the need for reevaluation of the appropriateness of insulin administration protocols. Indeed, conventional subcutaneous insulin administration produces slowly changing blood insulin levels and suboptimal hepatocyte insulinization resulting in impaired hepatic capacity for processing incoming dietary glucose. The novel approach to insulin administration known as chronic intermittent intravenous insulin therapy (CIIIT) delivers insulin in a pulsatile fashion and achieves physiological insulin concentration in the portal vein. Done as a weekly outpatient procedure combined with daily intensive subcutaneous insulin therapy, this procedure has been shown to (1) significantly improve glycemic control while decreasing the incidence of hypoglycemic events, (2) improve hypertension control, (3) slow the progression of overt diabetic nephropathy, and (4) reverse some manifestations of diabetic autonomic neuropathy (e.g., abnormal circadian blood pressure pattern, severe postural hypotension, and hypoglycemia unawareness).

INTRODUCTION

ALTHOUGH A RELATIVE OR ABSOLUTE insulin deficiency is generally considered as having the pivotal role in the development of diabetes mellitus (DM) and its complications, the availability of insulin for therapy over the last eight decades has led to only partial success in achieving glycemic control and even less in preventing or limiting the development of the chronic complications of this disease. Why have we not done better? As the quality of exogenous insulin has not been an issue since the advent of human insulins, the appropriateness of its administration regimens should be carefully reevaluated.

Normally, insulin is secreted in a pulsatile fashion[1] and in various amounts, in close relationship with meals.[2,3] Though not unanimous, the balance of available experimental evidence suggests a more potent hypoglycemic effect of pulsatile insulin as opposed to continuous insulin infusion.[4,5] Continuous exposure to insulin and glucagon is known to decrease the hormones' metabolic effectiveness on splanchnic glucose production in humans.[6] Down-regulation at the cellular level may partially explain the decreased action of steady-state levels while pulsatile hormone secretion may allow recovery of receptor affinity or receptor numbers. Intermittent intravenous insulin administration with peaks of insulin concentrations

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may enhance suppression of gluconeogenesis and reduce hepatic glucose production (HGP).[4] Goodner et al.[7] showed in fasting rhesus monkeys that HGP oscillates in synchrony with the islet cells secretory cycle suggesting that the greater metabolic effects of pulsatile insulin occur at the liver. Similar results were obtained in *in vitro* systems.[5]

For induction and maintenance of insulin-dependent fuel-processing enzyme synthesis (e.g., hepatic glucokinase, phosphofructokinase, and pyruvate kinase), the hepatocytes require a defined insulin level (200–500 μU/mL in the portal vein)[8,9] concomitant with high glucose levels ("bimolecular signal").[10–12] In nondiabetic subjects, portal insulin concentrations are 2–3-fold greater than those in the peripheral circulation.[8] During the first pass through the liver, 50% of the insulin is removed,[13] pointing to the liver as the principal metabolic target organ of the gastrointestinal tract and the pancreas. The insulin retained by the hepatocytes may itself be essential for the long-term effects of insulin on hepatic glucose metabolism as well as growth and *de novo* enzyme synthesis.[14] After oral glucose intake, the liver accounts for an equal or greater proportion of total net glucose uptake as compared to the periphery.[15] Insulin exerts pivotal control of BG levels through its ability to regulate HGP directly[16] or indirectly.[17] The traditional subcutaneous (s.c.) insulin administration regimens used by diabetic patients (a) lack the pulsatile aspect (s.c. insulin administration achieves steady or slowly changing plasma concentrations), and (b) do not reach high enough insulin concentration at the hepatocyte level (e.g., 10 U regular insulin injected s.c. produce a peak systemic circulation concentration of 30–40 μU/mL and an even lower portal vein concentration of 15–20 μU/mL[18]).

A relative deficiency of insulin at the hepatocyte level leads to impaired capacity for processing of incoming dietary glucose. With the liver being the target organ of the pancreas, it appears, therefore, that the primary purpose of giving insulin to the diabetic patient should not be to control BG level ("control theory"), but rather the normalization of hepatic metabolism.

RATIONALE AND METHODOLOGY

It has been shown that the diabetic patient's capacity to oxidize and store exogenous carbohydrate is markedly impaired.[19] In the resting postabsorptive nondiabetic subject, the energy requirement is met primarily by fat oxidation reflected by a respiratory quotient (RQ; V CO_2/V O_2) of 0.7–0.8 (indirect calorimetry[20]). After glucose administration, CO_2 production (and consequently the RQ) increases (0.9–1.0), indicating that glucose has become the primary source of energy. In contrast, in the patient with diabetes mellitus on conventional insulin therapy, no such increase in RQ[21,22] or CO_2 production[23] is observed. The possible fate of ingested glucose is (a) oxidation (liver, brain, muscle), (b) conversion to fat (liver, muscle, adipose tissue), (c) storage as glycogen (liver, muscle) or transamination of intermediary metabolites to form amino acids (e.g., alanine). Only the first two processes generate CO_2 to increase the RQ. Liver and muscle appear to be the most active tissues for glucose oxidation. In 1985, Meistas et al.[23] showed in nondiabetic postabsorptive men that resting muscle is not the source of the increase in CO_2 production after ingestion of a 100-g glucose meal. Glucose utilization by fat is minimal (ca. 2%),[24] and adipose tissue production of CO_2 after glucose administration has been reported to be insignificant.[25] Carbon dioxide production by the heart,[26] kidney,[27] brain,[28] and gut[29] has also been measured in other mammals, and cannot account for the large increment in total CO_2 production. Thus, both indirect *in vivo* human studies[23] and direct *in vitro* experimental data support the concept that the liver is the source of the majority of the CO_2 production associated with glucose ingestion.

The lack of increase in RQ (and CO_2 production) after glucose ingestion in patients with diabetes on conventional insulin therapy is consistent with the hypothesis that their liver is metabolically "dormant" and relatively incapable of oxidizing ingested carbohydrates. However, this ability to oxidize dietary-derived glucose can be restored to normal after several days of artificial beta cell-directed insulin administration (Biostator; Fig. 1),[22] or

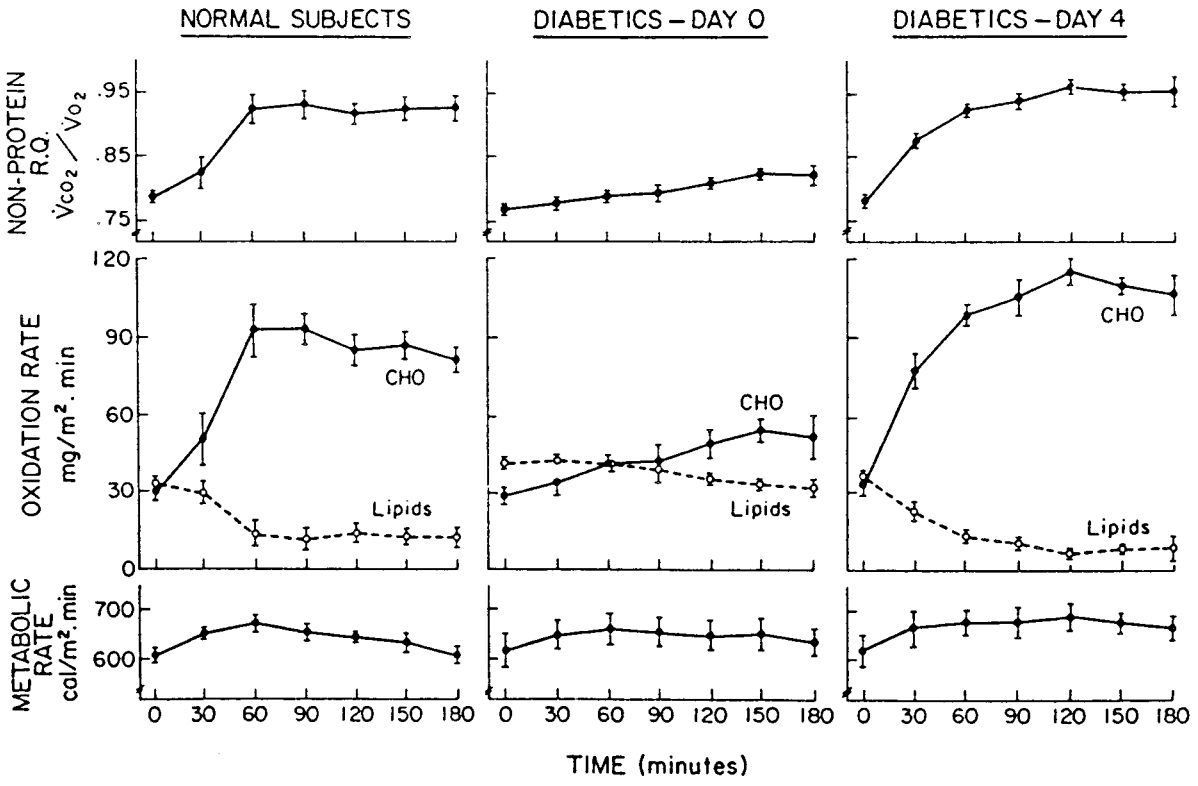

FIG. 1. Nonprotein respiratory quotient (npRQ), carbohydrate (CHO), and lipid oxidation rates, and metabolic rates of normal subjects and diabetic patients on day 0 (conventional insulin therapy) and on day 4 (after 72 h on artificial B-cell), before (0 time = postabsorptive state) and during the 3-h oral 100-g glucose tests. Values shown are X ± SEM. (Adapted from Foss et al.[22])

with CIIIT within 6–7 h.[30] This process was initially called "hepatic activation." Though not tried (due to the obvious extreme practical difficulties), it is conceivable that several days of hyperinsulinemic euglycemic clamp procedure could also achieve RQ normalization.

This novel approach to insulin administration known as "hepatic activation" or "chronic intermittent intravenous insulin therapy" (CIIIT) corrects the above outlined drawbacks of conventional s.c. insulin therapy as follows:

1. It delivers insulin to the hepatocyte in the physiologically appropriate portal vein concentrations range (over 200 μU/mL).
2. Insulin is administered in pulses intravenously (i.v.) similar to the physiological insulin secretion pattern.

In essence, CIIIT uses a novel insulin algorithm consisting of a series of intravenous insulin pulses administered concomitantly with oral glucose. Pulses of insulin should have greater potential for hepatic activation than a continuous infusion of insulin since it is possible to manipulate the rate at which insulin concentration changes, the magnitude of each pulse, the duration of hepatic insulin exposure, and to superimpose the pulses on a rising baseline. Any or all of these may be metabolically important signals The insulin is injected by a programmed Bionica MD-100 infusion pump into a forearm vein, and each insulin pulse achieves a peak venous "free" insulin of at least 200 μU/mL (Fig. 2). The pulses are given during the first hour of a three hour treatment with three consecutive treatments given each treatment day. Initial CIIIT consists of two consecutive treatment days, followed by weekly treatment days. RQ measurements, using a Sensormedic Metabolic Measurement Cart (Sensormedics, Anaheim, CA), are obtained before and throughout the treatment period at 60-min intervals. An increase in the RQ to greater

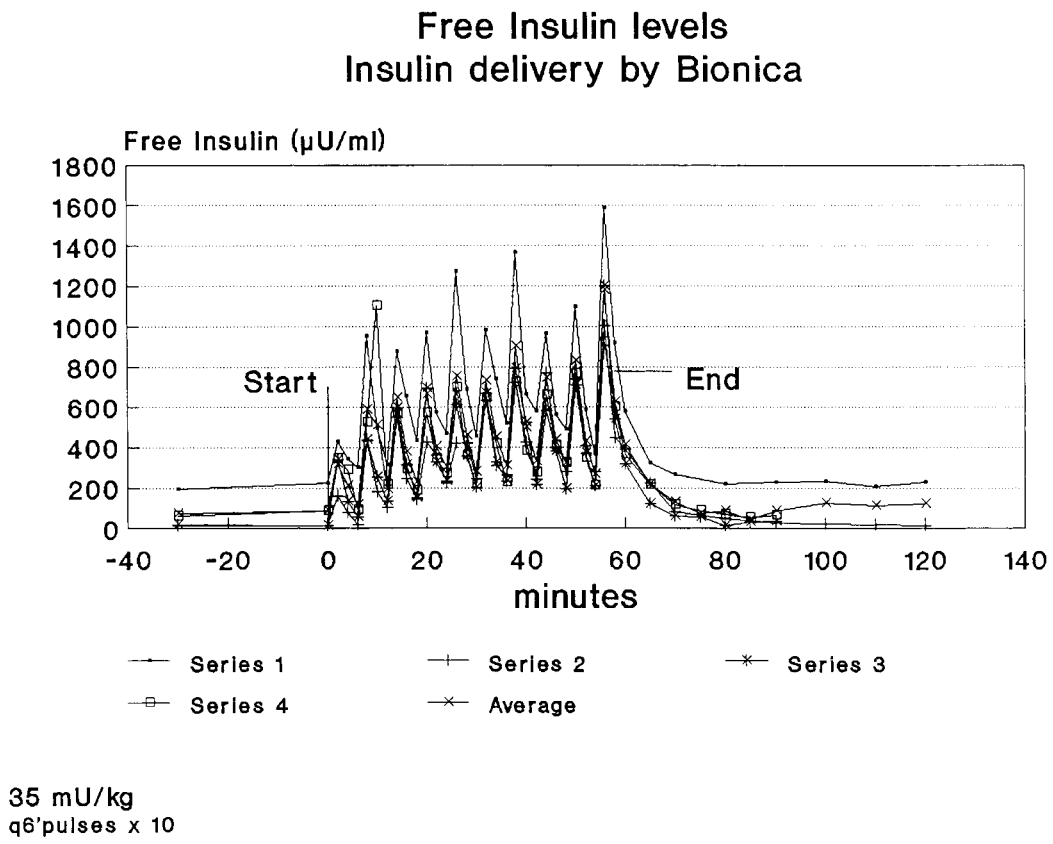

FIG. 2. Peripheral venous free insulin levels following intravenous insulin delivery by Bionica pump (35 mU/kg body weight, q6 min pulses × 10).

than 0.90 is used as the index of therapeutic efficacy.[21–23] It was postulated that if hepatic activation was achieved and maintained in patients with "brittle" IDDM by this treatment, the glycohemoglobin Alc (HbAlc) blood levels and the frequency of hypoglycemic reactions should decrease.

CLINICAL EFFECTS OF CIIIT IN DIABETES

CIIIT effect on glycemic control

In a study published in 1993,[30] the results of long-term CIIIT on 20 IDDM patients with "brittle" disease (wide swings in fingerstick blood glucose concentrations and frequent hypoglycemic episodes despite being on intensive subcutaneous insulin therapy [ISIT]—four daily insulin injection regimen—for at least 1 year) were reported. The patients received CIIIT for an average of 41 months. The major results of the study indicated:

(a) A significant decline in HbAlc from the baseline of 8.5% to 7.0% at the end of the observation period ($p < 0.0003$; Fig. 3)

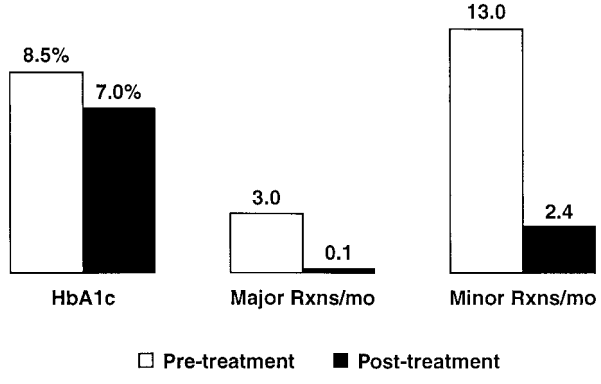

FIG. 3. Changes in HbAlc levels and incidence of major and minor hypoglycemic events with chronic intermittent intravenous insulin therapy. (Adapted from Aoki et al.[30])

(b) A decline in the frequency of major hypoglycemic events from 3.0 to 0.1/month ($p < 0.0001$)
(c) A decline in the frequency of minor hypoglycemic events from 13.0 to 2.4/month ($p < 0.0001$)

The last two effects are contrary to the results of Diabetes Control and Complication Trial (DCCT) where the improvement in HbAlc was accompanied by a threefold increase in the frequency of major hypoglycemic events.[31] In many of the study patients, a gradual improvement in awareness to impending hypoglycemia was noted which became apparent after 3–4 months of therapy and led to a marked decrease in the frequency of major hypoglycemic events. Furthermore, the patients reported increased energy level and required shorter daily periods of rest leading to increased productivity and quality of life. There was no significant change in the patients' body weight during the study.

The exact mechanism by which CIIIT lowered HbAlc blood levels and decreased the frequency of hypoglycemic events is yet to be determined. Nondiabetic individuals stimulate hepatic processes, by way of high portal-vein concentrations of insulin and glucose, with every meal. The study patients' livers were stimulated three times during 1 day of the week rather than three times daily as in nondiabetic individuals. The reason for the effectiveness of CIIIT may lie in the long half-life of glucokinase. The half-life of rat glucokinase is 3–4 days[11] and that of the human enzyme may be longer because of the lower rate of human metabolism.[30]

CIIIT effect on hypertension

Systemic hypertension is a frequent complication found in both IDDM and NIDDM patients and has proved to be an important risk factor for the development of microangiopathy[32] and macroangiopathy.[33] In IDDM, the prevalence of hypertension increases with the duration of the disease and develops mainly in connection with the clinical emergence of nephropathy.[34] There appears to be a positive correlation between plasma glucose elevation and systolic blood pressure (BP) raising the possibility that the metabolic disorders associated with diabetes are acting to either cause or amplify the concurrent BP problem.[35] Significant reductions in systolic and diastolic BP after improvement in metabolic control in diabetic subjects have been reported.[36] Conversely, in IDDM subjects studied during controlled insulin withdrawal,[37] the worsening of metabolic control was accompanied by BP increases. These reports suggest that tight metabolic control in diabetic subjects may provide beneficial effects on BP levels.[38] We have recently assessed the effects of CIIIT on BP control in a prospective, randomized, crossover clinical trial involving 26 IDDM subjects with hypertension and nephropathy.[39] After a stabilization period (ISIT for glycemic control and normalization of BP on medication), the study subjects were randomly assigned to control (ISIT) or treatment (ISIT + CIIIT) groups for 3 months and then crossed over into the opposite phase for another 3 months. Addition of weekly CIIIT during the treatment phase was the only procedural difference between the control and treatment phases. Throughout the control and treatment phases, the BP values were maintained at the level established in each subject at the end of the stabilization period through appropriate adjustment in the antihypertensive medication (AHM) dosage. The AHM dosage requirements decreased significantly (46%; $p < 0.0001$) and linearly over time ($p < 0.0058$) during the treatment phase while remaining essentially unchanged during the control phase (Fig. 4). This study indicates that CIIIT markedly improves BP control in subjects with IDDM and hypertension.

Increased vascular smooth muscle (VSM) tone is the hallmark of the hypertensive state in both IDDM and NIDDM.[40] Human and animal studies suggest a role for insulin in the regulation of VSM tone.[41–43] Such insulin regulation of VSM function may be lost in insulinopenic states. Recent evidence suggests that insulin causes endothelium-derived nitric oxide-dependent vasodilation and that insulin's vasodilating action serves to both amplify insulin's overall effect to stimulate skele-

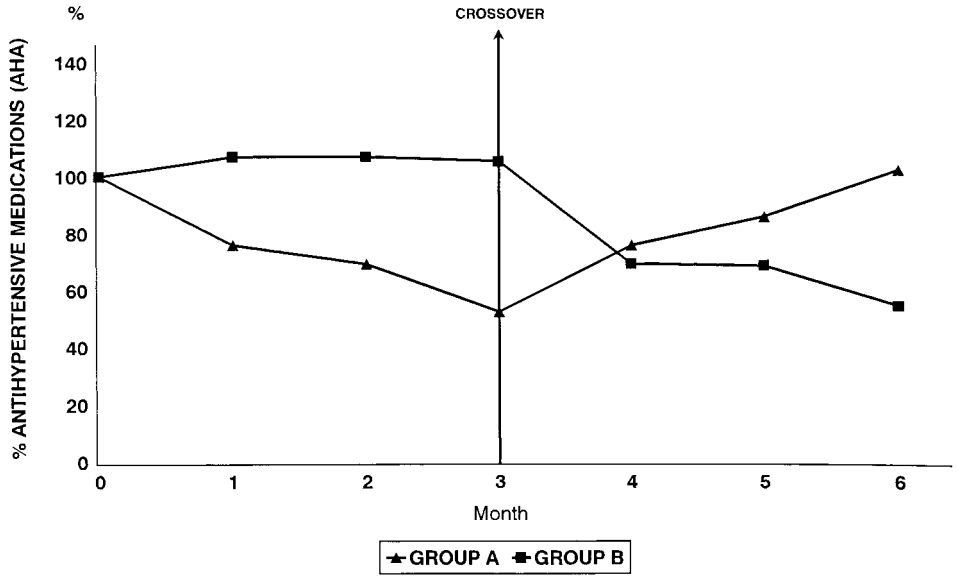

FIG. 4. Changes in antihypertensive medication requirements of patient groups A and B during the postrandomization period. (Adapted from Aoki et al.[39])

tal muscle glucose uptake and modulate vascular tone.[44] It is possible that CIIIT partially normalizes the "vascular reactivity," thus lowering the AHM dosage requirements.

CIIIT effect on diabetic nephropathy

Diabetic nephropathy (DN) develops in 35–40% of patients with IDDM,[45] and it is the most common cause of end-stage renal disease (ESRD) in the United States.[46] It is generally agreed that DN is the result of hyperglycemia, whether alone or in combination with other factors.[47,48] However, once nephropathy is clinically overt (macroalbuminuria, decreased glomerular filtration rate), the degree of metabolic control is believed to have lost its significance as a risk factor with other mechanisms having greater influence.[47] Until recently, there was no known therapeutic strategy able to stop or reverse the progression to ESDR.[45] Suggested conventional ways to slow the progression of DN are effective antihypertensive therapy[49] and reduced protein intake.[50]

Several studies have indicated no effect of tight glycemic control on the progression of overt nephropathy.[51,52] The effect of CIIIT on the progression of DN was evaluated in a multicenter, retrospective, longitudinal study, involving 31 patients with type 1 diabetes mellitus and overt DN, on intensive subcutaneous insulin therapy (ISIT) and weekly CIIIT.[53] All studied patients were followed weekly for at least 12 months (average 37 ± 4.6 months), and appropriate adjustments were made weekly in their insulin dosage (ISIT) and in their antihypertensive medication with the goal of maintaining optimum glycemic control and blood pressures at or below 140/90 mm Hg for each patient. All patients had monthly HbAlc (HPLC) and semiannual creatinine clearance (CrCl) determinations. The HbAlc levels declined from 8.64 ± 0.57% to 7.60 ± 0.3% (p = 0.0062) during the study period. The CrCl remained essentially unchanged (from 46.1 ± 2.19 mL/min at baseline, to 46.0 ± 3.9 mL/min at the end of the observation period, with an average annualized slope increase of 3.39 ± 1.5 mL/min/year (p = NS). This study suggests that addition of CIIIT to ISIT in patients with type 1 DM appears to arrest or markedly reduce the progression of overt diabetic nephropathy. Similarly favorable results with CIIIT added to ISIT were reported in a larger multicenter, prospective, controlled clinical trial in patients with type 1 DM and overt DN.[54]

The mechanism by which CIIIT reduces the deterioration rate of renal function in patients with overt DN remains to be established. In a recent study, McLennan et al.[48] have shown

that a high glucose concentration inhibits mesangium degradation and could promote the mesangium enlargement known to occur in DN. Enlargement of the mesangium, the most consistent morphological finding in DN, can compress the glomerular capillaries and thus alter intraglomerular hemodynamics.[55] Improved glycemic control, as obtained in the CIIIT treated subjects, could promote mesangium degradation and improve renal hemodynamics. Indeed, we already have evidence that CIIIT improves systemic hemodynamics,[39] and it is likely that it has a similar effect on renal hemodynamics (e.g., decrease in glomerular efferent arteriolar vasoconstriction) resulting in the noted decrease in the progression of DN towards ESRD. Several animal experiments have demonstrated that glomerular expression of transforming growth factor–β, the key mediator between hyperglycemia and mesangial cell stimulation toward overproduction of extracellular matrix, is stimulated by hyperglycemia and/or hypoinsulinemia.[56] Both hyperglycemia and hypoinsulinemia are improved through the CIIIT procedure.

CIIIT effect on diabetic autonomic neuropathy

Though clinical symptoms of diabetic autonomic neuropathy (DAN) develop in relatively few patients, the measurable autonomic defects are extremely common in diabetes.[57] DNA is known to be associated with a higher morbidity and mortality rate,[58] as well with elevated HbAlc levels.[59]

CIIIT effect on abnormal circadian blood pressure pattern. Several studies have demonstrated a blunted diurnal variation in blood pressure (BP) in patients with DAN.[60,61] Insufficient BP decline during the night might be associated with increased target organ damage.[62,63] No data are available regarding the effects of tight glycemic control or intensive insulin therapy on the abnormal circadian BP pattern in patients with IDDM. We have recently reported the results of a randomized controlled clinical study involving 74 IDDM patients on intensive subcutaneous insulin therapy (ISIT)[64] of which 36 (group A) underwent, in addition, weekly CIIIT for 3 months. Group B (controls, $n = 38$) continued on ISIT alone. All study patients were seen weekly by the investigators and underwent monthly HbAlc determinations and monthly 24-h ambulatory BP monitoring. Glycemic control improved significantly in group A subjects (HbAlc declined from 7.9% to 7.2%, $p = 0.0002$), but remained essentially unchanged in group B (control). The night/day systolic BP ratio decreased from 0.97 to 0.94 (−3.10%) in group A and increased from 0.95 to 0.98 (+3.16%) in group B subjects ($p = 0.0224$), while the night/day diastolic BP ratio decreased from 0.93 to 0.90 (−3.23%) in group A and increased from 0.91 to 0.94 (+3.29%) in group B subjects ($p = 0.0037$; Fig. 5). Consider-

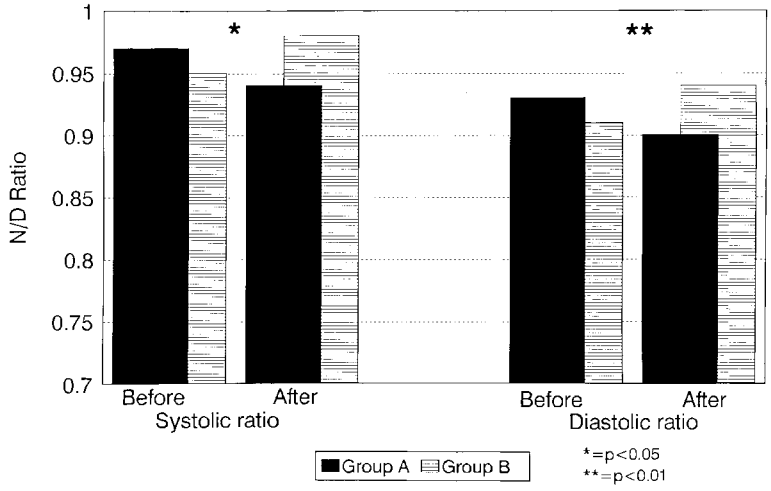

FIG. 5. Changes in mean night/day blood pressure ratio with CIIIT in groups A (treated) and B (control) patients. (Adapted from Aoki et al.[64])

ing that all other aspects of therapy were similar for the two patient groups, the further improvement in the glycemic control and the significant improvement in the abnormal circadian BP pattern noted in group A patients was likely due to the addition of weekly CIIIT. The cause of the abnormal circadian BP pattern is secondary to or associated with abnormal glucose metabolism and reduced arterial wall distensibility[65,66] as well as the development of diabetic autonomic neuropathy.[67] The improvement/stabilization of this abnormal circadian pattern obtained in the group A patients might be the result of an improved metabolic milieu as suggested by the decline in HbAlc, with possible consequent improvement in arterial distensibility and diabetic autonomic neuropathy. The practical importance and clinical consequences of the improvement in the circadian BP pattern is conjectural at present. Insufficient BP decline during the night might be associated with increased target organ damage.[62,63] The reversal or at least prevention of further deterioration of the abnormal circadian BP pattern obtained in the patient group treated with ISIT + CIIIT might lessen target organ damage. Further studies with extended follow-up are necessary to confirm this possibility.

CIIIT effect on orthostatic hypotension of diabetes. Orthostatic hypotension (OH) of diabetes, another likely manifestation of DAN,[68] is defined as a decrease in diastolic BP greater than 10 mm Hg[69] or decline of systolic BP greater than 30 mm Hg after 2 min of standing,[70] in the presence of adequate blood volume. Diabetic patients with OH have decreased ability to release norepinephrine, leading to low plasma norepinephrine levels and supersensitive α and β receptors.[71] Diabetic OH is likely due to impaired sympathetic vasoconstrictor activity, leading to an impaired compensatory increase in total peripheral resistance upon standing.[72] The current conventional therapy for orthostatic hypotension of diabetes is less than satisfactory.[73] Even the promising newer agents such as the somatostatin analogues, have a very limited duration of action and require frequent injections.[74]

We have recently reported[75] the correction of postural hypotension with CIIIT in three patients with IDDM and severe disabling postural hypotension who had previously failed all conventional therapeutic attempts. The patients underwent weekly CIIIT for 3 months while continuing their usual regimen of four daily subcutaneous insulin injections. Before and at the end of this therapeutic trial the patients had tilt-table tests, 24-h ambulatory BP measurements, cardiac autonomic function testing, and HbAlc determinations. Within the first month of CIIIT, a marked decrease in the intensity and frequency of postural dizziness was noted in all subjects, as well as the disappearance of syncopal episodes. After 2 months of CIIIT, the postural dizziness ceased entirely, and at the end of the third month of therapy, the subjects were able to resume their customary activities. The tilt-table test normalized in two and improved in one patient, HbAlc levels declined, the initial abnormal circadian BP pattern was corrected, and the score of the cardiovascular reflex tests also improved. These results suggest an improvement in the vasoconstrictor mechanisms in response to postural changes, possibly as a result of the improvement in diabetic autonomic neuropathy, as indicated by the normalization of the circadian blood pressure pattern and by the improved cardiovascular reflex score. The improvement in the autonomic neuropathy was likely secondary to the improved metabolic milieu during CIIIT as reflected by decreased HbAlc levels. The vascular endothelial cell secretion of the potent vasoconstrictor endothelin (ET1), has been shown to be enhanced by insulin in cultured cells.[76] An enhancement of endothelial cells' ET1 production following exposure to the high pulsatile insulin levels of CIIIT could have contributed to the improvement of the vasoconstrictor mechanism in our patients.

CONCLUSIONS

The studies briefly reviewed above indicate that CIIIT improves glycemic control, concomitantly with marked decrease in the frequency of both major and minor hypoglycemic events and improved hypoglycemia awareness,[30] improves control of hypertension in diabetes,[39] retards progression of overt nephropathy,[53,54] reverses

the abnormal circadian BP pattern,[64] and corrects postural hypotension of diabetes.[75]

Anecdotal clinical experiences suggest that CIIIT also improves diabetic peripheral polyneuropathy, diabetic cardiomyopathy,[77] diabetic retinopathy, and diabetic foot ulcer healing. Confirmation of these latter observations requires future larger, prospective clinical studies.

We believe that the above clinical outcomes with CIIT are due to weekly pulsatile insulin administration. As mentioned under the Rationale and Methodology sections, RQ normalization can also be achieved after several days of artificial beta cell–directed insulin administration (Biostator)[22] or, conceivably, after several days of a hyperinsulinemic euglycemic clamp procedure; however it is clearly impractical to perform weekly clamp procedures for extended period of time (years) and on a large scale. Furthermore, though we recognize that patients' enthusiasm and enhanced compliance might be a component of any research program's good results, the published results with CIIIT on improving glycemic control, decreased frequency of hypoglycemic events, and on chronic complications of diabetes (e.g., overt nephropathy), have been superior to intensive s.c. insulin therapy (multiple insulin injections or external insulin infusion pumps[31]).

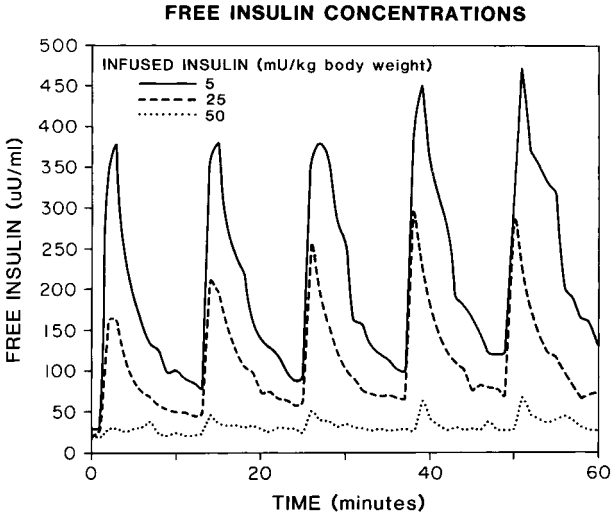

FIG. 6. Venous free insulin concentrations in 6 type 1 diabetic patients following 5, 25, and 50 milliunits of insulin per kg body weight pulses using the artificial pancreas (GCIIS).

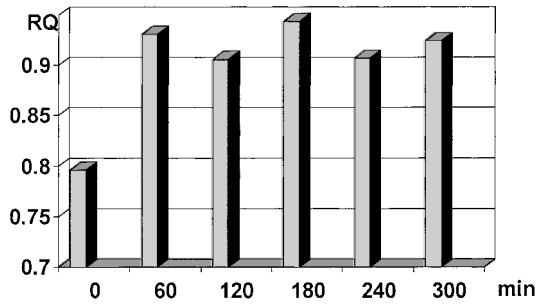

FIG. 7. Rapid increases in respiratory quotient (RQ) in 14 type 1 diabetic patients following the administration of insulin pulses using the Bionica MD-110 infusion pump during the first day of CIIIT.

HISTORICAL NOTE

Although the use of pulsatile insulin infusions in the treatment of diabetic patients, as opposed to square wave insulin infusions, had occurred to us in the 1970s, the need for such a waveform was not immediately apparent. During the course of our initial studies with the artificial pancreas (Biostator, Glucose Controlled Insulin Infusion System, Life Science Division, Ames, Elkhart, IN), which used a square wave infusion pattern, it quickly became apparent that a more efficient and powerful algorithm was needed. The GCIIS required 72 h to "activate" a type 1 diabetic patient and needed a great deal of "hands on" time. Could this period of enzyme induction be shortened?

The use of insulin pulses to stimulate hepatic metabolism was revisited. The liver appeared to respond to (1) the rate of change of insulin levels, (2) the peak insulin concentration, (3) a rising baseline (a pseudo second phase insulin release), and (4) the prompt return to baseline

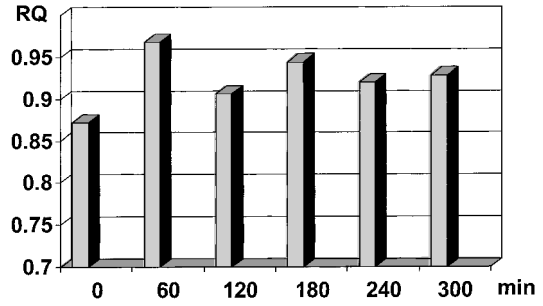

FIG. 8. Rapid increases in respiratory quotient (RQ) in six type 2 diabetic patients following the administration of insulin pulses using the Bionica MD-110 infusion pump during the first day of CIIIT.

insulin levels, that is, wide dynamic range. It was therefore decided to see if insulin pulses could more rapidly initiate the synthesis and activation of hepatic enzymes (e.g., hepatic glucokinase and pyruvate dehydrogenase complex respectively) with the biochemical outcome reflected by an increase in the respiratory quotient.

The artificial pancreas was first reversed engineered so that all of its functions could be controlled from the keyboard of an independent but linked Digital Equipment Company computer. Thus, insulin could be pulsed independent of the glucose levels, and glucose levels could be continuously monitored. In addition, the amounts of insulin and glucose infused could be quantified on a minute to minute basis.

The first question to be answered was whether the roller pumps used in the GCIIS could generate insulin pulses. Using this instrument, 5, 25, and 50 milliunits of insulin per kilogram body weight were successively infused into type 1 diabetic patients ($n = 6$) whose blood glucose levels were maintained at elevated levels with intermittent oral glucose administration. Arterial blood samples were withdrawn at 2-min intervals. As seen in Figure 6, even pulses of 5 milliunits of insulin/kg body weight could be identified and measured.

The next question to be answered was whether the insulin pulses generated by the reverse engineered GCIIS were physiologically and, hence, therapeutically more effective than square waves infusions of insulin. Using the respiratory quotient as the endpoint, studies were performed to determine if insulin pulses could accelerate the "activation" process in type 1 diabetic individuals, as reflected by rapid increases in the baseline respiratory quotient from 0.75 to values equal to or greater than 0.90. Fortunately, the answer was yes, and we quickly switched to simpler infusion pumps.

Initially, McGaw AccuPro pumps interfaced to an Epson laptop computer equipped with a floppy disc drive were used, but the BIONICA MD-110 pump subsequently replaced these. Using the latter pump, intravenous insulin pulses (Fig. 2) were administered to both type 1 and 2 diabetic patients concomitant with oral glucose ingestion, and the respiratory quotient responses monitored. In Figure 7, the increases in RQ during the first day of pulsatile intravenous insulin therapy in 14 type 1 diabetic patients new to the procedure are shown. In contrast to the modest RQ responses reported in type 1 diabetic patients after 24 h of GCIIS insulin administration,[22] marked increases in RQ to values consistently greater than 0.90 are seen within hours of initiating pulsatile intravenous insulin therapy. In Figure 8, prompt and marked increases in RQ during the first day of CIIIT in six type 2 diabetic patients are shown.

The implications of these observations were enormous. This procedure could be done efficiently, quickly, and relatively inexpensively on an outpatient basis for both patient care and research purposes. For these reasons, intravenous insulin pulses were used exclusively in all our studies, reviewed in this manuscript, from 1983 to the present.

ACKNOWLEDGMENTS

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