The Effect of Metabolic Control on Hemodynamics in Short-Term Insulin-dependent Diabetic Patients

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SUMMARY

Hemodynamics variables (heart rate, arterial blood pressure, cardiac output, hepato-splanchnic blood flow, forearm blood flow, and plasma catecholamines) were measured during good (median blood glucose 4.7 mmol/L) and poor (median blood glucose 16.3 mmol/L) metabolic control in eight young, short-term, insulin-dependent diabetic patients. The measurements were performed twice within 2 wk, in random order. Continuous subcutaneous insulin infusion (CSII) was applied for 1 wk in order to obtain good control. All eight patients had elevated cardiac output (median 9%) and forearm blood flow (median 34%) during poor compared with good metabolic control, $P < 0.01$. In contrast, hepato-splanchnic blood flow was lower (median 12%) during poor compared with good metabolic control, $P < 0.05$. Heart rate remained unchanged, while mean arterial blood pressure was slightly higher during poor control, $P < 0.05$. Five of six patients had elevated plasma noradrenaline concentration during poor metabolic control. Due to the small number of patients investigated, no valid conclusion regarding the activity of the sympathoadrenal system can be drawn.

Our study suggests that both increased cardiac output and reduced hepato-splanchnic blood flow (redistribution) contribute to the elevated blood flow previously demonstrated in various other organs and tissues in diabetic patients during poor metabolic control.

DIABETES 1985; 34:1301–305.

In all organs and tissues of short-term insulin-dependent diabetic patients studied so far, blood flow (cerebrum,[1] retina,[2] kidney,[3,4] and forearm[5–7]) has been found elevated, particularly during poor metabolic control. Strict metabolic control for 1–2 wk induced normalization of blood flow.[8] Cardiac output measured before and after 1 yr of insulin treatment remained unchanged in newly diagnosed insulin-dependent diabetic patients.[9]

Our study was performed to elucidate the contribution of cardiac output and/or blood flow redistribution (reduced hepato-splanchnic blood flow) to the blood flow elevation in insulin-dependent diabetic patients during poor metabolic control.

PATIENTS

Eight insulin-dependent male diabetic patients volunteered for the study after giving informed consent (Table 1). The study was approved by the local Ethical Committee. None of the patients had retinopathy, nephropathy, neuropathy, or clinical evidence of heart disease. None was taking drugs other than insulin. All patients had hemoglobin A_{Ic} >9%, corresponding to a mean blood glucose level >12 mmol/L. All patients were treated with a mixture of fast- and intermediate-acting insulin at 7:30 a.m. and 6:00 p.m.

PROCEDURES

All patients were studied both during good and poor metabolic control (random order), using identical experimental procedures. The interval between the two investigations was <2 wk. The patients received their usual dose of fast- and intermediate-acting insulin at 7:30 a.m. and 6:00 p.m. during the whole period of poor metabolic control. Good metabolic control was achieved by the use of continuous subcutaneous insulin infusion (CSII; Autosyringe, Hooksett, New Hampshire), initiated 8 days before the experiments were performed. All patients had their usual diet consisting of three main meals and three snacks; standard meals were not applied. All patients were asked to keep their physical activity unchanged during the investigation period. None of the patients was hospitalized during the last 3 days before the start of the investigations. On the day of the study, the patients

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Received for publication 25 September 1984 and in revised form 26 June 1985.

TABLE 1
Clinical data of eight short-term IDDM patients

Patients	Age (yr)	Duration of diabetes (yr)	Height (m)	Body wt (kg)	HbA_{Ic} (%)
1	28	6	1.74	72	9.1
2	28	4	1.84	63	10.1
3	28	6	1.86	85	11.6
4	23	4	1.76	59	10.1
5	26	9	1.98	89	9.1
6	19	7	1.88	84	11.2
7	21	8	1.85	91	9.9
8	27	5	1.91	78	9.3
Median	27	6	1.86	81	10.0

had their usual breakfast at 8:00 a.m. and a snack at 10:00 a.m., but no lunch. During good metabolic control, a bolus dose of 4–10 U of Velosulin (Nordisk, Gentofte, Denmark) was given at 7:30 a.m., and the basal infusion was continued throughout the study period. During poor metabolic control the usual morning insulin dose was omitted, and all patients received 4 U of Velosulin at 7:30 a.m. on the day of the study. Room temperature was kept constant at 27°C. The patients rested in the supine position for 1 h before the start of the experiment (2:00 p.m.).

Arterial blood pressure was measured with a standard clinical sphygmomanometer (cuff 25 × 12 cm) on the right arm. Blood pressure was measured twice during each investigation and was recorded to the nearest 5 mm Hg. Diastolic blood pressure was taken as the disappearance of Korotkoff sounds (phase V). Mean arterial blood pressure (MAP) was calculated as follows: diastolic pressure + 1/3 × (systolic − diastolic blood pressure).

Heart rate was measured by palpation for 30 s during the cardiac output measurements.

Cardiac output was measured as rate of acetylene wash-in into pulmonary capillaries, using the acetylene rebreathing method. The correlation between acetylene and dye dilution cardiac output measurements is 0.94 ($N = 22$, $P < 0.001$), with no significant difference in mean cardiac output values.[10,11] The subjects rebreathed six times from a rubber bag containing 2 L of a gas mixture containing 2% acetylene, 9% argon, and 45% oxygen in nitrogen. Respiratory frequency was normal. The gas was sampled from the mouthpiece of the rubber bag and continuously analyzed in a quadropol 8-channel mass spectrometer (Centronic MGA 200, 20th Century Electronics, Croydon Surrey, United Kingdom). Cardiac output was measured five times with 10-min intervals in each subject. The last four measurements were used to calculate the mean value. The intraindividual coefficient of variation was 7%.

Stroke volume was estimated from cardiac output/heart rate.

Pulmonary tissue volume was calculated from gas fractions during rebreathing as the difference between distribution space for a water-soluble gas (acetylene) and a water-insoluble gas (argon).[12] The last four measurements were used to calculate the mean value. The intraindividual coefficient of variation was 9%.

Hepato-splanchnic blood flow was estimated by measurements of peripheral indocyanine green (ICG) clearance after an intravenous bolus injection of 12.5 mg ICG.[13] Blood samples were drawn at 1 min before and 5, 7, 9, 11, 13, and 15 min after the injection of ICG. Plasma ICG concentrations were read spectrophotometrically at 805 nm. Plasma ICG fractional clearance rate (k, disappearance rate constant) was calculated from the regression line (least-square

TABLE 2
Blood glucose standard bicarbonate and insulin dose in eight IDDM patients during good and poor metabolic control

	Blood glucose before experiments* (mmol/L)		Blood glucose during experiments† (mmol/L)		Standard bicarbonate (mmol/L)		Insulin dose (U/24 h)	
	Good	Poor	Good	Poor	Good	Poor	Good	Poor
1	7.3	14.3	4.7	20.8	25.5	25.5	46	50
2	6.6	11.5	5.3	11.2	25.4	25.0	46	54
3	6.5	20.0	4.5	21.9	25.5	25.3	70	82
4	6.0	20.6	4.2	19.5	26.8	20.6	52	48
5	5.9	—	4.6	12.0	23.6	26.0	53	48
6	7.3	—	4.7	11.9	25.8	25.8	44	44
7	6.7	15.6	5.0	16.0	—	26.3	71	68
8	7.3	14.2	4.6	17.5	27.2	24.1	56	56
Median	6.7	15.0	4.7	16.3	25.5	25.3	53	52
	$P < 0.05$		$P < 0.01$		NS		NS	

*Median values of a seven-sample blood glucose profile/day taken the last 2 days before investigations.
†Median values of blood glucose measured at the start and end of the investigations.

TABLE 3
Hemodynamic variables during good and poor metabolic control in eight IDDM patients

	Cardiac output (L/min)		Forearm blood flow (ml/min/1000 ml tissue)		Hepato-splanchnic blood flow (k) (min^{-1})		Blood pressure (mm Hg)		Heart rate (beats/min)	
Patients	Good	Poor	Good	Poor	Good	Poor	Good	Poor	Good	Poor
1	4.15	5.66	73	82	0.44	0.39	127/72	139/83	71	63
2	4.78	5.25	50	100	0.36	0.18	105/70	116/70	65	60
3	5.91	5.97	52	96	0.20	0.18	124/87	132/78	64	66
4	4.02	5.38	117	122	0.22	0.22	116/79	125/79	68	84
5	6.62	6.68	70	84	0.21	0.19	112/78	134/86	49	52
6	5.84	6.91	140	176	0.19	0.15	120/78	125/80	78	78
7	5.66	5.75	56	70	—	—	150/90	150/95	99	100
8	4.46	4.93	36	68	0.16	0.11	112/70	123/76	70	70
Median	5.22	5.71	63	90	0.21	0.18	118/78	129/80	70	68
	$P < 0.01$		$P < 0.01$		$P < 0.05$		Syst. BP, $P < 0.01$ Diast. BP, NS		NS	

method) of the logarithmically transformed plasma concentrations versus time. The measurements were performed twice during each investigation, using the obtained mean value. The intraindividual coefficient of variation was 8%.

Forearm blood flow was measured by venous occlusion plethysmography.[14] Blood flow was measured five times with 5-min intervals during each investigation. The mean value was calculated from the last four measurements. The intraindividual coefficient of variation was 9%.

Total peripheral vascular resistance was estimated as MAP/cardiac output.

Blood glucose concentrations were measured by the hexokinase method.[15] All patients collected a seven-sample blood glucose profile for 1 day during the last 2 days before the investigations were performed. Finger-prick samples were taken into 10-μl end-to-end capillary tubes, before and 90 min after the three main meals and at bedtime. The samples were sent to the hospital for analysis. In addition, blood glucose was measured at the start and at the end of each investigation. Standard bicarbonate, hematocrit, and plasma protein concentrations were measured using conventional laboratory techniques. Hemoglobin A_{Ic} was measured before the start of the study (normal range in our laboratory, 4.1–6.4%).[16]

Plasma concentrations of noradrenaline and adrenaline were determined by a double-isotope derivative assay.[17,18] Urine was tested for ketone bodies using dip-stix.

Statistical analysis was made by Wilcoxon matched-pairs signed-ranks test. Level of statistical significance was $2P < 0.05$.

RESULTS

Table 2 shows the state of metabolic regulation during the last 48 h before the investigations and during investigations in good and poor metabolic control (median blood glucose 4.7 mmol/L and 16.3 mmol/L, respectively, $P < 0.01$). During the investigations no significant change in blood glucose was seen. None of the patients had ketone bodies in their urine and standard bicarbonate was normal. The daily insulin dose remained the same during the study. Hematocrit and plasma protein remained the same during good and poor metabolic regulation.

Cardiac output and forearm blood flow were elevated (median 9% and 34%, respectively) in all eight patients during

TABLE 4
Hemodynamic variables during good and poor metabolic control in eight IDDM patients

	Stroke volume (ml)		Total peripheral vascular resistance (mm Hg/L/min)		Pulmonary tissue volume (L)		Plasma adrenaline (ng/ml)		Plasma noradrenaline (ng/ml)	
Patients	Good	Poor	Good	Poor	Good	Poor	Good	Poor	Good	Poor
1	58	90	22	18	1.70	1.04	0.07	0.05	0.13	0.16
2	74	88	17	16	2.19	1.29	0.02	0.03	0.18	0.19
3	92	91	17	16	1.48	1.74	0.02	0.00	0.08	0.10
4	59	64	23	18	1.23	0.92	0.10	—	0.10	—
5	135	129	13	15	1.50	1.24	0.03	0.04	0.21	0.25
6	75	89	15	14	—	—	0.03	0.02	0.11	0.20
7	57	58	19	20	1.76	1.97	0.01	0.02	0.14	0.09
8	64	71	19	19	1.54	1.70	—	0.33	—	0.17
Median	69	89	18	17	1.50	1.29	0.03	0.03	0.13	0.17
	$P < 0.1$		NS		NS		NS		NS	

poor compared with good metabolic control ($P < 0.01$, Table 3). In contrast, hepato-splanchnic blood flow was lower (median 12%) during poor compared with good metabolic control ($P < 0.05$).

Mean and systolic blood pressures were slightly higher during poor metabolic regulation ($P < 0.05$). Heart rate remained stable (Table 3), and, consequently, stroke volume tended to be higher during poor control compared with normoglycemia. The median figures were 89 ml and 69 ml, respectively ($P < 0.1$, Table 4). Pulmonary tissue volume did not change significantly in relation to metabolic control (Table 4). Plasma adrenaline concentration remained unchanged, while plasma noradrenaline concentration was elevated in five of six patients during poor metabolic control (Table 4). Total peripheral vascular resistance tended to decrease during poor compared with good metabolic control, but a statistically significant difference was not achieved.

DISCUSSION

The major novel observation in our study is that poor metabolic control (i.e., nonketotic hyperglycemia with a mean blood glucose of 16 mmol/L) is associated with a 9% increase in cardiac output, a 34% increase in peripheral (forearm) blood flow, and a 12% decrease in (hepato-splanchnic) blood flow, compared with values obtained during normoglycemia (mean blood glucose 4.7 mmol/L). The factor(s) responsible for the hemodynamic alterations during poor metabolic control cannot be identified at present. The fact that venous hematocrit and plasma protein concentrations did not vary during the study indicates that major changes in plasma volume did not occur. Five of six patients had elevated plasma noradrenaline concentration during poor metabolic control. Due to the small number of patients investigated, no valid conclusion regarding the sympathoadrenal system can be drawn. Heart rate was the same in the two stages of metabolic control and, consequently, stroke volume tended to be higher during poor control than during normoglycemia. Pulmonary tissue volume, which reflects central venous pressure,[19] was identical in the two experimental situations, and afterload (blood pressure) was higher in spite of no significant fall in total peripheral vascular resistance during poor metabolic control. Although myocardial contractility was not directly measured in this study, it may be suggested that myocardial contractility is increased during poor metabolic control. Myocardial contractility may be increased due to slightly elevated sympathetic activity or due to increased "intrinsic" myocardial performance. The nature of factors responsible for the increase in myocardial contractility, which recently has also been observed during exercise during poor metabolic control in patients with IDDM,[20] requires further investigation.

The increase in total peripheral flow comprised two opposing components, namely an increase in forearm (muscle) flow and a decrease in hepato-splanchnic flow. The mechanisms involved in these changes and the importance of hypoinsulinemia or hyperglycemia cannot be identified at present. In the kidney, hyperglycemia per se (not lack of insulin) has been held responsible for increased perfusion during hyperglycemia.[21] Atherton et al.,[22] using high-speed fluorescein angiography, showed that acutely induced hyperglycemia increased retinal blood flow in cats. The flow increment represented an overriding of the normal autoregulatory response, i.e., the maintenance of constant blood flow despite changes in perfusion pressure. Intravenous bolus injection of 6–8 U of insulin induces a rise in heart rate and blood pressure.[23] Thus, it is not likely that insulin per se causes the increase in cardiac output during poor metabolic control (hypoinsulinemia). The decrease in hepato-splanchnic flow may be compensatory to vasodilatation in other areas, since the hepato-splanchnic vascular bed is a major determinant of human blood pressure regulation.[24] It has been suggested that augmented blood flow is significant for the development of long-term vascular complications.[25] Further studies are needed to identify the mechanisms responsible for the marked hemodynamic differences observed in our study in insulin-treated patients during everyday changes in metabolic control.

ACKNOWLEDGMENTS

This study was supported by the Danish Space Board Project 1112-33/84 and by Forskningsrådet Danmark.

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