The Case for Intravenous Arginine Stimulation In Lieu of Mixed-Meal Tolerance Tests as Outcome Measure for Intervention Studies in Recent-Onset Type 1 Diabetes

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Residual β-cell function in patients with type 1 diabetes has been generally determined by C-peptide response to stimulation by a liquid mixed-meal tolerance test (MMTT) or intravenous glucagon (1). Early trials assessed benefits of therapy by frequency and duration of the clinical remission phase in which minimal or no exogenous insulin was needed to maintain euglycemia (reviewed in 2). What is now needed is the most sensitive, and not necessarily the most physiologic measure, so that any improvement in β-cell function during a clinical trial can be detected. Both the MMTT and the intravenous glucagon test have practical limitations. The MMTT takes 2–4 h to complete, and the stimulus is subject to variations in gastrointestinal absorption, while the intravenous glucagon test often invokes nausea.

In contrast, the use of intravenous arginine to stimulate and measure β-cell secretion takes only a few minutes to perform, circumvents gastrointestinal variation, and is clinically well tolerated. In addition, responses to this nonglucose secretagogue have been demonstrated to persist after the diagnosis of diabetes at a time when responses to glucose are gone (3–6). Our goal was to determine whether arginine-stimulated C-peptide could be used in lieu of MMTT as an outcome measure for intervention studies in recent-onset type 1 diabetes.

RESEARCH DESIGN AND METHODS

— Institutional review board approval and informed consent were obtained before the study began. Nineteen subjects between 7–42 and 1–24 months postdiagnosis of type 1 diabetes came to the Clinical Research Center after an overnight fast. Morning insulin was withheld. Subjects on insulin pumps continued their basal rate until the start of the test. Tests were not performed if fasting glucose was ≤4.0 or ≥11 mmol/l. Subjects underwent paired MMTT (baseline samples, oral Boost [6 mg/kg to maximum of 360 ml], samples at 30, 60, 90, and 120 min) and arginine testing (baseline samples, intravenous arginine [0.07 mg/kg to maximum of 5 g], samples at 2, 3, 5, 7, and 10 min) on separate days within 4 weeks of each other.

RESULTS

— There was no difference in basal C-peptide (1.0 ± 0.3 nmol/l for MMTT and 1.1 ± 0.3 nmol/l for arginine [mean ± SE]) or glucose (7.3 ± 0.6 mmol/l for MMTT and 7.7 ± 0.4 mmol/l for arginine) values. Likewise, there was no difference in mean or peak C-peptide values between MMTT and arginine-stimulated tests. There was a strong relationship between C-peptide values obtained from MMTT and arginine-stimulated tests whether assessed by mean ($r = 0.96$), peak ($r = 0.95$), or area under the curve ($r = 0.95$) calculations. In addition, a strong relationship between basal and stimulated C-peptide values was observed for both MMTT and arginine.

Glucose values poststimulation were markedly higher in the MMTT (peak 14.8 ± 0.9 mmol/l for MMTT and 7.9 ± 0.4 mmol/l for arginine). There was no relationship between basal glucose values and stimulated C-peptide results for arginine, whereas a weak relationship was seen for MMTT ($r = -0.31$ between basal glucose and mean C-peptide). A strong inverse relationship between time to peak on MMTT and arginine-stimulated C-peptide responses was seen (Fig. 1).

CONCLUSIONS

— This study demonstrates that C-peptide stimulation with an intravenous arginine bolus in recently diagnosed patients with type 1 diabetes provides a similar measure of residual β-cell function to that of MMTT. In addition, the arginine test is easier to perform and better tolerated since it requires only a short time and does not result in hyperglycemia.

This study also demonstrates no impact of basal glucose level on C-peptide values poststimulation during arginine treatment. Investigators have often noted that one characteristic of mildly abnormal β-cell function is an apparent delay in the peak of C-peptide secretion to oral stimulation whether by oral glucose or a liquid mixed meal. We observed a strong inverse relationship between time to peak on MMTT and C-peptide responses to arginine. These data suggest that the amplitude of C-peptide response to arginine can be used in place of a time delay to peak value on MMTT.

Our data also provide somewhat reassuring information about the reproduc-

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Abbreviations: MMTT, mixed-meal tolerance test.

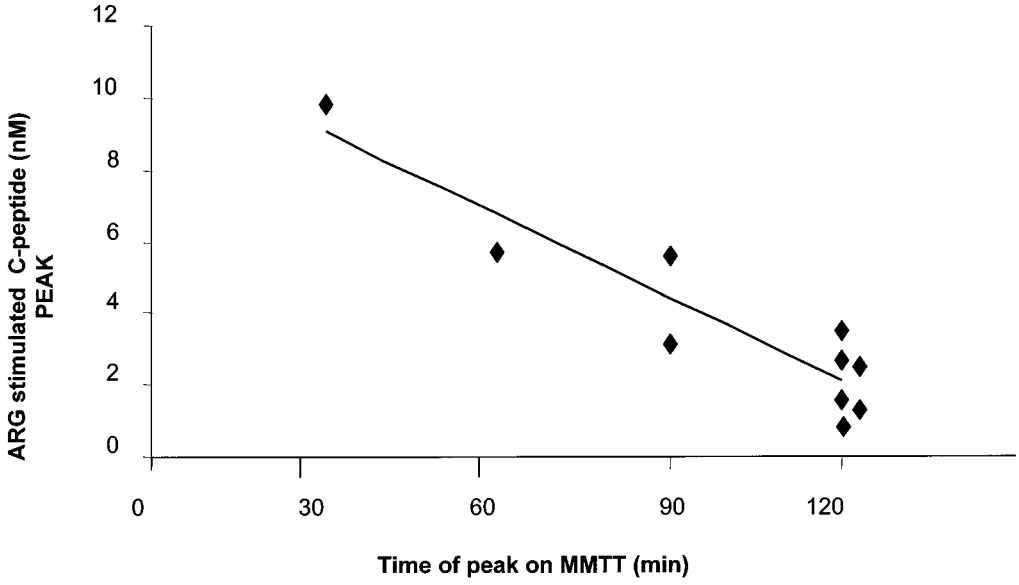

Figure 1—*Relationship between time to peak C-peptide value on MMTT and arginine (ARG)-stimulated peak C-peptide responses* (r = −0.93) (n = 10).

ibility of β-cell function testing. There was remarkable concordance in results between β-cell function tests performed up to 4 weeks apart. In addition, the mean percentage difference between C-peptide values obtained poststimulation with arginine compared with MMTT was ~12%, which was about the same as the mean difference in the basal C-peptide levels obtained on different days and is similar to reproducibility noted for other measures of β-cell function (7).

The choice of what measure to use to assess β-cell function depends on the question. The MMTT was originally developed to mimic the activity of the β-cell under real-life conditions (in response to a meal with multiple dietary components). However, a goal of current clinical trials in subjects newly diagnosed with type 1 diabetes is to determine whether intervention therapies have any effect on β-cell function. Such a test should have minimal impact on participants and should provide a reproducible and sensitive measure of the health of the β-cell. The arginine test clearly meets these requirements. Several investigations have suggested that the β-cell response to arginine correlates with β-cell mass. Ryan et al. (8) have recently reported a close relationship between the number of islet equivalents transplanted and the insulin response to intravenous arginine. Similarly, changes in the glucose-potentiated arginine response have been shown to correlate with islet mass in a baboon model of diabetes (9). Several studies have now shown that responses to arginine correlate with clinical status (i.e., remission), whether tested during a clinical trial (10) or natural history studies (5,11–15).

In conclusion, the arginine-stimulated test provides similar data as the MMTT, prevents hyperglycemia, and is better tolerated by subjects than the MMTT. Thus, this test should be considered as an alternative end point in clinical trials aimed at preserving β-cell function.

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