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Originals

Haemodynamic changes in insulin-induced hypoglycaemia in normal man

J. Hilsted[2, 3], F. Bonde-Petersen[1], M.-B. Nørgaard[1], M. Greniman[1], N. J. Christensen[5], H.-H. Parving[4] and M. Suzuki[1]

[1]August Krogh Institute, University of Copenhagen; [2]Surgical Department I and Department of Anaesthesia, Kommunehospitalet; [3]Hvidøre Hospital; [4]Department of Clinical Physiology and Medical Department C, Bispebjerg Hospital; and [5]Department of Internal Medicine and Endocrinology F, Herlev Hospital, Copenhagen, Denmark

Summary. Haemodynamic variables (plasma volume, heart rate, blood pressure, cardiac output, stroke volume, pulmonary tissue volume, total peripheral vascular resistance, hepato-splanchnic vascular resistance, lower extremity vascular resistance and plasma catecholamines) were measured before and after insulin-induced hypoglycaemia in seven healthy men. Plasma volume decreased significantly at the nadir of glucose (mean decrease 222 ± 41 ml) and subsequently increased to pre-hypoglycaemic values within 30 min. Cardiac output increased in response to hypoglycaemia (mean increase 2.8 ± 0.6 l/min). The early rise in cardiac output was primarily due to an increase in heart rate, but later mainly due to increased stroke volume. Since pulmonary tissue volume was constant, the observed changes in cardiac output are unlikely to be due to a Frank-Starling mechanism but rather to increased sympatho-adrenal activity. Total peripheral vascular resistance as well as lower extremity vascular resistance decreased, whereas hepato-splanchnic vascular resistance was unaffected. Thus insulin-induced hypoglycaemia has marked transient effects on the circulation.

Key words: Insulin-induced hypoglycaemia, plasma volume, heart rate, cardiac output, cardiac stroke volume, blood pressure, plasma catecholamines, vascular resistance.

Insulin-induced hypoglycaemia – a frequent complication of insulin therapy – has profound effects on the circulation. Indeed, although infrequent, cardiac arrest and angina pectoris have been reported [1]. Previous investigations of haemodynamic events during hypoglycaemia have focussed mainly on the circulation in the extremities [2–4] and there are few reports on the central circulation [1, 5, 6]. The aim of the present study was to characterize the circulatory changes during hypoglycaemia in healthy subjects by means of simultaneous measurements of plasma volume, blood pressure, heart rate, cardiac output, pulmonary tissue volume, hepato-splanchnic blood flow, lower extremity blood flow and plasma catecholamines.

Subjects and methods

Study population

Seven healthy male students (age 22 ± 0.6 years, mean ± SEM, height 180 ± 3 cm, weight 72 ± 4 kg) volunteered for the study after giving informed consent. The study was approved by the local Ethical Committee. The subjects were physically fit, maximal oxygen uptake ($\dot{V}o_2$ *max*) determined during ergometer cycle exercise was 4.10 ± 0.3 l/min (normal range 2.25–4.65 l/min) or 57 ± 3 ml · kg^{-1} · min^{-1}. None had a family history of diabetes mellitus, nor were they taking any drugs.

Procedures

Experiments were performed in the afternoon, the subjects having fasted and abstained from tobacco for at least 5 h before the study. A cannula was inserted into a cubital vein in each arm, whereupon they rested supine throughout the experiment. Room temperature was 25 ± 1 °C. The patients wore shorts; blankets were not used. Over a period of 30 min, the experimental procedures were explained to the subjects; subsequently, pre-hypoglycaemic measurements were made for 1 h.

Hypoglycaemia was induced by IV injection of soluble insulin (Actrapid, Novo) 0.15 IU/kg body weight. The following variables were determined:

Plasma volume was measured by means of ^{125}I- labelled serum albumin during the pre-hypoglycaemic period [7], and the haematocrit at this time was used in relation to subsequent determinations to estimate percentage change in plasma volume. Plasma protein concentrations were read refractometrically in triplicate with a total-solid meter (American Optical Corporation, Scientific Instrument Division, Buffalo, New York). No subject had interfering hyperlipaemia.

Arterial pressure was measured by the indirect auscultatory method, using a sphygmomanometer and a cuff. Mean arterial blood pressure (MAP) was calculated as: diastolic blood pressure + 1/3 × (systolic – diastolic blood pressure).

Heart rate was registered continuously with precordial electrodes and displayed as the ECG on an oscilloscope (S&W Diascope 521, Simonsen & Weel, Copenhagen, Denmark).

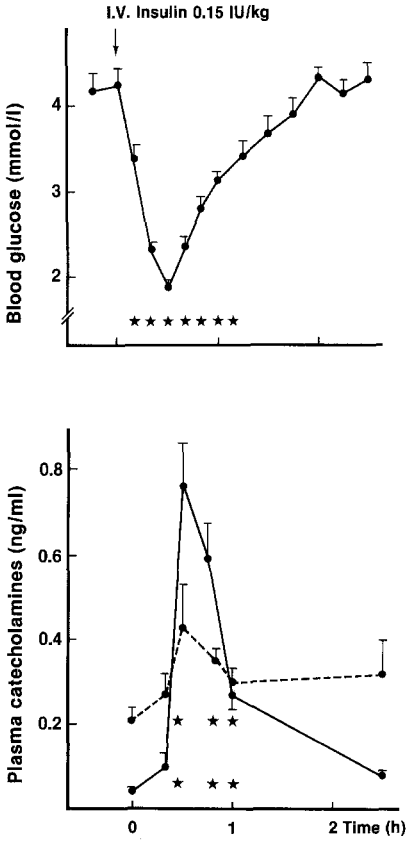

Fig. 1. Blood glucose concentrations and plasma concentrations of adrenaline (●——●) and noradrenaline (●---●) in seven healthy subjects before and after IV injection of 0.15 IU insulin/kg body weight. $*p<0.05$, significant changes from values obtained before injection of insulin

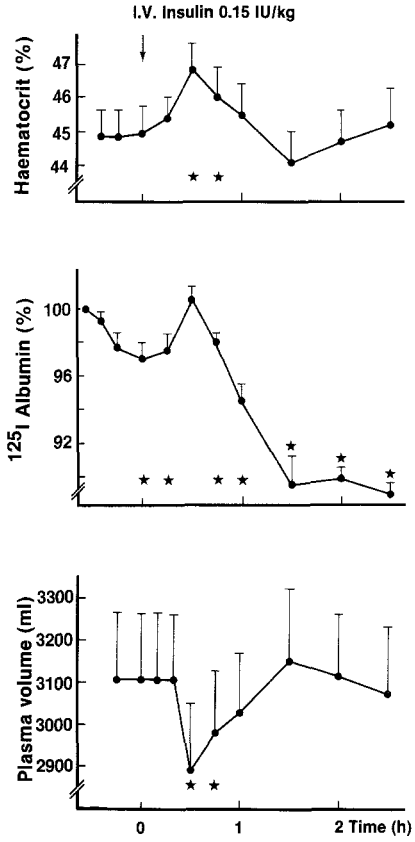

Fig. 2. Haematocrit, percentage change in activity of IV injected ^{125}I-albumin and plasma volume before and after IV injection of 0.15 IU insulin/kg body weight in seven healthy subjects. $*p<0.05$, significant changes from values obtained before injection of insulin

Cardiac output was measured as rate of acetylene wash-in into pulmonary capillaries, the subject rebreathing from a rubber bag at normal frequency and tidal volume [8]. Respiratory frequency and tidal volume were slightly increased at blood glucose nadir. Gas was sampled from the mouthpiece of the rubber bag and continuously analysed for acetylene, argon, oxygen and nitrogen in a mass spectrometer (Centronic MGA 200, 20th Century Electronics, Croydon, Surrey, UK). Coefficient of variation in 13 measurements of cardiac output was 5% in a normal subject.

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) [9]. Coefficient of variation in 13 measurements of pulmonary tissue volume was 8% in a normal subject.

Total peripheral resistance (TPR) was estimated as mean arterial pressure/cardiac output, total peripheral vascular conductance (TPR^{-1}) as cardiac output/mean arterial pressure.

Hepato-splanchnic vascular resistance (R_{SPL}). Hepato-splanchnic blood flow was estimated by measurements of peripheral Indocyanine Green (ICG) clearance after a bolus injection [10]. Plasma Indocyanine Green fractional clearance rate (k) (disappearance rate constant) was calculated from the regression line (determined by the method of least squares) for the logarithmically transformed plasma concentrations versus time. Plasma clearance (PC), which parallels hepatic blood flow, was then calculated from the equation $PC = k \times PV$ (PV: plasma volume). ICG is cleared from the circulation within 15 min of a bolus injection [10]; ICG was in the present study injected 7.5 min before every time point that a value is given for R_{SPL} (Fig. 5). Estimated splanchnic vascular resistance R_{SPL} was calculated from the equation $R_{SPL} = MAP/(k \times PV)$, R_{SPL} denoting resistance to plasma flow.

Lower extremity vascular resistance. Lower extremity blood flow (F_{LE}) was measured by venous occlusion plethysmography [11]. Coefficient of variation in 13 measurements of lower extremity blood flow in normal subjects was 6%. Lower extremity vascular resistance (R_{LE}) was calculated from the equation

$$R_{LE} = \frac{MAP}{F_{LE}}$$

Plasma concentrations of noradrenaline and adrenaline were determined by a single isotope derivative assay [12].

Glucose concentrations were measured by the hexokinase method [13].

Statistical analysis was made by Student's t-test for paired comparisons. The level of statistical significance chosen was $p<0.05$.

Results

The nadir of blood glucose was reached 30 min after IV insulin in all subjects (Fig. 1); by 2 h after insulin blood glucose levels had returned to normal levels.

Plasma adrenaline and noradrenaline increased significantly 30 min after insulin and returned to prehypoglycaemic levels 2 h 30 min after insulin (Fig. 1).

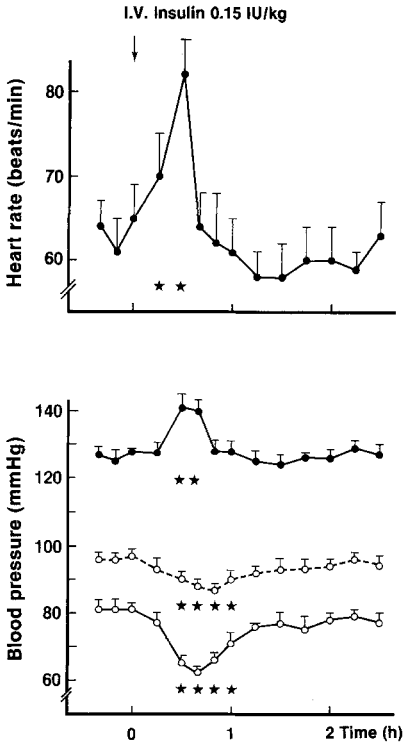

Fig. 3. Heart rate and blood pressure before and after IV injection of 0.15 IU insulin/kg body weight in seven healthy subjects. $*p<0.05$, significant changes from values obtained before injection of insulin

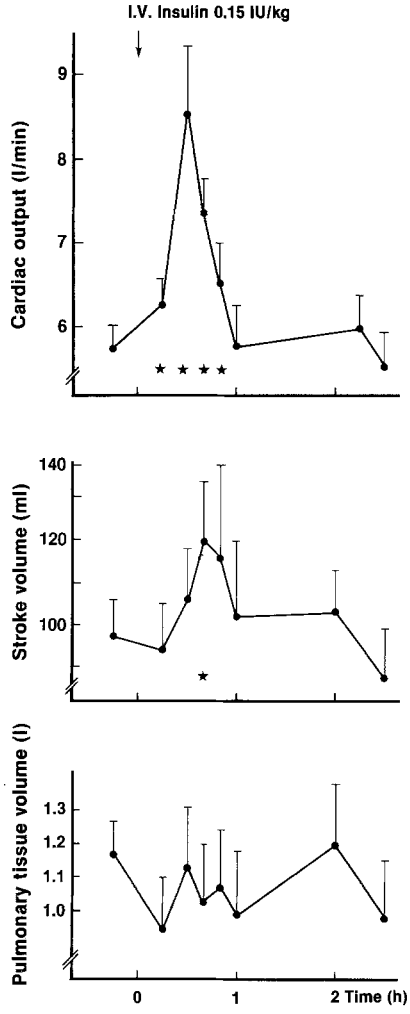

Fig. 4. Cardiac output, cardiac stroke volume and pulmonary tissue volume in seven healthy subjects before and after IV injection of 0.15 IU insulin/kg body weight. $*p<0.05$, significant changes from values obtained before injection of insulin

Plasma volume decreased significantly (mean decrease 222 ml) at 30 min and returned to prehypoglycaemic values by 60 min after insulin (Fig. 2). No significant changes occurred in total intravascular protein mass (mean ± SEM, 217 ± 11 g before hypoglycaemia, 210 ± 10 g at glucose nadir and 209 ± 11 g after hypoglycaemia). The percentage ^{125}I- albumin activity in plasma (^{125}I/ml plasma at the various time points as a percentage of the value at time 0 in the pre-hypoglycaemic period) increased significantly from 20 to 30 min after insulin (Fig. 2).

Heart rate increased significantly 30 min after insulin and fell to pre-hypoglycaemic levels 10 min later (Fig. 3). Systolic blood pressure increased significantly 30 min after insulin and returned to pre-hypoglycaemic levels 20 min later, whereas diastolic blood pressure decreased significantly after insulin, minimum values being obtained 40 min after insulin. Pre-hypoglycaemic values were re-established 90 min after insulin. MAP decreased significantly, but was also normalized 90 min after insulin (Fig. 3).

The increments in systolic blood pressure and heart rate 30 min after insulin coincided with an increase in cardiac output. Cardiac output returned to basal levels within 60 min after insulin (Fig. 4).

Stroke volume increased later than cardiac output (40 min after insulin) and returned to basal in values at 60 min (Fig. 4). No significant changes occurred in pulmonary tissue volume (Fig. 4).

A significant decrease was found in total peripheral resistance at 30 min after insulin, which became normal at 60 min. The decrease in total peripheral resistance was paralleled by a decrease in lower extremity vascular resistance, while no significant changes were found in hepato-splanchnic vascular resistance (Fig. 5).

Total peripheral conductance increased significantly from 60 ± 4 to $82 \pm 61 \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \cdot 10^{-3}$ at 30 min after insulin and returned to 62 ± 5 at 2 h after insulin. Lower extremity vascular conductance increased from 0.26 ± 0.04 to 0.46 ± 0.04 ml $\cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \cdot 1000\,\text{g}^{-1}$ tissue at 30 min, returning to 0.29 ± 0.03 after 60 min. Provided that vascular conductance increased in parallel in all four extremities and assuming a mean extremity weight of 8 kg, the increase in extremity vascular conductance may account for $\frac{32 \times 0.20 \times 10^{-3}}{22 \times 10^{-3}} \times 100\% = 29\%$ of the increase in total peripheral conductance.

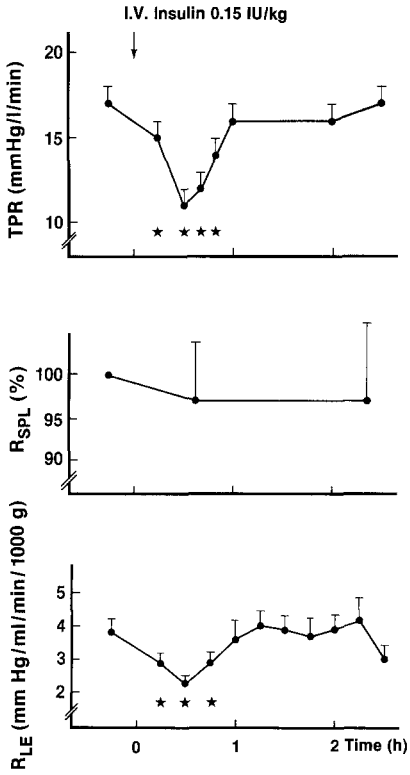

Fig. 5. Total peripheral vascular resistance (TPR), percentage change in hepato-splanchnic vascular resistance (R_{SPL}), and lower extremity vascular resistance (R_{LE}) before and after IV injection of 0.15 IU insulin/kg body weight in seven healthy subjects. R_{SPL} is given in percentage of values obtained before injection of insulin. $*p<0.05$, significant changes from values obtained before hypoglycaemia

Discussion

The present study has shown that insulin-induced hypoglycaemia is associated with a transient but significant reduction in plasma volume.

Previous investigations of the effect of insulin on plasma volume in diabetic subjects by three groups [14–16] have all used inravenous insulin in doses similar to ours. However, conflicting results were obtained in these reports, which are not directly comparable to the present study, because we found – in contrast to the previous ones – that blood glucose concentrations decreased to hypoglycaemic levels and plasma adrenaline increased. The increase in adrenaline is probably of major importance, since plasma volume decreases after intravenous injection of adrenaline [17].

The plasma volume changes in the present study may be ascribed to α-adrenergic stimulation. It has been shown that infusions of catecholamines reduce plasma volume to an extent similar to that found in the present study, probably due to an increase in capillary pressure mediated by an increase in post-capillary resistance, together with a decrease in pre-capillary resistance [17]. Furthermore, in a recent study by Frier et al. [18] haematocrit responses to hypoglycaemia were abolished in patients with cervical cord transection, yet were intact in patients having undergone splenectomy as well as in normal man during β-receptor blockade. These findings suggest that autotransfusion of erythrocytes from the spleen does not contribute significantly to the increase in haematocrit observed during hypoglycaemia, whereas an intact sympathetic nervous system is essential for the reduction in plasma volume during hypoglycaemia. Since β-receptor blockade does not alter the plasma volume response, alpha-adrenergic stimulation may be mainly responsible for the plasma volume reduction during hypoglycaemia. Sweating may also contribute; an average sized man loses about 200 ml of water during a hypoglycaemic reaction [19]. However, since this is lost from the total extracellular volume (about 49 l), the plasma volume reduction induced by sweating is probably small.

The increase in cardiac output in response to hypoglycaemia was similar to previous findings [1, 5]. Cardiac output increased simultaneously with heart rate at glucose nadir whereas stroke volume increased 15 min later, indicating that during hypoglycaemia the early increase in cardiac output is mainly due to an increase in heart rate whereas later, cardiac output is elevated due to an increased stroke volume. Pulmonary tissue volume, which reflects central venous pressure [20], did not change significantly. It may therefore be concluded that the increase in cardiac output during hypoglycaemia is not due to a Frank-Starling mechanism but rather to the increased sympathoadrenal activity, resulting in increased heart rate and contractility.

The increase in lower extremity blood flow found in the present study is similar to earlier observations [2–4]. Since hand blood flow during hypoglycaemia is increased in normal man and decreased in sympathectomized man [2], it has been suggested that the increase in extremity blood flow is to a large extent due to withdrawal of vasoconstrictor tone. The lack of change in hepato-splanchnic vascular resistance observed in the present study and in a previous study [6] may suggest that withdrawal of vasoconstrictor tone does not occur in the hepato-splanchnic vascular bed or that withdrawal of vasoconstrictor tone is counteracted by vasoconstriction elicited by increased sympathoadrenal activity. It should be noticed however, that some hepato-splanchnic vasodilation may occur about 30 min after glucose nadir [6]. Vasoconstriction may result from circulating catecholamines or from stimulation of sympathetic nerves since circulating noradrenaline during hypoglycaemia is at least in part derived from sympathetic nerve endings [21].

Increases in total peripheral vascular conductance during hypoglycaemia were, judged from estimates of extremity mass and from hepato-splanchnic blood flow and lower extremity blood flow, larger than the increase in conductance in the hepato-splanchnic vascular bed and the lower extremities. Accordingly, increased vascular conductance in vascular areas not investigated in the present study (brain and kidneys) might contribute

to the increase in total vascular conductance. Reliable human data on the circulation in these areas during hypoglycemia are lacking. Judged from animal studies however, a substantial increase occurs in cerebral blood flow during hypoglycaemia [22]. Alternatively, lower extremity blood flow may not be representative of total extremity blood flow.

In summary, in normal man insulin-induced hypoglycaemia is associated with a transient decrease in plasma volume, and an increase in cardiac output due to increase in heart rate and cardiac contractility. Hepato-splanchnic vascular resistance is unaffected, whereas lower extremity vascular resistance is decreased during hypoglycaemia. Increased cardiac output, haemoconcentration, hypercoagulability [23] and electrolyte shifts [24] may indicate a cardiac risk, associated with hypoglycaemia, especially in patients with overt cardiac disease and in the elderly.

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Dr. J. Hilsted
Medical Department F
Glostrup Hospital
D-2600 Glostrup
Denmark