technique we applied is not without risk for these patients. We observed induction of cardiac arrhythmia (single extrasystolic beat) in one patient (no. 5) without known coronary artery disease but decreased beat-to-beat variation. For routine studies, balloon stimulation (7,9), a less-invasive and probably more physiologically stimulating technique, may be more appropriate for the investigation of afferent pathways from the gut to the brain in diabetes mellitus.

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Effect of Antihypertensive Drugs on Insulin Absorption

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Objective: To examine the effects of antihypertensive drugs on the absorption of subcutaneously injected insulin. Research Design and Methods: Eleven healthy volunteers (group 1) were given 1 mg/kg body wt propranolol three times a day during 48 h and a single dose on the morning of investigation. Seven other healthy volunteers (group 2) were given 10 mg nifedipine 30 min before subcutaneous injection of 10 U ^{125}I-labeled soluble insulin. Absorption was measured by counting radioactivity externally. In both groups, control experiments were conducted under the same conditions without administration of propranolol or nifedipine. Results: Propranolol usage was associated with higher mean percentages of remaining activity ($P < 0.05$ by analysis of variance [ANOVA]) than in the control experiment. In the nifedipine experiment, mean percentages were significantly lower compared with the control experiment ($P < 0.02$ by ANOVA). The mean decline in activity of all 30-min periods was 6.8 ± 3.5 vs. 3.6 ± 3.7% for control versus propranolol (group 1) ($P < 0.05$) and 6.3 ± 1.8 vs. 9.6 ± 3.2% for control versus nifedipine (group 2) (NS). Conclusions: Antihypertensive drugs can influence insulin absorption. Propranolol (a peripheral vasoconstrictor) decreases insulin absorption, whereas nifedipine (a vasodilatator) increases insulin absorption. *Diabetes Care* 14:1089–92, 1991

Many factors influence the absorption of insulin. These factors have been grouped according to insulin preparation (i.e., concentration, volume, dose, species), method of administration (i.e., injection technique, mixing of insulins),

TABLE 1
Characteristics, heart rate, and blood pressure of groups 1 (propranolol) and 2 (nifedipine)

Group	Age (yr)	Height (cm)	Weight (kg)	Heart rate (beats/min)		Blood pressure (mmHg)	
				Control	Propranolol	Control	Propranolol
Propranolol	33.9 ± 8.2	172.0 ± 10.7	65.1 ± 11.2	67.2 ± 23.8*	49.0 ± 15.4	121/76 ± 12/6*	106/65 ± 11/6
Nifedipine	31.0 ± 11.1	180.0 ± 6.2	70.0 ± 6.1	66.9 ± 8.9†	69.9 ± 5.8	122/97 ± 7/6†	119/76 ± 7/6

Values are means ± SD.
*During control experiment (without propranolol).
†During control experiment (without nifedipine).

and factors originating in the patient (1). Variation in subcutaneous blood flow is perhaps one of many variables in the process of insulin resorption. To our knowledge, the effect of antihypertensive drugs on the absorption of insulin has not yet been investigated.

Propranolol has a peripheral vasoconstrictor effect (2), whereas nifedipine causes peripheral vasodilation (3). We studied the influence of these two antihypertensive drugs on the absorption of insulin in two groups of healthy volunteers.

RESEARCH DESIGN AND METHODS

Eleven healthy subjects (group 1; 9 men, 2 women) volunteered for the propranolol experiment, and another seven healthy subjects (group 2; all men) volunteered for the nifedipine experiment. None of the subjects normally used medication. They were informed of the nature, purpose, and possible risks of the investigation before they consented to participate in the study. Each participant was a hospital employee. The study was approved by the ethics committee of the Onze Lieve Vrouwe Gasthuis.

The investigations began after an overnight fast. Smoking was prohibited. Room temperature varied <1°C within and between days. To reduce thyroid uptake of radioactive iodide, sodium perchlorate was given orally before injection of ^{125}I-labeled insulin and during 4 days thereafter. Subjects rested 30 min before and throughout the study in a semirecumbant position. At 0900, 10 U ^{125}I-labeled Actrapid human insulin (40 U/ml, Novo, Copenhagen) was injected subcutaneously perpendicular to a marked place on an anterior midthigh area by an investigator. At 0930, each subject consumed a standard breakfast of 350 kcal. The radioactivity of ^{125}I-insulin was measured within 5 min immediately after injection. This measurement was repeated every 30 min until 150 min after injection. A γ-counter with a 2-inch NaI crystal was used. Blood pressure and pulse rate were measured every 30 min.

In each group, an identical study was performed 3 days after the control experiment with propranolol and nifedipine administered in groups 1 and 2, respectively. Each subject in group 1 was given 1 mg/kg body wt propranolol three times a day during a 48-h period and a single dose on the morning of investigation. The subjects in group 2 took 10 mg nifedipine 30 min before injection on the experimental day only. Measured radioactivity was expressed as a percentage of initial counts obtained immediately after injection of the ^{125}I-insulin. In addition, for each subject, the fractional decline in radioactivity was calculated by averaging the results of the five 30-min episodes in each study. Comparisons of two experimental conditions over different time points were made with a two-way repeated-measures analysis of variance (ANOVA). Individual time points and the mean fractional decline of radioactivity were compared with Student's paired *t* test. Results are means ± SD.

RESULTS

Table 1 shows mean age, height, and weight of groups 1 and 2 when propranolol or nifedipine, respectively, were administered, and heart rate and blood pressure during the control, propranolol, and nifedipine experiments. The disappearance rates of ^{125}I-insulin in the control, propranolol, and nifedipine experiments are depicted in Figs. 1 and 2. In the propranolol experiment, mean percentages of remaining activity were significantly higher after medication ($P < 0.05$ by ANOVA) at the individual time points 90 and 120 min after injection ($P < 0.02$ by Student's *t* test). The nifedipine experiment

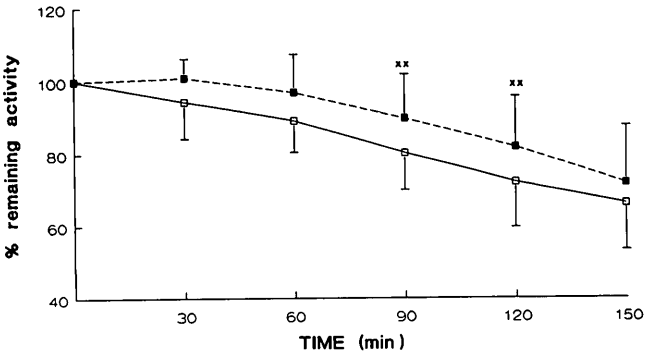

FIG. 1. Disappearance rate of ^{125}I-labeled insulin from injection site in control (*solid line*) and propranolol (*dashed line*) experiments. Values are means ± SD. $^{xx}P < 0.02$.

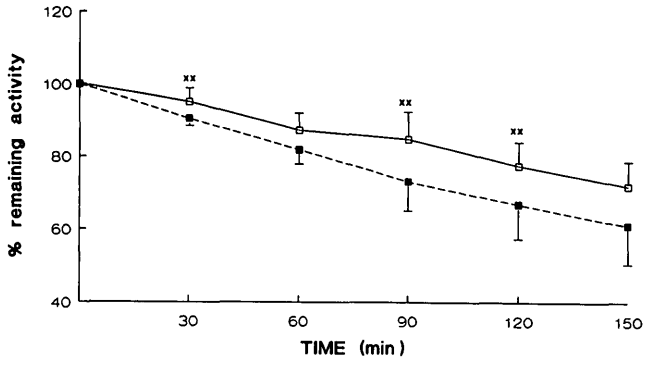

FIG. 2. Disappearance rate of ^{125}I-labeled insulin from injection site in control (*solid line*) and nifedipine (*dashed line*) experiments. Values are means ± SD. $^{xx}P < 0.02$.

showed significantly lower mean percentages of remaining activity ($P < 0.02$ by ANOVA) 30, 90, and 120 min after injection ($P < 0.02$ by Student's t test). The mean fractional decline in radioactivity was 6.8 ± 3.5%/30 min in the control experiment and fell to 3.6 ± 3.7% ($P < 0.05$) in group 1. In group 2, the initial mean fractional decline was 6.3 ± 1.8% in the control experiment and rose to 9.6 ± 3.3% (NS) in the nifedipine experiment.

CONCLUSIONS

Subcutaneous circulation affects insulin absorption. The influence of the injection site depends on differences in blood flow at different sites of the body (4). The influence of temperature and posture has been proven to occur through an effect on blood flow (5,6).

Antihypertensive medication can have an effect on subcutaneous blood flow. β-Blockers have a vasoconstrictor effect, and calcium-entry blockers have a vasodilator effect. Diabetic patients show a prevalence of hypertension 1.2–4.2 times that of nondiabetic subjects, and thus there is a need for strict treatment of hypertension (7,8).

The aim of our study was to determine the effect of vasoactive drugs on the absorption of insulin. We studied the rate of ^{125}I-insulin absorption by externally measured disappearance of radioactivity from the injection site. We used a perpendicular injection technique with a standard 13-mm needle (the usually recommended injection technique). Injection depth was not measured in each subject; intramuscular injection in lean individuals is not excluded (9). Studies in animals have shown that the radioactivity registered externally correlates with the amount of extractable insulin at the injection site (10). In human studies, a correlation has been observed between the disappearance rate of ^{125}I-insulin from a particular injection site and changes in plasma glucose measurement at rest or during exercise, indicating that the absorbed insulin is biologically active (10,11).

We found that propranolol, given in a 1-mg/kg body wt dose three times a day over 2.5 days, caused a reduction in the insulin absorption in healthy subjects. Oral administration of 10 mg nifedipine 30 min before insulin injection increased the absorption of insulin in healthy subjects. The effect of differences in exogenous absorption rates on plasma glucose in healthy subjects is obviously less profound compared with what might be expected in insulin-dependent diabetic subjects, because of a variable suppression in endogenous insulin secretion during the test. The vasoconstrictor effect of β-blockade without partial agonist activity is most pronounced in the initial phase of treatment. In the chronic phase, vascular resistance will frequently remain elevated, often above pretreatment values (12).

It has been suggested that the initial rise in vascular resistance after propranolol is caused by unopposed α-adrenoreceptor–mediated vasoconstriction after blockade of vasodilator β_2-adrenoreceptor. We studied our subjects in the resting condition. It is well established that exercise leads to enhanced insulin absorption (11), however, it also leads to an increased sympathetic drive. The latter phenomenon generally causes more pronounced effects of β-blockade compared with the resting state. Hence, the difference in insulin absorption might have been greater had we performed our study in mobile healthy subjects. In diabetic subjects, skin temperature decreases during exercise in a warm environment (13). The significance of this phenomenon for changes in absorption induced by vasoactive drugs is unknown. Our results show that comedication can influence insulin absorption by its effect on subcutaneous circulation. In group 1, insulin absorption was decreased by propranolol (av 47%), and in group 2, insulin absorption was increased by nifedipine (av 52%). The delay and acceleration of insulin absorption by these commonly used antihypertensive and antianginal drugs could probably cause clinically relevant changes in glucoregulation in insulin-dependent diabetic subjects.

Further investigation of these effects in diabetic subjects at rest and during exercise after different periods of treatment is required. In diabetic subjects with affected vasomotor response due to neuropathy, the effect of antihypertensive drugs might be different.

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Relationship Between Normal Oral Glucose Tolerance Test in Women at Risk for Gestational Diabetes and Large For Gestational Age Infants

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Objective: To determine whether the glycemic status of pregnant women with a normal 3-h 100-g oral glucose tolerance test (OGTT) is related to outcome with respect to large for gestational age (LGA) infants. Research Design and Methods: A prospective study of 2631 women was conducted. One hundred seventy-six women had an OGTT based either on a 1-h 50-g OGTT (n = 105) or clinical risk factors (n = 71). Thirty-three women were diagnosed as having gestational diabetes mellitus. Results: Negligible discriminatory capacity for the variables with respect to prediction of LGA infants was indicated by the areas under the receiver operating characteristic (ROC) curves for fasting blood glucose, 2-h OGTT blood glucose, and the OGTT response curve area for women with a normal OGTT (n = 143). However, a statistically significant increased incidence of LGA infants was established for both the OGTT-positive and normal OGTT groups ($P < 0.0001$). Multiparity, a maternal weight ≥70 kg, and birth of a male infant were other factors associated with a significantly increased frequency of LGA infants. Conclusions: The results may be interpreted as either indicating a role for confounding variables, i.e., maternal weight, multiparity, and birth of a male infant, or the imprecision of the OGTT in assessing physiologically important changes in maternal hyperglycemia. ***Diabetes Care* 14:1092–94, 1991**

Gestational diabetes mellitus is associated with a significant incidence of large for gestational age (LGA) and macrosomatic infants. However, the definitive diagnostic procedure for gestational diabetes, the oral glucose tolerance test (OGTT), has many inherent limitations, including the designation of threshold levels unrelated to immediate adverse maternal-fetal outcome and poor reproducibility (1,2). Under this dichotomous strategy, there will arise a high proportion of misclassification not only because of test irreproducibility but also because a woman's glycemic status may be equivocal. It the degree of glucose intolerance is an important determinant of excess fetal weight gain, then a predictive relationship should exist between maternal glycemic status, as estimated by the OGTT, and the incidence of LGA infants. This hypoth-