Provocation of Postural Hypotension by Insulin in Diabetic Autonomic Neuropathy

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SUMMARY

The effect of insulin administration on blood pressure has been investigated in eight diabetics with autonomic neuropathy. Systolic and diastolic pressures fell considerably after insulin in all of them. This effect was aggravated by tilting to the vertical position. Five patients fainted when upright with systolic blood pressures less than 50 mm. Hg.

This hypotensive effect of insulin occurs whether it is administered intravenously, intramuscularly, or subcutaneously. The onset of the effect is almost immediate after intravenous insulin, is progressive, and may last for several hours. It coincides with a falling blood glucose level and occurs before hypoglycemic levels are reached, and it may be present when the blood glucose level is still elevated. Diurnal variations of postural hypotension have been recorded in some patients, the standing blood pressure falling with the onset of insulin action and rising again as the latter declines.

Some of our patients were unable to differentiate between symptoms of hypoglycemia and hypotension. Postural hypotension may account for some episodes of sudden loss of consciousness without warning, usually attributed to hypoglycemia. DIABETES *25*:90-95, **February, 1976.**

Diabetic autonomic neuropathy may affect the cardiovascular system, the main clinical manifestation being postural hypotension. Maintenance of blood pressure on standing depends on afferent impulses from baroreceptors (mainly in the carotid sinus and aortic arch) and on efferent sympathetic impulses to the heart and blood vessels, resulting in a compensatory tachycardia and increased peripheral vasoconstriction. If one or more parts of this reflex system are impaired, postural hypotension may occur. In normal people there is a 20 per cent fall in cardiac output on standing; about 700 ml. of blood accumulates in the legs and abdomen,[1] but compensatory mechanisms prevent a fall in blood pressure.

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Postural hypotension is subject to many influences and varies considerably at different times. An effect of insulin on blood pressure has been shown by Miles and Hayter[2] in diabetics with abnormal Valsalva responses. The present investigation was designed to study the effect of insulin on postural hypotension in a series of diabetics with severe autonomic neuropathy. It was prompted by discovery of severe hypotension occurring during hypoglycemia in one of our patients.

PATIENTS

Eight diabetics with clinical features of automonic neuropathy were studied on a tilt table. Clinical features are shown in table 1. All gave informed consent.

Other diabetics with postural hypotension were included in studies of diurnal variation of lying/standing blood pressure.

PROCEDURE

Patients remained supine and fasting overnight and took no medication on the day of study. An indwelling catheter was inserted into an antecubital or forearm vein half an hour prior to baseline readings. Blood pressure was measured by auscultation with a standard mercury sphygmomanometer. Readings were taken on supine subjects until three consecutive recordings of systolic pressure were within 5 mm. Hg. Patients were then tilted to 80° on a tilt table; this provided no additional support and so weight was mainly transmitted through the legs, as in normal standing. Blood pressure was recorded once each at one half, one, and three minutes after tilting. Because there was often a variation of pressure with the phases of respiration (sometimes $>$ 10 mm. Hg), especially after tilting, the systolic pressure was taken as the maximum pressure at which two or more consecutive pulse beats could be heard repeatedly during each normal inspiration. Diastolic pressure was taken as the lowest pressure at which pulse beats could be heard

TABLE 1

Patient	Age	Sex	Duration (yr.)	Diabetic diarrhea	Postural* hypotension	Gustatory[3] sweating	Impotence	Beat-to-beat[4] variation on† deep breathing
Case 1	44	M	32	‡	‡	‡	‡	4
2	37	M	12	‡	‡	0	‡	2
3	49	M	26	‡	‡	‡	‡	1
4	45	M	35	0	‡	‡	‡	2
5	39	F	35	‡	0	‡	—	2
6	21	M	11	0	‡	0	0	13
7	29	M	22	‡	0	‡	0	3
8	74	F	49	0	‡	0	—	5

*These patients had been noted on two or more occasions to have a fall of systolic blood pressure on standing of >30 mm. Hg.
†Normal value >10 beats/min.; ‡Present; 0 Absent.

continuously, as shown by muffling (phase 4) of the Korotkov sounds.

Pulse rate was counted at the wrist supine for one minute and then from 1.5 to 2.5 minutes after tilting; in most experiments continuous recording of supine and erect pulse rate was made with a Hewlett Packard 8025B cardiotachometer.

After three minutes of tilting, patients were returned to the supine position, and the procedure was repeated quarter-hourly. Thus, each supine recording was preceded by at least 10 minutes of lying at rest.

Serial readings were taken before and after the administration of soluble bovine insulin, which was given intramuscularly or intravenously in a variable dose. Some patients had several injections. The total dose of insulin given ranged from 9 to 52 I.U., with a mean of 35 I.U.

Blood samples (2 ml.) for glucose determination were taken every 15 minutes after insulin. In four patients, 20 ml. blood was also taken immediately after return to the supine position before insulin was given, and again in the supine position two to three hours later, just after maximal hypotension had occurred. Blood volume was maintained by immediate replacement with the same quantity of isotonic saline.

In an additional study, diurnal recordings of blood pressure were made in nine diabetics with autonomic neuropathy (including cases 2, 3, 5, and 7). In these diurnal studies, the tilt table was *not* used and the lying/standing blood pressure was recorded hourly by the same observer (M.P.) while the patient had his normal subcutaneous insulin regime and meals during a routine ward day. No restrictions were imposed on activity, but each set of supine recordings was preceded by at least five minutes of lying at rest. Blood pressure was again recorded three times supine and at one-half, one, and three minutes after standing, and the mean was used for calculation.

METHODS

Plasma glucose was measured by AutoAnalyzer by the ferricyanide method; plasma sodium and potassium by AutoAnalyzer; plasma osmolarity by a Fiske (Model G. 66) osmometer; plasma catecholamines by a colorimetric method;[5] motor-nerve conduction studies were performed with a Medelec AA6 Mark II.

RESULTS

Blood Pressure

In all eight patients both systolic and diastolic blood pressures fell after parenteral insulin, especially after tilting to the upright position (table 2). Five of the eight patients fainted when upright, with unrecordable blood pressures. None had ever previously fainted.

TABLE 2

Case	Baseline B. P. before insulin		Lowest B. P. after insulin	
	Supine	Erect	Supine	Erect
1	190/100	180/90	158/92	92/68
2	146/88	94/70	96/70	<52*/44
3	160/78	118/74	128/68	70/63
4	167/90	159/95	132/76	<80*/64
5	150/83	127/78	138/78	94/66
6	120/80	83/74	101/77	<50*/?
7	161/109	154/114	108/92	<50*/?
8	133/68	110/65	104/55	<54*/44

*Lowest blood pressure recorded before fainting occurred.

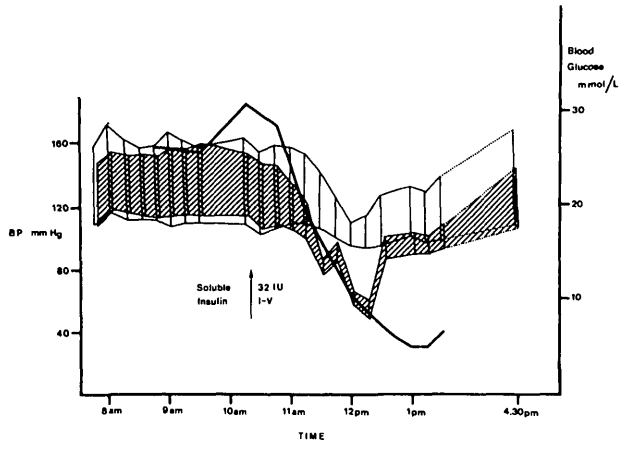

FIG. 1. The effect of intravenous insulin on supine and upright blood pressures, shown by unhatched and hatched areas, respectively (case 7). Blood glucose is shown by the continuous line.

Some of the individual experiments gave dramatic results (figure 1). After stable blood pressures in the baseline period, there was a progressive fall in supine and erect systolic and diastolic pressures starting within five minutes of administration of intravenous insulin and lasting for several hours. The fall of blood pressure usually preceded that of blood glucose. Fainting from hypotension in each case occurred when the blood glucose was above 10 mmol/L., and hypoglycemia never developed. After intramuscular insulin, the fall of blood pressure was more gradual (figure 2).

A control experiment in which the identical procedure was followed on the tilt table, except that insulin was not given, did not cause progressive postural hypotension (figure 3).

Pulse Rate

There was an increase in pulse rate after insulin both when supine and after tilting in some patients

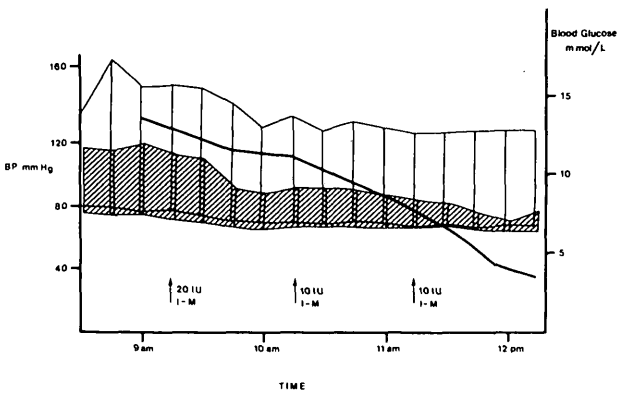

FIG. 2. The effect of intramuscular insulin on supine and upright blood pressures, as in figure 1 (case 3).

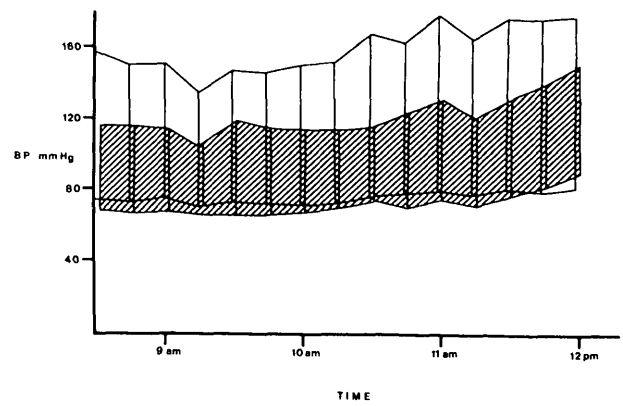

FIG. 3. The effect of serial tilting in a control experiment when no insulin was given, as in figure 1 (case 3).

(table 3). The effect on pulse rate varied widely, and in one case there was a slight fall. In a few subjects, rapid increases in pulse rate developed within five minutes of administration of intravenous insulin (figure 4).

Blood Glucose

There was a striking similarity between the effects of insulin on blood pressure and on blood glucose (figures 1, 2, and 5). In all cases, progressive postural hypotension was associated with a falling blood glu-

TABLE 3

Case	Baseline pulse rate before insulin		Fastest pulse rate after insulin	
	Supine	Erect	Supine	Erect
1	74	78	71	73
2	76	110	80	120
3	56	64	59	72
4	88	98	90	105
5	96	100	98	108
6	102	154	127	150
7	100	120	134	146
8	72	84	69	105

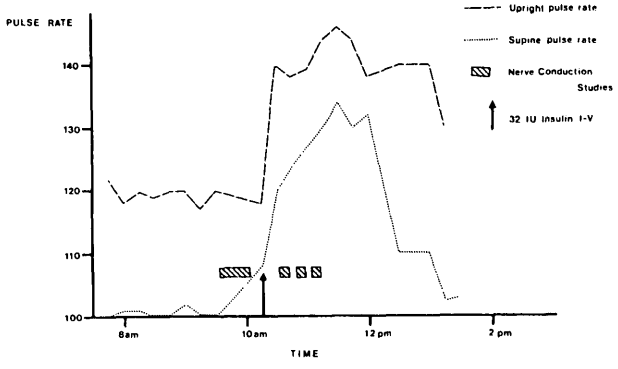

FIG. 4. The effect of intravenous insulin on supine and upright pulse rate. Nerve conduction studies were performed at the times indicated (case 7).

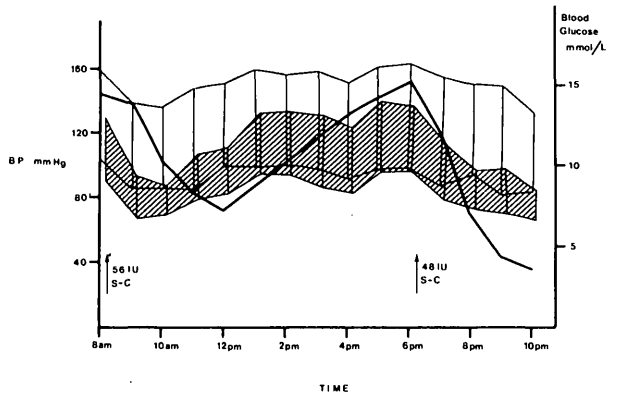

FIG. 5. Diurnal variation of lying and standing blood pressures in a 48-year-old man with severe autonomic neuropathy during a routine ward day, as in figure 1. The arrows indicate administration of soluble insulin subcutaneously.

cose, although hypoglycemic levels were not reached. Fainting from hypotension occurred at normal or raised blood glucose levels.

There was no obvious correlation between the rate of fall of blood glucose and the maximal hypotensive effect.

Other Measurements

There was no change in motor-nerve conduction velocity (median nerve) in cases 6 and 7 between the baseline period before insulin (43 and 41 m./sec.) and the time of maximal hypotension after insulin (42 and 44 m./sec., respectively).

There was also no change in plasma sodium (three cases), potassium (three cases), or catecholamines (table 4) after insulin. Changes in plasma osmolarity (three cases) were commensurate with those expected from the fall in blood glucose alone.

Diurnal Variations of Blood Pressure

In nine diabetics with autonomic neuropathy diurnal studies of lying/standing blood pressure showed variations during the day. These changes were particularly striking in two patients receiving considerable doses of soluble insulin twice daily, when blood pressure fell markedly after the administration of the morning and evening doses of insulin given subcutaneously (figure 5) and were repeatable. Blood glucose and blood pressure generally fell and rose together. However, in most cases diurnal fluctuations of blood pressure were less marked, with falls of 10-20 mm. Hg after subcutaneous insulin.

TABLE 4

Case	Norepinephrine		Epinephrine	
	Before	After insulin*	Before	After insulin*
2	3.94	4.52	0.27	0.20
3	0.55	0.54	0.02	0.01
4	0.60	0.71	0.02	0.04
5	0.53	0.51	0.02	0.01

*At time of maximal hypotension.

Normal basal range: norepinephrine 0.1 - 1.0 ng./ml.; epinephrine 0.01 - 0.1 ng./ml.

DISCUSSION

These results show that insulin aggravates and may even initiate postural hypotension in autonomic neuropathy. A hypotensive effect of insulin has been reported by other workers. French and Kilpatrick[6] reported a progressive and unexplained fall in supine blood pressure after insulin in sympathectomized patients. Miles and Hayter[2] have shown that intravenous insulin causes a fall in right atrial pressure and cardiac output in diabetics (and, to a lesser extent, in normal controls), causing postural hypotension in those with abnormal baroreceptor reflexes. Thus, insulin lowers blood pressure only if circulatory reflexes are abnormal. In two of our diabetics without neuropathy, insulin caused no change in blood pressure.

The presence of a diurnal variation in postural hypotension after subcutaneous insulin, with a fall after morning and evening doses, confirms the hypotensive effect of insulin. In the normal individual, blood pressure rises from its lowest level on awakening and increases steadily through the day, to reach a maximum at bedtime,[7] and is unaffected by meals,[7,8] although deterioration of baroreceptor reflexes and postural hypotension have been reported after high doses of oral glucose.[9] In the present studies, apart from the insulin the only intervening external factors were breakfast and the evening meal. It is unlikely that the ingestion of a high carbohydrate load provokes a rapid shift of fluid into the bowel lumen, thus causing hypotension (as in the early dumping syndrome), since in no patient was a similar fall recorded after the midday meal.

The changes in pulse rate broadly correspond with the changes in blood pressure. Thus, a fall in blood pressure is associated with an increase in pulse rate. Some of the diabetics with postural hypotension have cardiac sympathetic denervation reducing their ability to increase the pulse rate.[10] In others a considerable tachycardia when upright failed to prevent a fall in blood pressure after insulin. This suggests that under these conditions peripheral vasoconstriction is more important than tachycardia in maintaining blood pressure. At the time of fainting from hypotension, our patients had tachycardia, in contrast to the

bradycardia present in fainting associated with prolonged tilting[11] or with the fear and anxiety engendered by intra-arterial and intracardiac catheters.[12] The five patients who fainted had all shown a sustained and progressive fall in blood pressure over the preceding hour, unassociated with subjective distress.

Despite the close association between a falling blood glucose and a falling blood pressure after insulin, it does not necessarily follow that one causes the other. The rapidity of onset of the circulatory changes after intravenous insulin (figure 4), within five to ten minutes when blood glucose has fallen little, makes it unlikely that the rate of fall of blood glucose is the trigger. This effect of insulin is not due to hypoglycemia. It has not yet been possible to determine whether the hypotensive effect of insulin is independent of its hypoglycemic action.

The mechanism of the action of insulin on the circulation does not appear to be due to ionic flux, since measurements of plasma sodium and potassium showed no change after insulin. The fall in plasma osmolality corresponded exactly with that expected from the measured fall in blood glucose. This does not exclude a shift of fluid and electrolytes in isotonic proportions from the extracellular to the intracellular compartments.

Relatively small changes in blood volume may underlie the large changes in blood pressure. Barraclough and Sharpey-Schafer[13] have stressed that if circulatory reflexes are absent, a slight change in venous return may drastically alter stroke output and, hence, blood pressure.

The effect on the circulation seems unlikely to be mediated by an alteration in nerve function, since no difference in motor-nerve conduction velocity was found before and after insulin. The two patients in whom these measurements were made developed severe postural hypotension after insulin and fainted as a result.

There was little significant change in plasma catecholamines measured prior to and at the time of maximal hypotension after insulin (table 4). Catecholamine responses to tilting have been shown to be blunted in diabetics with neuropathy.[14] Christensen[15] has also reported a rise in norepinephrine in diabetics after intravenous insulin while the blood glucose is still falling but no increase in epinephrine unless hypoglycemic levels (< 20 mg./100 ml.) are reached. Norepinephrine should cause peripheral vasoconstriction and raise blood pressure.

A fall in right atrial pressure after insulin[2] implies a reduced venous return and a diminution in peripheral vasomotor tone. Several of our patients have mentioned a feeling of warmth after intravenous insulin and clinically are vasodilated, even at the moment of fainting from hypotension. Thus, insulin may cause a redistribution of blood volume by altering tone in blood vessels of skin and/or perhaps muscle and the splanchnic bed. Middleton and French[16] found an increase in hand blood flow (i.e. vasodilatation of skin) occurring after insulin-induced hypoglycemia and attributed this to inhibition of vasoconstrictor tone. Our findings could be similarly explained if the vasodilatation occurring after insulin is secondary to the falling blood glucose or even the administration of insulin per se rather than the hypoglycemia.

The clinical relevance of this effect of insulin lies in the assessment of postural hypotension and its response to treatment, when the time relationship to routine insulin administration needs to be considered. Confusion of symptoms of hypotension and hypoglycemia is also possible and this occurred in two of our patients who fainted from hypotension after insulin when tilted. This may account for some diabetics who feel hypoglycemic with a falling but normal blood sugar and for some cases of loss of consciousness without warning, previously attributed to hypoglycemia. We have found only one patient (case 8) in whom we have established that such confusion between hypoglycemia and hypotension occurred in clinical practice.

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