

# Higher Glycemic Thresholds for Symptoms During $\beta$ -Adrenergic Blockade in IDDM

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**We tested the hypotheses that nonselective  $\beta$ -adrenergic blockade does not cause absolute hypoglycemia unawareness but shifts the glycemic thresholds for symptoms to lower plasma glucose concentrations and that neither neuroglycopenic symptoms nor cognitive impairments during hypoglycemia are altered by  $\beta$ -adrenergic blockade. To do so, we applied the euglycemic and stepped hypoglycemic clamp techniques to patients with moderately controlled insulin-dependent diabetes mellitus (IDDM) in the absence ( $n = 8$ ) and presence ( $n = 9$ ) of the nonselective  $\beta$ -adrenergic antagonist propranolol. Compared with the corresponding euglycemic clamps, total symptom scores first increased at the 4.4-mM plasma glucose step (a higher level than that of 2.8 mM in nondiabetic subjects studied previously) in the absence of propranolol.  $\beta$ -Adrenergic blockade did not produce absolute hypoglycemia unawareness. Indeed, at the frankly hypoglycemic step of 2.8 mM, total symptom scores tended to be higher in the presence than in the absence of propranolol. This was largely the result of greater ( $P < 0.01$ ) perception of diaphoresis. However, symptom scores did not increase until the 3.3-mM plasma glucose step during  $\beta$ -adrenergic blockade. The perception of hunger, and perhaps that of tremulousness, was reduced by propranolol at the higher glucose steps. Neuroglycopenic symptoms were not reduced by propranolol. The cognitive function of memory, but not that of attention, was impaired, also starting at the 4.4-mM glucose step. This was not impaired further by propranolol. Thus, we formed the following conclusions. 1) Nonselective**

**$\beta$ -adrenergic blockade does not cause absolute hypoglycemia unawareness but shifts the glycemic thresholds for symptoms to lower plasma glucose concentrations in patients with IDDM. 2)  $\beta$ -Adrenergic blockade does not reduce neuroglycopenic symptoms, and it does not further impair cognitive function during hypoglycemia in IDDM patients. *Diabetes* 40:1177–86, 1991**

**T**he  $\beta$ -adrenergic antagonists are effective drugs in the treatment of hypertension and ischemic heart disease among other disorders. However, administration of this class of drugs to patients with insulin-dependent diabetes mellitus (IDDM) has been criticized because the drugs might increase the frequency or severity of iatrogenic hypoglycemia (1–4). Compelling clinical evidence to support this possibility is lacking (5), but this issue has not, to our knowledge, been examined critically in the setting of intensive therapy of IDDM, in which hypoglycemia is particularly common (6).

$\beta$ -Adrenergic antagonists might increase hypoglycemia in IDDM through at least two mechanisms. First, there is considerable evidence that  $\beta$ -adrenergic antagonism impairs glucose recovery from experimental hypoglycemia in patients with IDDM (1,7–9). This effect is best attributed to blockade of the glycemic actions of epinephrine in the context of deficient glucagon secretory responses to hypoglycemia, which are the rule in patients with IDDM (reviewed in ref. 6). Second, it is widely suspected that  $\beta$ -adrenergic antagonists might mask the symptoms of developing hypoglycemia, i.e., produce hypoglycemia unawareness, although objective support for this concern is quite limited (10,11). Indeed, in a systematic study of six nondiabetic individuals, Cameron (11) found no evidence that the nonselective  $\beta$ -adrenergic antagonist propranolol prevented overall awareness of insulin-induced hypoglycemia (with plasma glucose nadirs of 2.4–2.9 mM). Similarly, Kerr et al. (12) found that neither propranolol nor the relatively selective

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$\beta_1$ -adrenergic antagonists metoprolol or atenolol reduced symptoms or overall awareness of hypoglycemia (2.5 mM plasma glucose) in nondiabetic humans.

The physiological mechanisms by which an individual normally recognizes (i.e., becomes aware of) developing hypoglycemia have not been fully defined. It is generally thought that the warning symptoms such as sweating, tremulousness, anxiety and palpitations, and perhaps hunger are the result of an autonomic discharge triggered by falling plasma glucose levels. Therefore, these are often termed *neurogenic* or *autonomic* symptoms (6). Although a role for neuroglycopenia per se or neuroglycopenic symptoms in the perception of hypoglycemia cannot be excluded, neurogenic, specifically sympathochromaffin, mediation is implicated by the observation that such warning symptoms do not occur during hypoglycemia in patients with cervical spinal cord transections (13). This does not mean that all of the symptoms are adrenergic, i.e., mediated by adrenomedullary epinephrine or sympathetic neural norepinephrine. The diaphoretic response, often a prominent symptom and sign of hypoglycemia, is prevented by prior atropine administration (14) but not by prior propranolol administration (15). It is often attributed to an effect of activation of cholinergic sympathetic postganglionic neurons. Indeed, the diaphoretic response to hypoglycemia is known to be increased rather than decreased during  $\beta$ -adrenergic blockade (12,15). Therefore, it is reasonable to anticipate that an intense non-adrenergic symptom such as sweating would permit awareness of frank hypoglycemia despite blockade of adrenergic symptoms. However, because of the involvement of adrenergic symptoms in the recognition of developing hypoglycemia, lower plasma glucose levels might be required before awareness of hypoglycemia develops during  $\beta$ -adrenergic blockade.

Based on these considerations, we hypothesized that  $\beta$ -adrenergic blockade does not cause absolute hypoglycemia unawareness but shifts the glycemic thresholds for symptoms to lower plasma glucose concentrations in patients with IDDM. We further hypothesized that neither neuroglycopenic symptoms nor cognitive impairments during hypoglycemia are altered by  $\beta$ -adrenergic blockade. To test these hypotheses, we used the stepped hypoglycemic clamp technique (16,17) along with euglycemic comparison studies to assess symptomatic, cognitive, and neuroendocrine responses to hypoglycemia in the presence and absence of nonselective  $\beta$ -adrenergic blockade produced with intravenous propranolol in IDDM patients.

## RESEARCH DESIGN AND METHODS

Nine patients with IDDM gave their written consent to participate in the four parts of this study, which was approved by the Washington University Human Studies Committee and performed at the Washington University General Clinical Research Center (GCRC). The four parts, performed in random sequence, included euglycemic and stepped hypoglycemic clamps in the absence and presence of propranolol infusion. Because one patient did not complete the study, the numbers of subjects were nine in both parts with propranolol infusion and eight in both parts without propranolol infusion. The subjects' clinical characteristics were as follows: mean  $\pm$  SD age  $24.3 \pm 4.2$  yr, duration of IDDM  $12.9 \pm 6.2$

yr, body mass index  $22.9 \pm 2.8$  kg/m<sup>2</sup>, daily insulin dose  $0.72 \pm 0.14$  U  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup>, and glycosylated hemoglobin  $9.2 \pm 1.2\%$  (normal  $<6.3\%$ ). Exclusions included a history of clinical hypoglycemia unawareness, seizures and contraindications to propranolol administration such as asthma; clinically overt autonomic neuropathy, proliferative retinopathy, and nephropathy as evidenced by proteinuria  $>1$  g/24 h or a serum creatinine level  $>130$   $\mu$ M; and hypertension, known coronary artery disease, and anemia (hematocrit  $<34\%$ ).

Stepped hypoglycemic and euglycemic control clamp techniques were used, as detailed elsewhere (16,17). Long-acting insulin therapy was discontinued 96 h before study; intermediate-acting insulin therapy was discontinued 24 h before study. Glycemia was managed with subcutaneous regular insulin until admission to the GCRC on the evening before study. Euglycemia was then maintained overnight with a modification of a published intravenous regular insulin algorithm (18). Starting at  $\sim 0700$  on the day of study, one of the four study parts was initiated. These included a hyperinsulinemic ( $2$  mU  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> regular human insulin [Humulin, Lilly, Indianapolis, IN]), euglycemic ( $5$  mM glucose) or stepped hypoglycemic ( $5, 4.4, 4.9, 3.3$ , and  $2.8$  mM glucose at 1-h intervals) clamp without or with infusion of propranolol (Inderal, Ayerst, New York) in a dose of  $1.4$   $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> (after a priming dose of  $143$   $\mu$ g/kg) started at  $-30$  min. Insulin infusions were begun at  $-60$  to  $-90$  min. Variable glucose infusions were used to establish stable plasma glucose levels of  $\sim 5$  mM. That time point was then designated  $-30$  min, and propranolol or saline infusion was begun. Infusions were continued through 300 min. Heart rate and blood pressure (Dynamap, Critikon, Tampa, FL) were monitored at 30-min intervals. Arterialized venous samples (from an indwelling needle in a hand vein with the hand kept in a box heated to  $\sim 65$ – $75^\circ\text{C}$ ) for glucose were drawn at at least 10-min intervals; those for hormones and substrates/intermediates other than glucose were drawn at 60-min intervals.

Symptom scores were determined at 15-min intervals throughout all four parts of the study (17,18). The subjects scored 12 symptoms from 1 (absent) to 7 (severe). These included 6 neurogenic symptoms (feeling sweaty, feeling shaky, nervousness, heart pounding, tingling, and being hungry), 5 neuroglycopenic symptoms (difficulty thinking, blurred vision, feeling dizzy, and feeling tired and faint), and 1 nonspecific symptom (feeling different in any way).

Cognitive function was assessed at baseline and over 15 min at the end (i.e., between 45 and 60 min) of each of the five glycemic steps (including the corresponding time points during the euglycemic control studies). Five measures focusing primarily on the cognitive domains of memory and attention were assessed. These included 1) immediate paragraph recall, 2) delayed paragraph recall, 3) serial addition, 4) vigilance, and 5) line orientation.

Paragraph recall was used as a measure of memory. To assess immediate and delayed paragraph recall, subjects heard a brief narrative containing  $\sim 25$  informational bits and were asked to recall as many details as possible immediately and after a 15-min delay (the remaining cognitive tests were conducted during the delay). Twenty paragraphs of approximately equal length were constructed based on pro-

cedures established for the Wechsler Memory Scale—Revised Logical Memory Subtest (19). This is a validated measure of declarative memory, as defined by Squire (20) and others as memory for events and information that is conscious in nature and does not involve a motor component. Subjects were given credit for each bit correctly recalled. Pilot testing with 45 nondiabetic subjects established intertest correlations ( $r = 0.91$ ) between the Logical Memory Subtest and the paragraph recall task used in this study.

Serial addition and vigilance tests were used to measure attention. For the serial addition test, subjects heard a digit from 1 to 10 followed by a series of 10 ones and twos. At the end of the digit string, they were asked to produce the sum of the numbers. Five series were presented, each containing two strings of digits. In series 1–5, digits were presented at 4-, 3-, 2-, 1.5- and 1-s intervals, respectively. The number of errors was recorded. This task measured subjects' ability to mentally manipulate numbers and required both simple attention and mental control over short durations (21). For the vigilance task, subjects heard a random series of letters at 1-s intervals. They were required to identify the letters of the alphabet in sequence at the first occurrence of each letter. Frank omissions, false positives, and late signals (those occurring 2 letters after the target letter) were scored as errors. This task measured the ability to sustain attention for prolonged periods (22).

For the Benton line orientation (23), subjects were presented with a template consisting of 11 radiating lines of differing orientations arranged in the shape of a half-wheel. Each line was numbered. Test items appeared below the template and consisted of segments of 2 of these lines without numbers. The subjects' task was to visually match the line segments to the corresponding lines on the template by identifying the appropriate numbers. Five test items were presented in each of the five cognitive testing sessions. Error scores were calculated as the number of incorrectly identified lines. This task measured integrity of the visuoperceptual processes and had only minimal attentional demands. It was included to determine whether disruption noted on other tests was the result of a gross global disturbance in cognitive function or whether such disruption could be attributed to more specific attentional or memory impairments.

The paragraph recall and line orientation tests were administered by a research nurse masked to the glycemic (hypoglycemic or euglycemic) and drug (propranolol or saline) status of the patient. The serial addition and vigilance tests were administered with prerecorded materials.

Plasma glucose was measured with a glucose oxidase method on a Beckman glucose analyzer; the intra-assay coefficient of variation (C.V.) was 1.1%. Plasma free insulin (24), glucagon (25), growth hormone (26), cortisol (27), and pancreatic polypeptide (28) concentrations were measured with radioimmunoassays, and epinephrine and norepinephrine were measured with a single-isotope-derivative (radioenzymatic) method (29). The intra-assay and interassay C.V.s, respectively, were 9.8 and 11.3% for insulin, 8.3 and 10.4% for glucagon, 8.6 and 12.1% for growth hormone, 8.9 and 12.1% for cortisol, 7.7 and 12.9% for pancreatic polypeptide, 11.1 and 14.3% for epinephrine, and 3.3 and 5.2% for norepinephrine. Serum nonesterified fatty acids (NEFAs) were measured with an enzymatic colorimetric method (30);

blood  $\beta$ -hydroxybutyrate (31) and lactate (32) were measured with microfluorometric techniques.

Except where the SD is specified, data are presented as means  $\pm$  SE. For each parameter, an SAS repeated-measures program was used to compare the values from the hypoglycemic clamps with those from the same time point in the corresponding euglycemic clamps, i.e., hypoglycemic clamp data were contrasted with euglycemic clamp data in the absence of propranolol and again in the presence of propranolol. Data across all four experimental conditions at time points corresponding to each glycemic step were compared by analysis of variance, with Duncan's test used to identify specific differences.

## RESULTS

Target plasma glucose concentrations were achieved during the euglycemic and hypoglycemic clamps both without and with propranolol infusion (Fig. 1).

Heart rate and blood pressure data are shown in Fig. 2. Mean resting heart rates of  $73 \pm 2$  and  $69 \pm 3$  beats/min (bpm) in the absence of propranolol were reduced ( $P < 0.02$ ) to  $65 \pm 3$  and  $63 \pm 2$  bpm during propranolol infusions. Heart rates increased from  $69 \pm 3$  to  $92 \pm 4$  bpm during hypoglycemia in the absence of propranolol ( $P < 0.001$ ) but were unchanged during hypoglycemia in the presence of propranolol. Similarly, resting systolic blood pressures of  $118 \pm 4$  and  $120 \pm 5$  mmHg tended to be reduced to  $112 \pm 5$  and  $109 \pm 3$  mmHg during propranolol infusions. Systolic blood pressures increased from  $120 \pm 5$  to  $138 \pm 6$  mmHg during hypoglycemia in the absence of propranolol ( $P < 0.0002$ ) but were unchanged during hypoglycemia in the presence of propranolol. These data provide hemody-

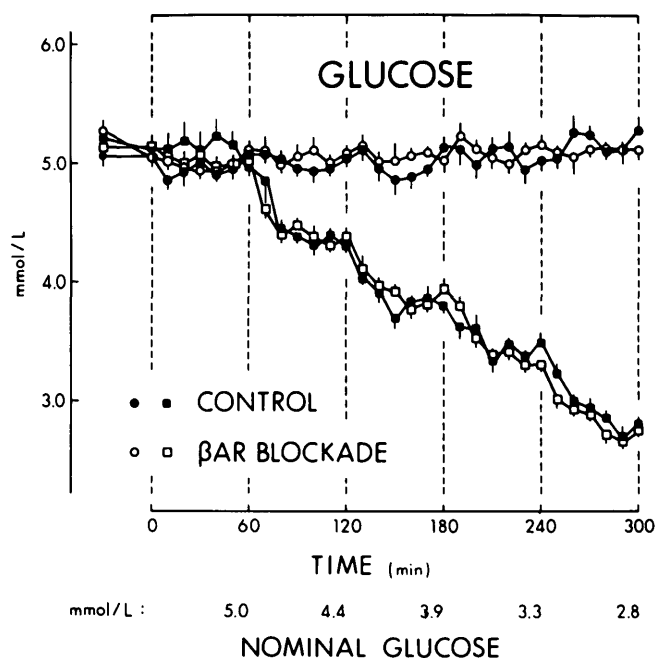


FIG. 1. Mean  $\pm$  SE plasma glucose concentrations during euglycemic and stepped hypoglycemic clamps in control studies and during  $\beta$ -adrenergic-receptor ( $\beta$ AR) blockade in patients with insulin-dependent diabetes mellitus. Nominal plasma glucose concentrations during both stepped hypoglycemic clamps are shown below.

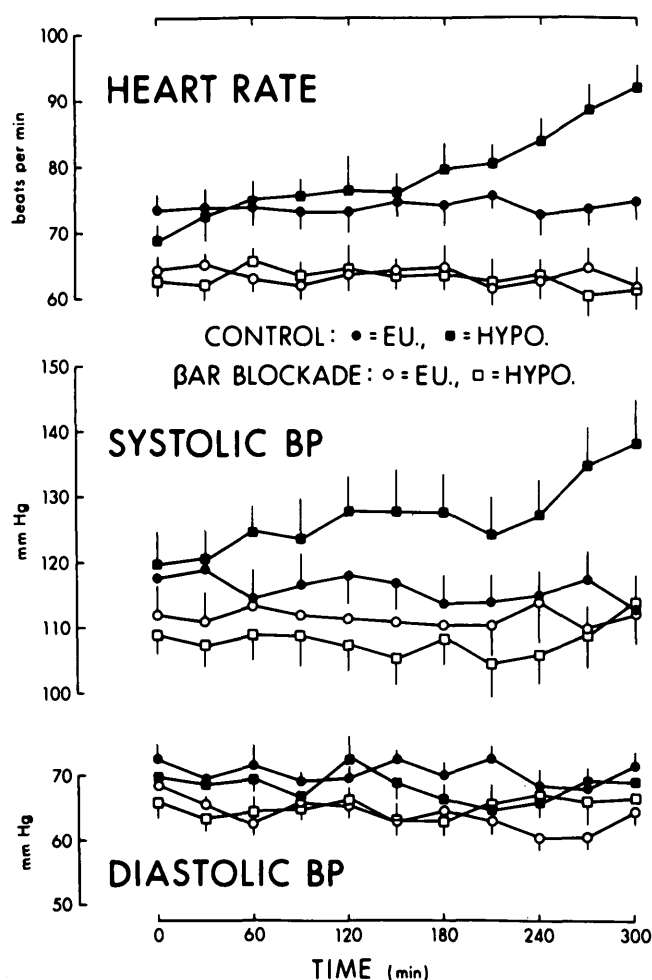


FIG. 2. Mean  $\pm$  SE heart rates and systolic and diastolic blood pressures (BP) during euglycemic (EU) and stepped hypoglycemic (HYPO) clamps in control studies and during  $\beta$ -adrenergic-receptor ( $\beta$ AR) blockade in patients with insulin-dependent diabetes mellitus. Resting heart rates were reduced ( $P < 0.02$ ), and increases in heart rate ( $P < 0.001$ ) and systolic blood pressure ( $P < 0.002$ ) during hypoglycemia were prevented during  $\beta$ -adrenergic blockade.

namic evidence of effective  $\beta$ -adrenergic blockade during the propranolol infusions.

Plasma insulin, glucagon, pancreatic polypeptide, and norepinephrine concentrations are given in Fig. 3. Mean plasma insulin concentrations were raised approximately sixfold and remained constant throughout all four parts of the study. As expected in patients with established IDDM, there was no glucagon response to hypoglycemia; mean plasma glucagon concentrations were comparable throughout. Pancreatic polypeptide levels in the absence and presence of propranolol differed significantly ( $P < 0.05$  and  $P < 0.02$ , respectively) from the corresponding euglycemic clamp values only at the lowest (2.8-mM) glucose step.

Plasma epinephrine, growth hormone, and cortisol concentrations are shown in Fig. 4. Mean plasma epinephrine concentrations were unchanged throughout both euglycemic clamps. In the absence of propranolol in the hypoglycemic clamp study, plasma epinephrine concentrations significantly exceeded the corresponding euglycemic clamp values at the 4.4-mM glucose step. As expected, because of the effect of propranolol to reduce the clearance of cate-

cholamines from the circulation (33,34), the plasma epinephrine response to hypoglycemia was exaggerated ( $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.01$  at the 3.9-, 3.3-, and 2.8-mM glucose steps, respectively) during  $\beta$ -adrenergic blockade. Mean plasma growth hormone concentrations, unchanged during the euglycemic clamps, increased during both hypoglycemic clamps. The levels first exceeded the corresponding euglycemic values at the 3.9-mM glucose step. Mean plasma cortisol concentrations tended to decline during both euglycemic clamps and rose ( $P < 0.01$ ) late in the hypoglycemic clamps but were unaffected by propranolol.

Mean serum NEFA concentrations were suppressed during hyperinsulinemia in all four parts of the study and did not rise above baseline during hypoglycemia (Table 1). Mean  $\beta$ -hydroxybutyrate levels were comparable throughout all parts of the study (Table 2). Mean blood lactate concentrations were also comparable except at the final (2.8-mM) glucose step in the hypoglycemic clamps when the levels were higher ( $P < 0.01$ ) in the absence ( $1600 \pm 146 \mu\text{M}$ ) than in the presence ( $1050 \pm 67 \mu\text{M}$ ) of propranolol (Table

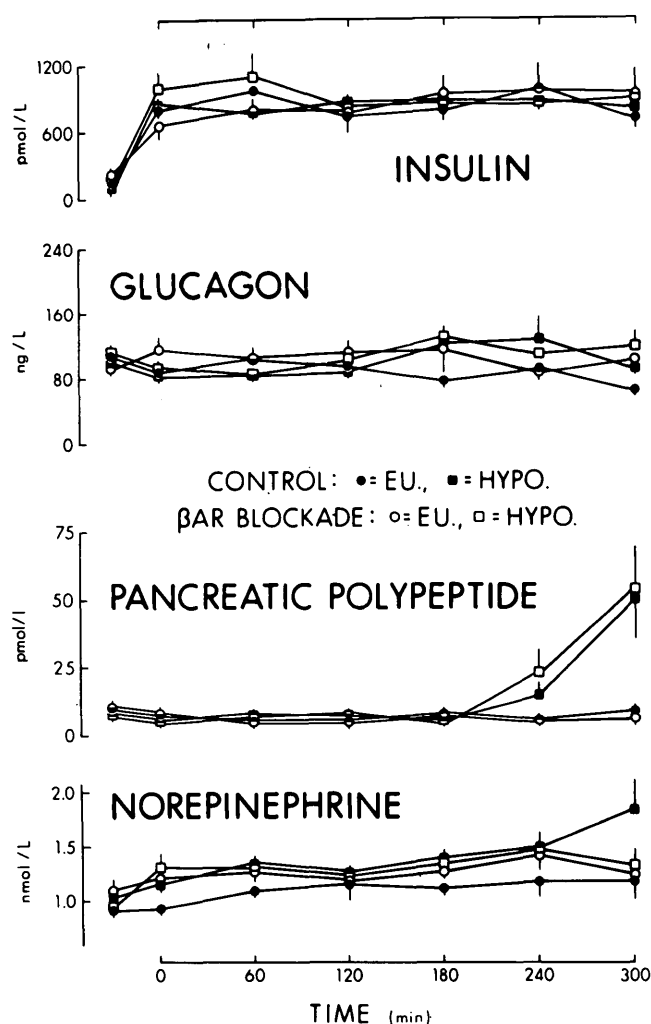


FIG. 3. Mean  $\pm$  SE plasma free insulin, glucagon, pancreatic polypeptide, and norepinephrine concentrations during euglycemic (EU) and stepped hypoglycemic (HYPO) clamps in control studies and during  $\beta$ -adrenergic-receptor ( $\beta$ AR) blockade in patients with insulin-dependent diabetes mellitus. Pancreatic polypeptide levels were increased by hypoglycemia (2.8 mM) in absence ( $P < 0.05$ ) and presence ( $P < 0.02$ ) of  $\beta$ -adrenergic blockade.

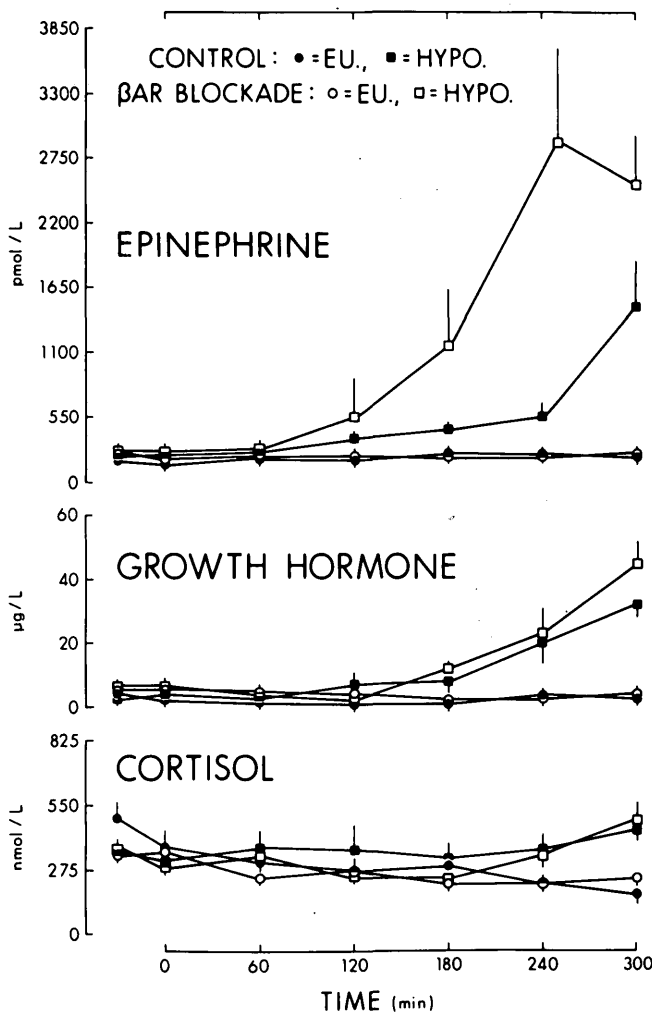


FIG. 4. Mean  $\pm$  SE plasma epinephrine, growth hormone, and cortisol concentrations during euglycemic (EU) and stepped hypoglycemic (HYPO) clamps in control studies and during  $\beta$ -adrenergic-receptor ( $\beta$ AR) blockade in patients with insulin-dependent diabetes mellitus. Epinephrine levels were first significantly increased at 120 min (4.4 mM plasma glucose) by hypoglycemia and were higher ( $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.01$ ) in presence of  $\beta$ -adrenergic blockade from 130 through 300 min. Growth hormone levels were first increased at 180 min (3.9 mM plasma glucose) by hypoglycemia, and cortisol levels were first increased at 240 min (3.3 mM plasma glucose).

3). Lactate levels during hypoglycemia were significantly higher than those in the corresponding euglycemic clamps only at that step.

TABLE 1  
Mean  $\pm$  SE serum nonesterified fatty acid concentrations

Nominal glucose hypoglycemic clamps (mM)	Control		$\beta$ -Adrenergic blockade	
	Euglycemic clamps	Hypoglycemic clamps	Euglycemic clamps	Hypoglycemic clamps
Baseline	142 $\pm$ 16	153 $\pm$ 28	195 $\pm$ 33	211 $\pm$ 31
Step 1:5.0	95 $\pm$ 18	85 $\pm$ 9	86 $\pm$ 14	78 $\pm$ 8
Step 2:4.4	85 $\pm$ 6	76 $\pm$ 7	77 $\pm$ 10	76 $\pm$ 8
Step 3:3.9	80 $\pm$ 7	76 $\pm$ 9	77 $\pm$ 5	73 $\pm$ 6
Step 4:3.3	75 $\pm$ 9	84 $\pm$ 9	76 $\pm$ 6	90 $\pm$ 9
Step 5:2.8	67 $\pm$ 10	102 $\pm$ 11	74 $\pm$ 10	68 $\pm$ 8

Nonesterified fatty acid concentrations ( $\mu$ M) were measured at baseline and at the end of each 60-min glycemic step during euglycemic and stepped hypoglycemic clamps without (control) and with  $\beta$ -adrenergic blockade with propranolol.

Mean total symptom scores are shown in Fig. 5. These did not differ among the four parts of the study at baseline. Thus, propranolol did not affect the symptoms assessed before hypoglycemia. As noted previously, symptom scores tended to drift upward over time during both euglycemic clamp studies (16,17). In the absence of propranolol, total symptom scores during the stepped hypoglycemic clamp part of the study first increased significantly above those in the corresponding euglycemic clamp part at the 4.4-mM glucose step. They remained elevated through the remaining glucose steps. In sharp contrast, during propranolol infusion, total symptom scores first rose above euglycemic values at the 3.3-mM glucose step and continued to increase through the 2.8-mM step. Thus, total symptom scores were significantly reduced by propranolol at plasma glucose concentrations of 4.4 and 3.9 mM. They were unchanged by propranolol at a plasma glucose concentration of 3.3 mM and tended to be increased by propranolol at a plasma glucose concentration of 2.8 mM.

Individual symptoms are illustrated in Figs. 6 and 7. Among the neurogenic symptoms, the most striking effect of propranolol administration during hypoglycemia was an increased score for feeling sweaty at the 2.8-mM step ( $3.8 \pm 0.8$  vs.  $1.5 \pm 0.3$ ,  $P < 0.01$ ) (Fig. 6). The score for being hungry was decreased ( $1.7 \pm 0.2$  vs.  $3.0 \pm 0.6$ ,  $P < 0.05$ ) at the 4.4-mM glucose step but not at the lower glucose steps.

Cognitive function data are shown in Fig. 8. Hypoglycemia per se, to a level of 2.8 mM plasma glucose, impaired memory but not attention and did not produce global disruption of cognitive function. Regarding memory, compared with the euglycemic comparison study during the stepped hypoglycemic clamp study (no propranolol), immediate paragraph recall was first impaired at the 3.9-mM glucose step ( $70 \pm 3$  vs.  $38 \pm 5\%$  of bits recalled,  $P < 0.001$ ) and remained significantly impaired at the lower glucose steps ( $63 \pm 5$  vs.  $40 \pm 4\%$  of bits recalled at the 3.3-mM glucose step,  $P < 0.01$ ; and  $52 \pm 2$  vs.  $40 \pm 8\%$  of bits recalled at the 2.8-mM glucose step,  $P < 0.05$ ). Delayed paragraph recall was perhaps more clearly impaired at the same glucose steps ( $56 \pm 4$  vs.  $36 \pm 6\%$ ,  $P < 0.02$ ;  $52 \pm 5$  vs.  $28 \pm 6\%$ ,  $P < 0.001$ ; and  $47 \pm 3$  vs.  $23 \pm 8\%$ ,  $P < 0.02$  bits recalled, respectively; Fig. 8). Regarding attention, neither the serial addition nor the vigilance tests were altered significantly by hypoglycemia at the levels tested, although the number of errors in the latter tended to increase somewhat at the

TABLE 2  
Mean ± SE blood β-hydroxybutyrate concentrations

Nominal glucose hypoglycemic clamps (mM)	Control		β-Adrenergic blockade	
	Euglycemic clamps	Hypoglycemic clamps	Euglycemic clamps	Hypoglycemic clamps
Baseline	74 ± 5	68 ± 10	75 ± 9	65 ± 8
Step 1:5.0	58 ± 7	50 ± 7	52 ± 6	47 ± 6
Step 2:4.4	61 ± 8	58 ± 14	55 ± 6	58 ± 12
Step 3:3.9	55 ± 8	46 ± 5	72 ± 8	56 ± 5
Step 4:3.3	57 ± 9	43 ± 5	51 ± 6	62 ± 10
Step 5:2.8	54 ± 9	58 ± 4	65 ± 12	62 ± 9

Blood β-hydroxybutyrate concentrations (μM) were measured at baseline and at the end of each 60-min glycemic step during euglycemic and stepped hypoglycemic clamps without (control) and with β-adrenergic blockade with propranolol.

2.8-mM glucose step (Fig. 8). Similarly, regarding global cognitive dysfunction, the number of line orientation errors was not affected by hypoglycemia, although again, the number tended to increase somewhat at the 2.8-mM glucose step.

Propranolol administration did not alter any of the cognitive functions tested at baseline (Fig. 8). In addition, it did not impair memory during hypoglycemia to a glucose level of 2.8 mM. If anything, it preserved memory, because, in contrast to the data in the absence of propranolol, the scores for both immediate and delayed paragraph recall were not significantly lower than corresponding euglycemic scores at the 3.9-mM and 3.3-mM glucose steps (or, for delayed recall, at the 2.8-mM step) during propranolol administration. The drug did appear to reduce attention during hypoglycemia at the 2.8-mM glucose step—the numbers of errors on both the serial addition ( $P < 0.01$ ) and vigilance ( $P < 0.02$ ) tests were higher than the corresponding euglycemic values—but not at the higher glucose steps. Similarly, the number of errors in line orientation were higher ( $P < 0.04$ ) only at the 2.8-mM step.

## DISCUSSION

These data indicate that nonselective β-adrenergic blockade with propranolol does not cause absolute hypoglycemia unawareness in patients with IDDM. This supports the findings of Cameron (11) and of Kerr et al. (12) in nondiabetic subjects. Indeed, at the frankly hypoglycemic plasma glucose concentration of 2.8 mM, total symptom scores tended to

be higher, rather than lower, in the presence of β-adrenergic blockade in our patients. This was largely the result of a substantially greater perception of the diaphoretic response to hypoglycemia, probably because the diaphoretic response was enhanced (12,15). The perception of palpitations also appeared to be increased during β-adrenergic blockade. None of the other neurogenic symptoms (tremulousness, anxiety, paresthesias, or hunger) or the nonspecific symptom (feeling different in any way) were increased significantly; none of the neuroglycopenic symptoms were increased significantly, with the possible exceptions of dizziness and faintness.

The finding, during stepped hypoglycemic compared with euglycemic clamps (in the absence of propranolol administration), that mean symptom scores increased at the 4.4-mM plasma glucose step in these patients with IDDM, whereas nondiabetic subjects would have symptoms only at the 2.8-mM glucose step (16), supports the previous findings of Boyle et al. (17) and Amiel et al. (35). Indeed, these data extend previous findings in that this phenomenon was demonstrable in patients with moderate glycemic control, as evidenced by a mean glycosylated hemoglobin level of 9.2% as well as in those selected for poor glycemic control (17). Thus, the data from this study and others (16,17,35) indicate that patients with IDDM with less than ideal metabolic control can suffer symptoms of hypoglycemia as plasma glucose falls at higher plasma glucose concentrations than nondiabetic individuals or patients with very-well-controlled IDDM (35).

TABLE 3  
Mean ± SE blood lactate concentrations

Nominal glucose hypoglycemic clamps (mM)	Control		β-Adrenergic blockade	
	Euglycemic clamps	Hypoglycemic clamps	Euglycemic clamps	Hypoglycemic clamps
Baseline	837 ± 54	960 ± 91	980 ± 48	970 ± 60
Step 1:5.0	1090 ± 65	1140 ± 74	1140 ± 65	1160 ± 41
Step 2:4.4	1190 ± 62	1210 ± 85	1260 ± 105	1160 ± 43
Step 3:3.9	1220 ± 71	1220 ± 77	1240 ± 97	1040 ± 46
Step 4:3.3	1140 ± 57	1270 ± 73	1200 ± 100	1150 ± 97
Step 5:2.8	1200 ± 74	1600 ± 146	1140 ± 96	1050 ± 67*

Blood lactate concentrations (μM) were measured at baseline and at the end of each 60-min glycemic step during euglycemic and stepped hypoglycemic clamps without (control) and with β-adrenergic blockade with propranolol.

\* $P < 0.01$  vs. hypoglycemic clamp control.

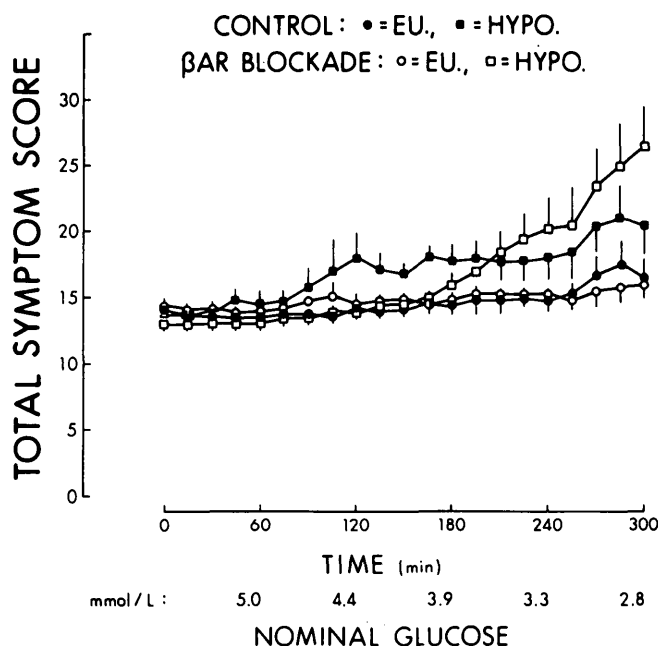


FIG. 5. Mean  $\pm$  SE total symptom scores during euglycemic (EU) and stepped hypoglycemic (HYPO) clamps in control studies and during  $\beta$ -adrenergic-receptor ( $\beta$ AR) blockade in patients with insulin-dependent diabetes mellitus. Nominal plasma glucose concentrations during both stepped hypoglycemic clamps are shown below. Note that lowest possible score (no symptoms) is 12. Scores were first significantly increased at 120 min (4.4 mM plasma glucose) by hypoglycemia in control study and at 240 min (3.3 mM plasma glucose) during  $\beta$ -adrenergic blockade.

These data indicate further that, although it does not produce absolute unawareness of hypoglycemia,  $\beta$ -adrenergic blockade shifts the glycemic thresholds for symptoms of hypoglycemia to lower plasma glucose concentrations in patients with IDDM. Compared with the corresponding eu-

glycemic clamp studies, total symptom scores increased at the 4.4-mM plasma glucose step in the absence of  $\beta$ -adrenergic blockade but not until the 3.3-mM plasma glucose step during  $\beta$ -adrenergic blockade with propranolol. The basis of this, from inspection of individual symptoms, is not entirely clear. Perception of the neurogenic symptom of hunger was reduced significantly and that of tremulousness also appeared to be reduced by propranolol at the higher plasma glucose steps, but none of the other neurogenic, neuroglycopenic, or nonspecific symptoms were reduced. In this context, the perception of hunger warrants comment. We have classified hunger as a neurogenic symptom because it apparently does not occur during hypoglycemia in patients with cervical spinal cord transactions (13). In our clinical experience, it is a common symptom of developing hypoglycemia and is frequently lost in patients with IDDM who develop clinical hypoglycemia unawareness.

Clearly, the finding that  $\beta$ -adrenergic blockade shifts the glycemic thresholds for symptoms to lower plasma glucose concentrations is potentially quite relevant to patients with IDDM. By delaying awareness of hypoglycemia until falling plasma glucose levels approach those that result in severe clinical hypoglycemia (6), administration of a  $\beta$ -adrenergic antagonist could result in increased frequency and/or severity of this sometimes devastating complication of insulin treatment. This reasoning assumes, plausibly in our view, that glycemic thresholds for symptoms are altered during long-term oral administration of a  $\beta$ -adrenergic antagonist, as shown here with short-term intravenous propranolol administration.

Compared with testing during euglycemic clamps, the cognitive domain of memory was impaired during hypoglycemia (in the absence of  $\beta$ -adrenergic blockade) as expected (36–40). Immediate and particularly delayed paragraph recall decreased progressively starting at the 3.9-

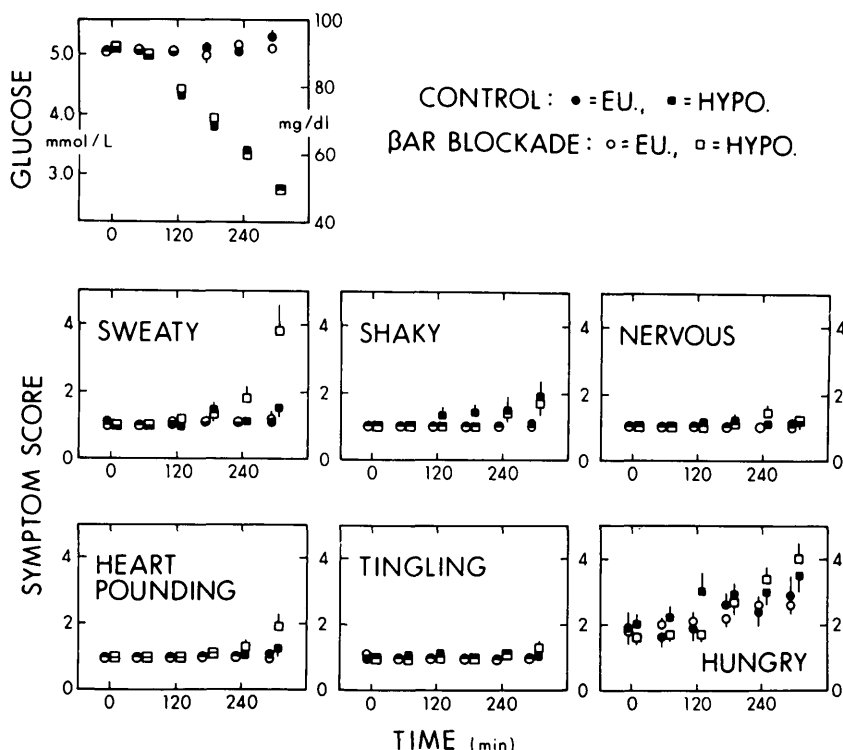


FIG. 6. Mean  $\pm$  SE individual neurogenic symptoms during euglycemic (EU) and stepped hypoglycemic (HYPO) clamps in control studies and during  $\beta$ -adrenergic-receptor ( $\beta$ AR) blockade in patients with insulin-dependent diabetes mellitus. In hypoglycemia parts of study, score for sweaty was increased ( $P < 0.01$ ) at 300 min (2.8 mM plasma glucose) and that for hungry was reduced ( $P < 0.05$ ) at 120 min (4.4 mM plasma glucose) during  $\beta$ -adrenergic blockade.

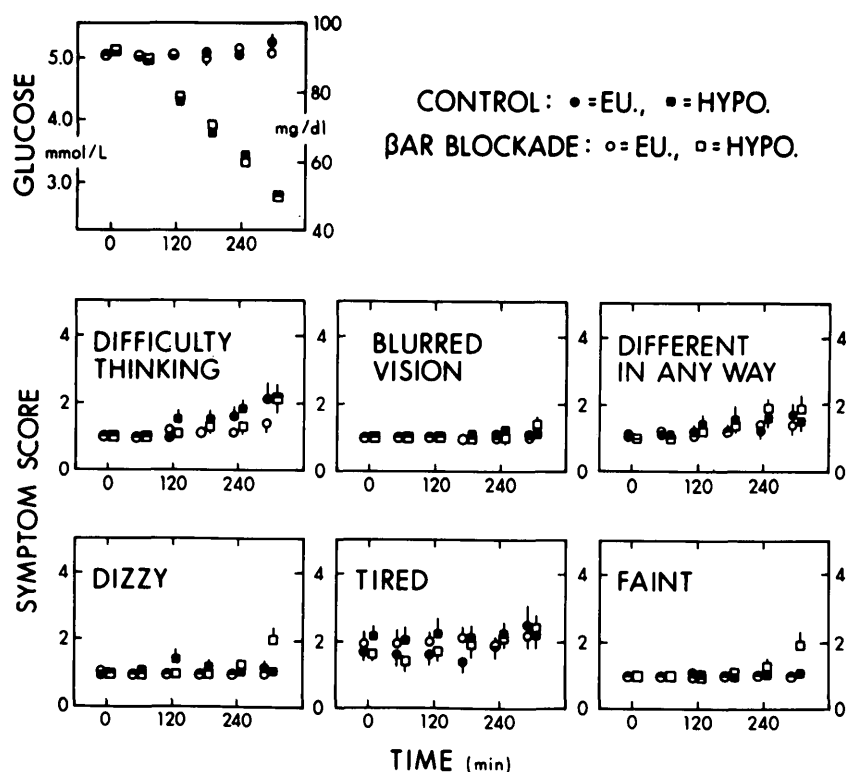


FIG. 7. Mean  $\pm$  SE individual neuroglycopenic and nonspecific (different in any way) symptoms during euglycemic (EU) and stepped hypoglycemic (HYPO) clamps in control studies and during  $\beta$ -adrenergic-receptor ( $\beta$ AR) blockade in patients with insulin-dependent diabetes mellitus. There were no significant effects of  $\beta$ -adrenergic blockade.

mM glucose step in these patients with IDDM. Glycemic thresholds for cognitive dysfunction have been reported to be between 3.3 and 2.6 mM (41), at  $\sim$ 3 mM (42), and at  $\sim$ 2.7 mM (43) in nondiabetic humans. Thus, this finding provides further evidence that the glycemic thresholds for neuroglycopenic and neurogenic manifestations of hypoglycemia are at higher plasma glucose concentrations in patients with IDDM that is not well controlled than in nondiabetic individuals (17). In contrast, attention, as measured by the serial addition and vigilance tests, was not clearly impaired during hypoglycemia, and there was no evidence of global cognitive dysfunction as measured by the line orientation test.

Notably,  $\beta$ -adrenergic blockade did not further impair memory during hypoglycemia. Indeed, we could suggest that propranolol preserved memory because hypoglycemia-associated impairments of both immediate and delayed paragraph recall demonstrated in the absence of propranolol were not demonstrated during propranolol administration at the 3.9- or 3.3-mM glucose steps or for delayed recall at the 2.8-mM step. It is tempting to associate this with the higher plasma epinephrine concentrations during hypoglycemia under that condition because there is evidence that peripheral epinephrine elevations enhance memory storage in animals (44). However, we would have to postulate an effect of epinephrine on the brain through receptors not blocked by propranolol and at sites in which epinephrine penetrates from the circulation into the brain or postulate an indirect effect of the hormone to invoke this explanation. The number of errors on the serial addition, vigilance, and line orientation tests was greater than euglycemic values in the presence of propranolol, but only at the 2.8-mM glucose step. Similar

differences were not observed in the absence of propranolol, although the trends were in the same direction for the vigilance and line orientation tests. Therefore, we would interpret this apparent effect of propranolol to impair attention and more global cognitive function during more pronounced hypoglycemia cautiously.

The neuroendocrine responses to hypoglycemia and the effects of  $\beta$ -adrenergic blockade on these responses were generally as anticipated.  $\beta$ -Adrenergic blockade had no effect on the absent plasma glucagon or the undoubtedly attenuated plasma pancreatic polypeptide responses in these IDDM patients (45). Plasma epinephrine concentrations rose to considerably higher levels during hypoglycemia in the presence of  $\beta$ -adrenergic blockade. This has been a consistent finding, which is best attributed to the effect of propranolol to reduce clearance of catecholamines from the circulation (33,34) in our experience. The plasma growth hormone response to hypoglycemia appeared to be enhanced at the final glucose step during propranolol administration. This was probably the result of an increased secretory response to hypoglycemia during  $\beta$ -adrenergic blockade (46). The cortisol response was not affected. NEFA and  $\beta$ -hydroxybutyrate levels were suppressed under these hyperinsulinemic conditions as expected. The NEFA and lactate responses to frank hypoglycemia (2.8 mM plasma glucose) appeared to be prevented by  $\beta$ -adrenergic blockade, but only the latter were statistically significant.

On the basis of these data in the context of other available information, we conclude that nonselective  $\beta$ -adrenergic blockade does not cause absolute hypoglycemia unawareness but shifts the glycemic thresholds for symptoms to lower plasma glucose concentrations in patients with IDDM. Fur-



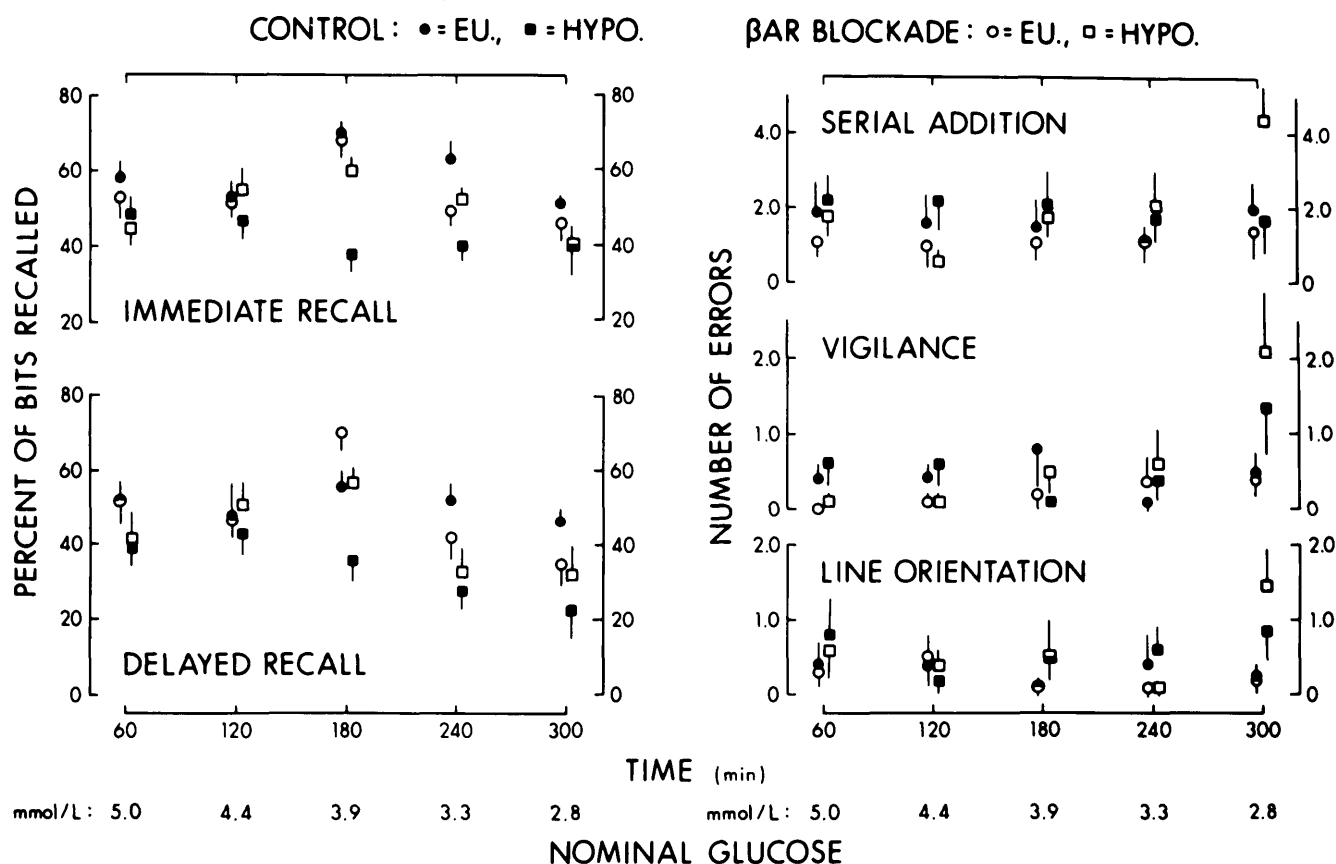


FIG. 8. Mean  $\pm$  SE cognitive function test scores during euglycemic (EU) and stepped hypoglycemic (HYPO) clamps in control studies and during  $\beta$ -adrenergic-receptor ( $\beta$ AR) blockade in patients with insulin-dependent diabetes mellitus. Immediate and delayed paragraph recall was first impaired by hypoglycemia at 3.9-mM glucose step ( $P < 0.001$ ,  $P < 0.01$ , and  $P < 0.05$  at 3.9-, 3.3-, and 2.8-mM glucose steps, respectively, for immediate recall and  $P < 0.02$ ,  $P < 0.001$ , and  $P < 0.02$  at same steps, respectively, for delayed recall) in control study. These were not further impaired during  $\beta$ -adrenergic blockade. Numbers of serial addition ( $P < 0.01$ ) and vigilance ( $P < 0.02$ ) errors were higher at 2.8-mM glucose step during  $\beta$ -adrenergic blockade.

thermore,  $\beta$ -adrenergic blockade does not reduce neuroglycopenic symptoms, and it does not further impair cognitive function during hypoglycemia in such patients.

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