Intravenous Insulin Causing Loss of Intravascular Water and Albumin and Increased Adrenergic Nervous Activity in Diabetics

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SUMMARY

Blood pressure, heart rate, plasma norepinephrine, forearm blood flow, plasma volume, plasma albumin, blood glucose, and plasma epinephrine were measured in six diabetic patients without neuropathy in the supine position and during feet-down tilting for seven minutes. The experiments were repeated after intravenous (i.v.) injection of 6 to 8 U. of insulin.

The mean blood glucose concentration averaged 205 ± 14 (S.E.M.) mg./100 ml. in the control experiment and had decreased by 97 ± 17 mg./100 ml. 45 minutes after the injection of insulin. None of the patients had hypoglycemia, and plasma epinephrine did not increase.

There was no change in arterial blood pressure after insulin was given either in the supine position or after tilting. The heart rate averaged 64 ± 5 beats per minute in the control experiment and had increased by 7 ± 2 beats per minute 40 minutes after the injection of insulin ($2p = 0.035$). The rise in heart rate in response to tilting was statistically significantly greater after administration of insulin ($2p = 0.0064$).

Plasma norepinephrine averaged 0.17 ± 0.03 ng./ml. in the control experiment and had increased by 70 ± 24 per cent 45 minutes after the i.v. injection of insulin ($2p = 0.045$). The rise in plasma norepinephrine in response to tilting was statistically significantly greater after the injection of insulin ($2p = 0.017$).

Forearm blood flow decreased from 2.13 ± 0.29 ml./100 ml. per minute in the control experiment to 1.63 ± 0.32 ml./100 ml. per minute 40 minutes after the injection of insulin ($2p = 0.011$). Plasma volume averaged 3,061 ± 67 ml. before injection of insulin and had decreased by 265 ± 59 ml. 45 minutes after insulin was given ($2p = 0.011$). The intravascular mass of albumin averaged 118 ± 3 gm. and 109 ± 3 gm. before and 45 minutes after the administration of insulin, respectively ($2p = 0.017$).

There was a close correlation between the relative increase in plasma norepinephrine in the supine position and the relative decrease in plasma volume after the injection of insulin ($r = -0.95$, $2p = 0.013$).

It is concluded that i.v. injection of insulin results in an increased adrenergic nervous activity that is due to a decrease in plasma volume. The effect of insulin is accompanied by a significant reduction in the intravascular pool of albumin.

These observations may explain the fact that patients with abnormal cardiovascular reflexes are unable to maintain arterial blood pressure, especially in the upright position, after the i.v. injection of insulin.

The observed decrease in plasma volume after the administration of insulin was much larger than could be expected from the decrease in blood glucose concentration and the ensuing decrease in plasma osmolality.

It is suggested that insulin either directly or secondarily to its metabolic effects may alter the function or the volume of the endothelial cells and thereby increase the transfer of fluid and albumin out of the vascular system.

DIABETES *26*:551-57, June, 1977.

It has been observed that intravenous injection of insulin results in a fall in arterial blood pressure in sympathectomized patients[1] as well as in diabetic patients with neuropathy[2,3] but not in normal subjects. The fall in arterial blood pressure is not due to hypoglycemia and is more pronounced in the feet-down tilted position.[2,3] Intravenous (i.v.) injection of insulin in diabetic patients without neuropathy has no effect on arterial blood pressure in the supine position; however, plasma norepinephrine increases even when the blood

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Accepted for publication December 10, 1976.

glucose concentration is high.[4,5] These results suggest that an increased adrenergic activity is necessary for the maintenance of arterial blood pressure after i.v. injection of insulin.

The aim of the present study was to elucidate the mechanism of the hypotensive action of insulin. Blood pressure, heart rate, plasma norepinephrine, forearm blood flow, plasma volume, and plasma albumin concentration were measured in diabetic patients without neuropathy before and after i.v. administration of insulin.

The main observation was that i.v. injection of insulin resulted in an unexpectedly large decrease in plasma volume and a reduction in the intravascular pool of albumin. The magnitude of these changes was closely related to the magnitude of the rise in plasma norepinephrine.

SUBJECTS

Six male diabetic subjects were studied. The mean age was 26 years. The duration of diabetes averaged three years (table 1). All patients received treatment with insulin and diet. The subjects had normal ankle jerks and knee jerks as well as normal values of vibratory perception threshold in the feet. An informed consent to the procedure was obtained from all subjects examined.

PROCEDURE

The patients were investigated in the supine position and during a 60° feet-down tilt for seven minutes (control experiment). The examination was repeated after i.v. injection of crystalline insulin.

The patients had a small carbohydrate-rich breakfast and fasted thereafter six to eight hours until the experiments were started, in the afternoon. Smoking was prohibited. The patients were not allowed to drink during the last two hours before the experiments started. The last dose of insulin was given in the morning the day before the experiment. The patients rested in their beds the whole morning and were brought to the laboratory from the ward in their beds and transferred to a tilting bed. The room temperature was controlled at 22° C. While the patients continued to rest in the supine position, venous catheters were placed in the antecubital space on both sides, and at least 15 minutes then elapsed before withdrawal of the first blood sample. Withdrawn blood was immediately replaced by intravenous injection of corresponding volumes of isotonic saline.

Blood was collected in the supine position for the determination of blood glucose and of norepinephrine, epinephrine, protein, albumin, sodium, potassium, and total CO_2 in plasma. Blood pressure, heart rate, and forearm blood flow were measured at two-minute intervals for 10 minutes. Thereafter the plasma volume was determined by injecting ^{125}I-labeled human serum albumin. Precisely 10 minutes later a blood sample was obtained for determination of plasma radioactivity.

The patients were tilted to a 60° feet-down position for seven minutes. Blood pressure and pulse rate were recorded every two minutes, and after seven minutes blood was withdrawn for the determination of norepinephrine and epinephrine.

After the tilting bed had been moved back to the horizontal position, blood was withdrawn for the de-

TABLE 1

Pertinent clinical data, blood glucose, and plasma epinephrine before insulin, and changes observed 45 minutes after i.v. injection of insulin

Patient indentification	Age (years)	Duration of diabetes (years)	I.v. dose of insulin (I.U.)	Blood glucose (mg./100 ml.)	Plasma epinephrine (ng./ml.)
1	26	3	8	186	0.01
				−135	0
2	28	3	6	215	0.04
				−53	0
3	23	3	8	243	0.11
				−58	−0.01
4	28	1	8	164	0.02
				−125	+0.02
5	28	4	6	215	0.02
				−112	+0.02
Mean (S.D.)				205 (30)	0.04 (0.04)
Mean (S.E.M.) of change				−97 (17)	+0.01 (0.01)
$2p$				0.0049	0.37
Control patient	21	4	0	228	0.07
				−14	−0.02

termination of glucose and 6 to 8 U. of crystalline insulin was injected intravenously. One patient received 0.2 ml. of isotonic saline instead of insulin. Blood pressure, heart rate, and forearm blood flow were measured at 10-minute intervals for 40 minutes and 35 minutes after the injection of insulin. ^{131}I-labeled human serum albumin was injected for the redetermination of plasma volume. Precisely 10 minutes later blood was withdrawn for counting of ^{131}I- and ^{125}I-radioactivity, as well as for the determination of blood glucose and catecholamines, proteins, and electrolytes in plasma. Sixty-two minutes elapsed between the two determinations of the plasma volume.

The patients were then tilted to the 60° feet-down position. Blood pressure and heart rate were measured as described above and blood was obtained after seven minutes for the determination of norepinephrine and epinephrine.

In two young, nondiabetic male volunteers the influence on plasma norepinephrine of a controlled reduction in blood volume was studied. After the insertion of an indwelling catheter, the subjects rested in the supine position for one hour, at which time 100 ml. of blood was withdrawn every 15 minutes for 60 minutes. In a previous experiment we have shown that plasma norepinephrine reaches steady state within 10 minutes after a constant cardiovascular stress.[6]

METHODS

Hemodynamic Measurements

Diastolic and systolic blood pressures were measured indirectly on the arm with a mercury sphygmomanometer. The calculated mean blood pressure was the diastolic pressure plus one third of the pulse amplitude. The pulse was counted over a period of 30 seconds. Forearm blood flow was measured by a mercury-in-rubber strain gauge and the venous occlusion technique.[7] The plasma volume was determined from the measured dilution precisely 10 minutes after the injection of ^{125}I- or ^{131}I-labeled human serum albumin. Three to five microcuries was injected intravenously without withdrawal of blood, and the syringe was weighed before and after the injection. Thyroid uptake of radioactive iodide was blocked by daily administration of potassium iodide. The labeled albumin (MIAK and MIMS, respectively, Kjeller, Norway) contained less than 1.5 per cent free iodide measured by equilibrium dialysis, and the difference in the content of free iodide in the two batches given to the same patient was less than 0.2 per cent. Plasma samples and standards were counted to 100,000 counts, and corrections for background activity and cross-over from ^{131}I- to the ^{125}I-channel were applied.

The plasma volume (PV) was calculated according to the formula:

$$\text{PV ml.} = \frac{\text{total counts injected}}{\text{counts/ml. plasma}}$$

The intravascular mass of albumin (IVMA) was calculated from:

$$\text{IVMA gm.} = \text{PV ml.} \times \text{albumin gm./ml. plasma}$$

and the specific activity at the time when the intravascular albumin pool was labeled with ^{125}I-albumin was calculated from:

$$\frac{^{125}\text{I-counts/ml. plasma}}{\text{albumin gm./ml. plasma}}$$

The disappearance of the ^{125}I-labeled intravascular pool of albumin between the two plasma volume determinations was calculated according to the formula:

$$\text{PV}_1 \text{ ml.} \times \text{albumin gm./ml.} - \text{PV}_2 \text{ ml.} \times \frac{^{125}\text{I-counts}_2\text{/ml. plasma}}{\text{specific activity of IVMA}_1}$$

where the subscripts 1 and 2 refer to the first and the second determination, respectively.

Biochemical Determinations

Blood glucose was measured by a glucose-oxidase method[8] and plasma norepinephrine and epinephrine by a double-isotope derivative technique.[9] Sodium, potassium, and total CO_2 in plasma were determined by AutoAnalyzer methods (SMA), plasma protein was measured by a biuret method, and plasma albumin was determined from an electrophoretic fractionation of plasma proteins (Beckman).

Statistical Methods

Student's *t*-test for paired comparison was used for testing the statistical significance of differences between mean values while correlation was measured by Pearson's product-moment correlation coefficient, r.

In the text the dispersion of the absolute mean values is given by the standard deviation (S.D.) whereas that of average differences is given by the standard error of the mean (S.E.M.).

In the phlebotomy experiment the slopes of the two individual regression lines and the statistical significance were calculated according to a procedure for regression lines passing through the origin.[10]

RESULTS

Table 1 shows pertinent clinical data as well as blood glucose and plasma epinephrine in the six diabetic patients studied. The mean blood glucose concentration averaged 205 ± 30 (S.D.) mg./100 ml. in the control experiment.

Forty-five minutes after the i.v. injection of insulin, blood glucose concentration had decreased on the average by 97 ± 17 (S.E.M.) mg./100 ml. ($2p = 0.0049$). None of the patients had symptoms of hypoglycemia in the supine position. Correspondingly, mean plasma epinephrine concentration in the supine position was 0.04 ± 0.04 ng./ml. in the control experiment and did not change after injection of insulin. Two of the patients (nos. 1 and 5) complained of dizziness in the 60° feet-down tilted position after the injection of insulin. Patient no. 5 almost fainted at four minutes in the tilted position, and the experiment had to be terminated (blood glucose concentration 103 mg./100 ml.). None of the patients had complaints in the tilted position during the control experiment. Plasma epinephrine rose in the tilted position in the control experiment from 0.04 ± 0.04 ng./ml. to 0.07 ± 0.05 ng./ml. ($2p = 0.018$). There was no statistically significant difference in plasma epinephrine before and after the injection of insulin.

Figure 1 shows blood pressure, pulse rate, plasma norepinephrine, forearm blood flow, and plasma volume in the control experiment and 40 to 45 minutes after injection of insulin in the five diabetic patients as well as in the single diabetic who received an injection of 0.2 ml. of isotonic saline instead of insulin.

Supine blood pressure averaged 118/82 ± 11/11 mm. Hg and remained unchanged at 40 minutes after the i.v. injection of insulin. There was no change in blood pressure in the tilted position either before or after insulin was given.

Heart rate averaged 64 ± 10 beats per minute in the supine position in the control experiment and had increased by 7 ± 2 beats per minute 40 minutes after insulin was given ($2p = 0.035$). At six minutes in the tilted position the heart rate had increased to 85 ± 6 and 108 ± 3 beats per minute before and after administration of insulin, respectively. The rise in heart rate in the tilted position was almost doubled after administration of insulin, the difference being 16 ± 3 beats per minute ($2p = 0.0064$).

Plasma norepinephrine averaged 0.17 ± 0.06 ng./ml. in the supine position in the control experiment and had increased by 70 ± 24 per cent 45 minutes after the i.v. injection of insulin ($2p = 0.045$). At seven minutes during tilting in the control

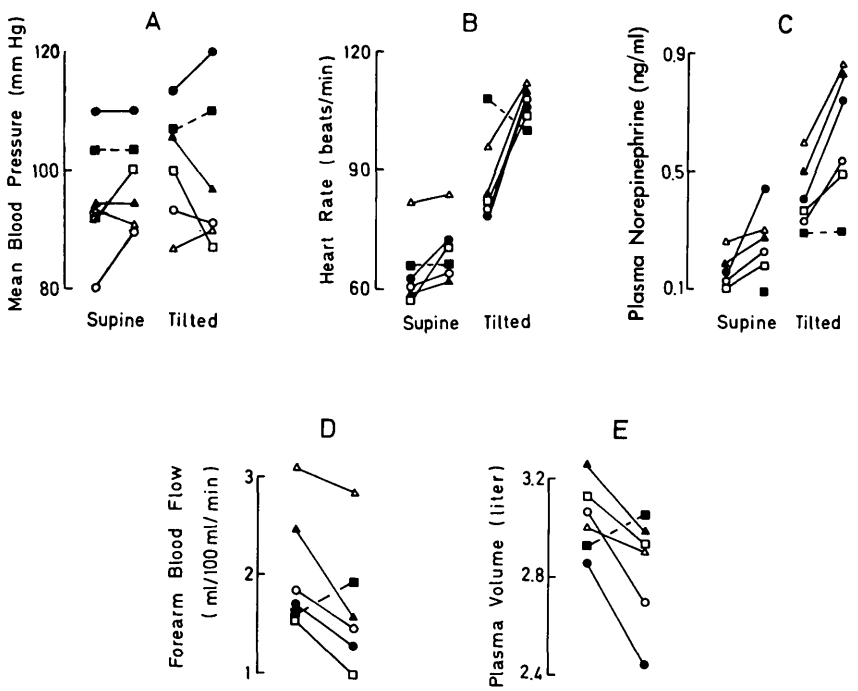


FIGURE 1

Mean blood pressure (A) mm. Hg, heart rate (B) beats per minute, plasma norepinephrine (C) ng./ml., forearm blood flow (D) ml./100 ml. tissue per minute, and plasma volume (E) liters obtained in the supine position (A, B, C, D, E) and during a feet-down tilt (A, B, C) in five diabetics in the control experiment and 40 to 45 minutes after i.v. injection of 6 to 8 U. of insulin (○ ● △ ▲ □) or isotonic saline (■). Results obtained in the same subject have been connected with a line (left: control experiment, right: after insulin or saline). The blood sample obtained in one subject (■) for plasma norepinephrine determination in the control experiment was lost by accident.

experiment plasma norepinephrine, expectedly, had increased to 0.44 ± 0.11 ng./ml. ($2p = 0.00039$). After injection of insulin plasma norepinephrine in the tilted position rose to 0.69 ± 0.17 ng./ml. ($2p = 0.0022$). The rise in plasma norepinephrine in response to tilting was 0.14 ± 0.04 ng./ml. greater after the injection of insulin ($2p = 0.017$).

Forearm blood flow averaged 2.13 ± 0.65 ml./100 ml./min. in the supine position and decreased to 1.63 ± 0.72 ml./100 ml./min. at 40 minutes after the i.v. injection of insulin ($2p = 0.011$).

Plasma volume averaged 3,061 ± 150 ml. in the supine position before insulin was given and had decreased by 265 ± 59 ml. 45 minutes after insulin was given ($2p = 0.011$).

There was a close exponential-type correlation between the relative rise in plasma norepinephrine in the supine position and the relative decrease in plasma volume after the injection of insulin (figure 2) ($r = -0.95$, $2p = 0.013$). No correlation obtained between the decrease in blood glucose concentration and the decrease in plasma volume.

In the diabetic patient who received saline instead of insulin the heart rate and the plasma norepinephrine concentration were unchanged in the two experiments, while blood flow and plasma volume were slightly higher in the second.

Table 2 shows that the plasma albumin concentration was the same before and after the injection of insulin. The total intravascular mass of albumin averaged 118 ± 7 gm. in the control experiments and had decreased to 109 ± 7 gm. 45 minutes after insulin was given ($2p = 0.017$). No change was observed in the diabetic patient who received saline instead of insulin (107 and 110 gm., respectively). The amount of albumin withdrawn during blood sampling between the two plasma volume determinations was 0.5 gm. The disappearance of the ^{125}I-labeled intravascular pool of albumin averaged 13.8 ± 3.1 gm. (S.D.) in the 62 minutes that elapsed between the two plasma volume determinations.

TABLE 2

Plasma albumin data before insulin, and changes observed 45 minutes after i.v. injection of insulin

Patient identification	Plasma albumin gm./100 ml.	Intravascular pool of albumin gm.	Disappearance of ^{125}I-labeled intravascular pool of albumin gm.
1	4.11	126.1	
	−0.11	−17.7	14.7
2	3.79	108.2	
	+0.30	−8.4	18.5
3	3.79	113.7	
	−0.06	−4.9	10.1
4	3.71	121.0	
	+0.15	−5.6	13.4
5	3.93	122.7	
	−0.02	−8.3	12.5
Mean (S.D.)	3.87 (0.16)	118.3 (7.3)	
Mean (S.E.M.) of change	+0.05 (0.08)	−9.0 (2.3)	13.8 (1.4)
$2p$	0.53	0.017	
Control patient	3.65	106.7	
	−0.06	+3.0	2.3

Plasma sodium concentration averaged 135 mmol per liter in the control experiment and was unchanged at 45 minutes after the injection of insulin. Plasma potassium decreased from 4.9 mmol per liter to 4.7 mmol per liter, but the difference was not significant. Plasma total CO_2 was 21 mmol per liter in the control experiment and remained unchanged at 45 minutes after the injection of insulin (22 mmol per liter).

The two normal subjects showed a rise in plasma norepinephrine during the phlebotomy experiment (figure 3). There was a significant correlation in both subjects between the relative rise in plasma norepinephrine and the amounts of blood removed ($2p = 0.015$ and 0.025, respectively). At 45 minutes after removal of 300 ml. of blood the plasma norepinephrine had increased 44 per cent.

FIGURE 2

The correlation between the logarithm of the relative rise in plasma norepinephrine in the supine position (ordinate) and the logarithm of the relative decrease in plasma volume 45 minutes after i.v. injection of insulin (abscissa).

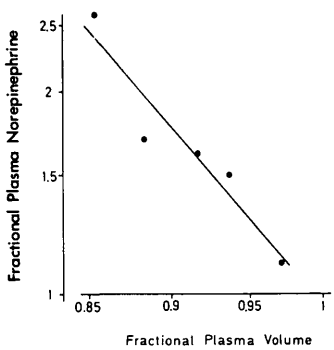
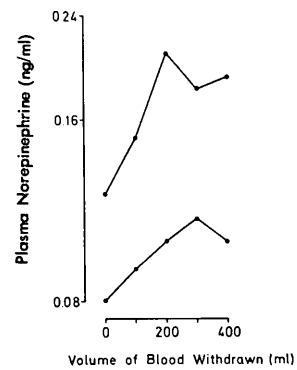


FIGURE 3

Rise in plasma norepinephrine in two normal subjects during phlebotomy. Ordinate: plasma norepinephrine (ng./ml.). Abscissa: amounts of blood removed (ml.). The ordinate is logarithmic.



DISCUSSION

The present study showed that after the i.v. injection of insulin heart rate and plasma norepinephrine had increased and forearm blood flow had decreased in five juvenile diabetics with a short duration of diabetes and without signs of diabetic neuropathy. The arterial blood pressure changed neither in the supine position nor in response to tilting. The hemodynamic effects of insulin were greater in the feet-down tilted position and were unrelated to symptoms of hypoglycemia. None of the patients had symptoms of hypoglycemia in the supine position after injection of insulin, while two subjects complained of dizziness in the tilted position. It is unlikely, however, that the discomfort in these two patients was due to cerebral hypoglycemia, because plasma epinephrine did not increase and because one of the patients had a blood glucose concentration of 103 mg./100 ml.

The fact that the disappearance of the ^{125}I-labeled intravascular pool of albumin increased after the injection of insulin means that the second plasma volume determination might have been slightly overestimated. Thus, the plasma-volume-lowering effect of insulin might have been slightly underestimated.

The various hemodynamic changes here reported were estimated from measurements made before and after the injection of insulin. We have thus assumed that the patients were close to steady-state condition before insulin was administered. It is clear that metabolic derangement per se cannot be responsible for the pronounced changes occurring during the 45-minute period following the injection of insulin: the changes in plasma volume and in the albumin pool alone correspond to a loss of plasma at a rate of 350 ml. per hour. Furthermore, the presence of a nearly steady-state condition was also indicated by the observations in the one diabetic who was given saline instead of insulin.

Our observations are in contradistinction to the findings in diabetic patients with neuropathy and in sympathectomized subjects[1-3] in whom the blood pressure decreased in response to i.v. injection of insulin. The rise in plasma norepinephrine after i.v. injection of insulin has previously been observed in diabetic patients in whom hypoglycemia was not attained and in whom plasma epinephrine did not increase.[4,5] Page, Smith, and Watkins[11] have recently reported that i.v. injection of insulin increased heart rate in seven diabetics with normal cardiovascular reflexes. This effect was not due to hypoglycemia and was also greater in the upright position.

The above-mentioned observations show that an increased adrenergic nervous activity is necessary for the maintenance of the arterial blood pressure after i.v. injection of insulin.

Furthermore, the present results strongly suggest that the increase in adrenergic nervous activity was caused by the large decrease in plasma volume that occurred after the injection of insulin. We observed a close correlation in the diabetic patients between the rise in plasma norepinephrine and the decrease in plasma volume after the insulin injection. The decrease in plasma volume after i.v. administration of 6 to 8 U. of insulin was of such a magnitude that one would expect that patients with neuropathy may be unable to maintain arterial blood pressure, especially in the upright position. Furthermore, the decrease in plasma volume is probably even greater in patients with abnormal cardiovascular reflexes due to lack of peripheral vasoconstriction, which normally counteracts plasma loss.

Finally, the phlebotomy experiments in the normal subjects showed that plasma norepinephrine increases after a rather small reduction in blood volume, and the changes were of a magnitude similar to that observed in the diabetic patients.

A decrease in blood glucose is followed by a decrease in plasma volume secondary to the intracellular transfer of glucose and the ensuing decrease in plasma osmolality. However, calculations[12] based on simple assumptions show that a fall in blood glucose concentration of 100 mg./100 ml. is followed by a decrease in plasma volume of less than 50 ml., which is one-fifth the decrease observed in the present study. Anyhow, such a small decrease in plasma volume could not be expected to lead to the pronounced increase in adrenergic activity observed in the present study. It is unclear whether the effect of insulin on plasma volume is totally independent of its effect on glucose transport, but we observed no relationship between the decrease in plasma volume and the fall in blood glucose concentration ($r = 0.15$).

The mechanism by which insulin decreases plasma volume is not known.

Insulin has been reported to decrease the inulin space and increase cell volume even in the absence of glucose.[13]

Our results suggest, however, that the decrease in plasma volume observed was not due solely to a transfer of water from the extracellular space to the intracellular space. In addition to the decrease in plasma volume we observed a considerable reduction in the intravascular

mass of albumin. The disappearance of the ^{125}I-labeled intravascular pool of albumin was also much larger than could be expected from measurements of transcapillary escape rate of albumin in poorly controlled diabetics during steady-state conditions.[14] Theoretically, the decrease in both plasma volume and in the intravascular mass of albumin may occur as a result of an increase in blood flow in the liver and the gastrointestinal tract. Studies of hepatic blood flow in diabetic patients after i.v. injection of insulin indicate, however, that insulin has no acute effect on hepatic blood flow, provided that hypoglycemia is avoided.[15,16] Urinary excretion of albumin was not measured in the experiments reported here. However, i.v. injection of insulin did not increase urinary excretion of albumin in preliminary experiments in other diabetic patients (unpublished results). The mechanism by which i.v. injection of insulin decreases plasma volume and accelerates the escape of intravascular albumin deserves further investigation. It is possible that insulin either directly or secondarily to its metabolic effects may alter the function or the volume of the endothelial cells and thereby increase the transfer of fluid and albumin out of the vascular system.

ACKNOWLEDGMENTS

Dr. H. Hvid Hansen, head of the Radiophysical Department, and Prof. Rud. Keiding, head of the Department of Clinical Chemistry, Municipality Hospital of Aarhus, are thanked for invaluable help. Mrs. E. Bang is thanked for conscientious technical assistance. This study was supported by grants from Statens lægevidenskabelige Forskningsråd, Novo's Fond, and Fonden til lægevidenskabens Fremme.

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