[2] Dailey GE, Boden GH, Creech RH, Johnson DG, Gleason RE, Kennedy FP, et al. Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. Metabolism 2000;49:1491-5.
[3] U.S. Department of Health & Human Services, Centers for Medicare & Medicaid Services: decision memo for outpatient intravenous insulin treatment (therapy) (CAG-00410N). Available at: http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?from2=viewdecisionmemo.asp&id=231&. [Accessed Jan 12, 2010].
[4] Aoki TT, Grecu EO, Arcangeli MA, Benbarka MM, Prescott P, Ahn JH. Chronic intermittent intravenous insulin therapy: a new frontier in diabetes therapy. Diabetes Technol Ther 2001;3:111-23.

What have trials of pulsatile intravenous insulin taught us?

To the Editor:

Dr Leinung expresses concern about a multicenter publication published a decade ago [1]. Recruitment began in 1992, at which time the Diabetes Control and Complications Trial and captopril studies had established that the preferred approach to therapy was multiple insulin injections plus angiotensin-converting enzyme (ACE) inhibitors. Baseline blood pressure and glycohemoglobin A_{1c} in this randomized study were not significantly different between study groups. Control vs pulsatile insulin infusion patients who were not treated with ACE inhibitors (9 of 34 controls, 17 of 37 infusions) had nearly identical slopes of creatinine clearance decline at −5.3 vs −5.2 mL/(min y) ($P = .98$) at 52 weeks and at −5.9 vs −5.5 mL/(min y) ($P = .91$) at 78 weeks. Control vs infusion patients treated with ACE inhibitors had slopes of −7.1 vs −0.96 at 52 weeks ($P = .11$) and −8.86 vs −0.60 at 78 weeks ($P = .016$). Thus, the infusion group with a lower percentage treated with ACE inhibition still had statistically significantly slower declines in creatinine clearance due to very different results in those treated with ACE inhibitors. As shown in the figure in that publication, there was no difference in the slope of the decline for patients in the original 52-week protocol vs those who elected to stay on for an additional 26 weeks. Dr Leinung refers to this as "dropout." We see this as electing not to continue after having completed one's agreed commitment.

Because ACE inhibition may have effects through both the angiotensin receptor signal (such as hyperkalemia) and extrareceptor pathways (such as the inflammation cascade) that might have a measurable impact on one individual and not another in a randomized population, we reviewed results at both extremes of loss of creatinine clearance. Ambulatory blood pressure recordings from 10 patients in both the control and the infusion groups with the highest slope of decline in creatinine clearance returned mean arterial pressures (MAPs) of 93.1 ± 2.3 mm Hg for controls vs 91.8 ± 2.0 mm Hg for the infusion group (P = not significant). The MAP results for 10 patients in the groups with the lowest slope of decline in creatinine clearance were 103.1 ± 3.0 mm Hg for controls vs 100.7 ± 3.0 mm Hg for infusion patients (P = not significant). Clearly, these associations questioned the concept that blood pressure alone controls renal function. One year after the final patient was enrolled at the Joslin Clinic, a study was published from the University of California at Davis: control and infusion patients who were studied in a crossover design, either by starting from control, proceeding to infusion, and back to control or by starting as infusion, moving to control, and back to infusion, were found to require significantly less antihypertensive medication during the infusion phases [2].

From observations on preservation of renal function in relationship to blood pressure control, we can summarize:

1. Pulsatile insulin infusion was associated with lower blood pressure in short-term observations.
2. Pulsatile insulin infusion had an added effect on preservation of renal function when ACE inhibition was used and did not have an added effect in the absence of ACE inhibition.
3. Level of blood pressure may not be the most important factor in preservation of renal function in type 1 diabetes mellitus patients with nephropathy treated with insulin and antihypertensive medications.

Dr Leinung claims our hypothesis to be that glycemic control is better with pulsatile insulin infusion than with multiple daily insulin doses alone. However, in the article criticized [3], we stated our hypothesis to be quite different from that related to insulin delivery systems and glycemia control. We analyzed potential roles of cardiac autonomic and hemostatic function in progression of renal disease among patients using 2 different methods of insulin delivery. Dr Leinung states that the statistically nonsignificant difference in baseline blood pressures favors the infusion group. In this connection, factors that were also not significantly different between infusion and controls, but "favored" the control group, included plasma fibrinogen, factor VII, fibrinolytic activity, as well as both platelet adhesion and aggregation. None of these test results were different to a statistically significant degree between groups during the course of the study; this was also the case for day/night MAP and autonomic function. Our hypothesis that autonomic and prothrombotic factors may have provided an explanation for renal function differences could not be confirmed in this small pilot study [3]. Dr. Leinung correctly identifies a typographical error in Table 1 regarding edema.

In prior studies from our group, we noted that improvement in glycohemoglobin and advanced glycemic end-products was associated with significant decreases in left ventricular mass and septal thickness despite similar blood pressures when compared with patients whose A_{1c} rose over 1 year [4]. We have also recorded statistically significant improvement in cardiac parasympathetic function [5] when glycohemoglobin improved as well as in plasma fibrinogen and factor VII [6] when advanced glycated end-product concentrations fell significantly. Dr Leinung also questions the benefits of pulsatile insulin infusion on glycemia, in that the control group glycohemoglobin A_{1c}

in the smaller study [3] was (not statistically significantly) lower than the treatment group at 52 weeks. We have recently demonstrated that higher mean and lower glycohemoglobin oscillations may be associated with stabilization of diabetic retinopathy [7]. Thus, the issue that requires further study may not be relatively minor subgroup glycohemoglobin differences, but rather variations in metabolism.

Respiratory quotient studies were performed to monitor the effect of insulin infusion procedures on an hourly basis. Inadequate delivery of glucose/insulin to the liver results in respiratory quotient levels in the lower range (0.8 or less), whereas excessive glucose/insulin could potentially result in levels greater than 1.0 [8]. An increase to 0.9 indicates generation of adenosine triphosphate as oxidation of fatty acid is replaced by oxidation of glucose when the message delivered by sufficient insulin reaches the relevant mitochondria. Renal interstitial pathology is responsible for the majority of functional loss once a glomerular pathologic process has begun. Unlike the renal cortex, the medulla is totally dependent upon glucose as fuel and has a limited capacity to increase generation of adenosine triphosphate under stress. Because, at the time of the multicenter study [1], it was unprecedented to demonstrate preservation of creatinine clearance over 18 months in more than 50% of individuals among type 1 diabetes mellitus patients with azotemic nephropathy, any metabolic information related to the capacity of the impaired kidney to sustain function stimulated our interest [3].

Fortunately, in the multicenter study, use of multiple daily insulin injections and ACE inhibitors resulted in a marked improvement in preservation of renal function when compared with treatment of the prior decade, that is, approximately 15-mL/(min y) loss of creatinine clearance in the captopril study era vs approximately 7.5-mL/min loss in our controls. It is not surprising that prolongation of the duration of the study was necessary to show the impact of the insulin infusion due to overall improved outcome. Of 90 patients, 71 completed a full year (dropouts were due to withdrawal of one center and patient-related issues such as change in work schedule, domicile, or injury/illness complicating compliance). All 71 patients completing the original 52-week protocol were offered the opportunity to continue for another 26 weeks. Patients willing to continue to give up a full day per week from work remained in the study until the 78th week. It is surprising that as many as 69% of the available study subjects did so. Many were disappointed that the study ended because they experienced neurologic improvement [9].

Neither we nor our collaborating institutions continued to offer pulsatile intravenous insulin infusion therapy after this partially supported trial (the promised grant support was not delivered because of bankruptcies). Economic circumstances make it unlikely that further research in this field will receive funding. We believe that thoughtful analysis of data collected in the only multicenter study ever performed on this subject is important especially in the light of anticipated huge outlays for renal replacement therapy (expected duration of remaining renal function: 5-6 years for the control group, 16-22 years for those treated).

Our studies focused on the physiologic importance of the metabolic pathways controlling type 1 diabetes mellitus microvascular complications. Whether insulin delivery systems or medications are involved, additional studies of the role of the metabolism in renal functional preservation appear warranted. Further controlled trials of therapies capable of delivering the insulin signal to mitochondria appear more likely to be of benefit than trials of therapies that attempt to alter autonomic function or hemostasis [3].

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References

[1] Dailey G, Boden G, Creech R, Johnson D, Gleason RE, Kennedy FP, Weinrauch LA, Weir M, D'Elia J. Effects of pulsatile intravenous insulin therapy (PIVIT) on the progression of diabetic nephropathy. Metabolism 2000;49:1491-9.

[2] Aoki T, Grecu E, Prendergast J, Arcangeli M, Meisenheimer R. Effect of chronic intravenous insulin therapy on antihypertensive medication requirements in IDDM subjects with hypertension and nephropathy. Diabetes Care 1995;18:1260-5.

[3] Weinrauch LA, Burger AJ, Aepfelbacher F, Lee AT, Gleason RE, D'Elia JA. A pilot study to test the effect of pulsatile insulin infusion on cardiovascular mechanisms that might contribute to attenuation of renal compromise in type 1 diabetic patients with proteinuria. Metabolism 2007;56:1453-7.

[4] Aepfelbacher F, Yeon SB, Weinrauch LA, D'Elia J, Burger AJ. Effect of improved glycemic control on left ventricular structure and function in patients with type 1 diabetes mellitus. Int J Cardiol 2004;94:47-54.

[5] Burger A, Weinrauch LA, D'Elia JA, Aronson D. Effect of glycemic control on heart rate variability in type 1 diabetic patients with cardiac autonomic neuropathy. Am J Cardiol 1999;84:687-91.

[6] D'Elia JA, Weinrauch LA, Gleason RE, Lipinska I, Pendse S, Roshan B, Lee AT, Tofler G. Fibrinogen and factor VII levels improve with glycemic control in type 1 diabetic patients with microvascular complications. Arch Intern Med 2001;61:98-101.

[7] Weinrauch LA, Sun J, Gleason RE, Boden GH, Creech RH, Dailey G, Kennedy FP, Weir MR, D'Elia JA. Progression of retinopathy in type 1 diabetic patients with nephropathy: impact of glycemia control as measured by glycohemoglobin A_{1c}. J Am Soc Nephrol 2009;20 [Abstract. Renal Week].

[8] Aoki TT, Vlachokosta FV, Foss MC, Meistas MT. Evidence for restoration of hepatic glucose processing in type I diabetes mellitus. J Clin Invest 1983;71:837-9.

[9] Weinrauch LA, Bayliss G, Gleason RE, Lee AT, D'Elia JA. Utilization of an abbreviated Diabetes Impact Management Scale to assess change in subjective disability during a trial of pulsatile insulin delivery demonstrates benefit. Metabolism 2009;58:488-91.