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The effects of insulin-induced hypoglycaemia on cardiovascular function in normal man: studies using radionuclide ventriculography

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Summary. The cardiovascular effects of an intravenous injection of soluble insulin and of acute hypoglycaemia were examined in six normal male subjects using multiple-gated radionuclide ventriculography. The basal left ventricular ejection fraction rose significantly from 47 ± 3% (mean ± SEM) to 54 ± 3% $p < 0.01$, within 5 min of the intravenous injection of insulin, and before any significant changes occurred in the blood glucose concentration. The ejection fraction subsequently rose to a peak of 72 ± 5% coinciding with the onset of the acute hypoglycaemic reaction. This corresponded to the nadir of blood glucose and was associated with rises in heart rate, stroke volume and cardiac output. The heart rate returned to the resting value within 30 min of the acute hypoglycaemic reaction, but the ejection fraction, stroke volume and cardiac output were still elevated 90 min later. The peak ejection fraction value immediately preceded the maximal increment of plasma catecholamines released in response to hypoglycaemia. Thus, administration of intravenous insulin had a small, immediate, discernible effect on the cardiovascular system. A subsequent rise in left ventricular ejection fraction of much greater magnitude was stimulated by the development of acute hypoglycaemia, and was associated temporally with sympatho-adrenal activation. The use of radionuclide ventriculography showed that the haemodynamic changes provoked by hypoglycaemia produced a sustained effect on cardiac contractility.

Key words: Radionuclide ventriculography; Insulin-induced hypoglycaemia; heart rate; blood pressure; plasma catecholamines.

Acute hypoglycaemia is associated with profound haemodynamic changes [1] and some of the cardiac manifestations of insulin-induced hypoglycaemia have been described in normal man [2]. It has been suggested previously that insulin has a direct effect upon the cardiovascular system, which is independent of hypoglycaemia [3, 4], although this was not confirmed in another study [5]. The aim of the present study was to examine the effects of intravenous insulin on cardiovascular function in normal subjects, using multiple-gated radionuclide ventriculography. This method provides a reliable, non-invasive estimate of cardiac function and performance [6]. The serial measurements of cardiac function were examined following an intravenous injection of insulin and during the development of, and recovery from acute hypoglycaemia.

Subjects and methods

The study was approved by the local Medical Ethical Advisory Committee and informed consent was obtained from all subjects. Six healthy male volunteers, aged 21-28 years (mean 24 years), none of whom were taking medications, were studied after an overnight fast, having remained in a recumbent position for 1 h. The consumption of alcohol, tobacco, tea and coffee was avoided for 12 h before and during each study. Basal blood samples were withdrawn from an indwelling teflon cannula, inserted into an antecubital vein. Each subject was given a placebo injection of 1 ml of 0.9% saline, 5 min before the administration of an intravenous injection of soluble insulin (Human Actrapid, Novo, Basingstoke, Hants, UK), in a standard dose of 0.15 U/kg body weight. Serial sampling of blood and estimations of haemodynamic variables were made every 5 min until the onset of the acute autonomic reaction (R), which coincided with the sudden development of a tachycardia. Subsequent blood sampling and cardiovascular measurements were timed from R to eliminate the individual variability in the time taken to develop hypoglycaemia after the intravenous injection of insulin. Blood sampling was continued to R + 90 min when the study was terminated.

The heart rate was measured continuously using precordial electrodes with the heart rate displayed on an oscilloscope (LifeTrace 12, Albury Instruments Ltd, London, UK). Blood pressure was measured using a mercury sphygmomanometer by one observer, with diastolic pressure being measured at Korotkoff's 5th sound. Mean arterial blood pressure (MAP) was calculated as diastolic pressure plus one third of the difference between systolic and diastolic blood pressures. For the calculation of changes in heart rate and blood pressure, readings were taken every 5 min.

Blood glucose was measured with the Cobas Bio Centrifugal Analyser (Roche Diagnostics, Basle, Switzerland) using the hexokinase

method, and plasma adrenaline and noradrenaline were measured using radioenzymatic assays [7]. Radionuclide ventriculography was performed using the multiple-gated technique with technetium-99m isotope (800 MBq) as described previously [8]. Briefly, erythrocytes were labelled in vivo by the injection of the isotope 30 min after the intravenous injection of Stannous pyrophosphate. Subjects were studied supine, using the Siemens LEM mobile gamma camera (Siemens Ltd, Des Plaines, Ill, USA) which was positioned to give the best separation of the left and right ventricles. This was usually in the left anterior oblique position with a cranio-caudal tilt to separate the atria from the ventricles. Data were obtained at a rate of 20 frames/cycle, with acquisition of the data during 5 min. The left ventricular ejection fraction (LVEF) was determined by standard methods using the formula:

$$\text{LVEF} = \frac{\text{end diastolic counts - end systolic counts}}{\text{end diastolic counts - background counts}}$$

A single fixed region of interest was used. The left ventricular ejection fraction was determined by a single observer who was unaware of the timing of the measurements. The reproducibility for this technique in our laboratory is $r = 0.98$, and the coefficient of variation is 4%. The relative left ventricular end-diastolic volume was calculated separately from the ejection fraction measurements by measuring counts in the end-diastolic frame. The results are expressed as a percentage of basal radioactivity. The relative stroke volume was calculated from the product of end diastolic volume × LVEF, and the relative cardiac output from the product of stroke volume × heart rate.

Statistical analysis

Statistical comparisons were made using Student's t-test for paired data, and results are expressed as mean ± SEM for all 6 subjects. The level of statistical significance chosen was $p < 0.05$.

Results

All subjects experienced a typical hypoglycaemic reaction (R) with the acute onset of adrenergic symptoms at 25 ± 4 min (mean ± SD) after insulin was administered. Symptoms of the acute autonomic reaction (R) commenced coincidentally with the onset of a tachycardia which was observed in all subjects, and which coincided also with the nadir of blood glucose.

Metabolic/hormonal changes (Fig. 1)

There was no change in the mean blood glucose following the injection of saline. The blood glucose began to fall in individual subjects at 10 min after the insulin injection. The mean blood glucose fell significantly from 4.6 ± 0.1 mmol/l to 2.1 ± 0.2 mmol/l at 0 + 15 min, and reached a nadir of 1.0 ± 0.2 mmol/l at R ($p < 0.01$). Thereafter the typical biphasic rise in blood glucose was observed with an initial rapid rise between R and R + 15 min, and a slower rise between R + 15 min and R + 90 min. At R + 90 min the blood glucose was 3.7 ± 0.4 mmol/l and had not returned to basal values.

Plasma adrenaline rose significantly from a basal value of 0.1 ± 0.1 nmol/l to a peak of 5.5 ± 1.1 nmol/l at R + 15 min ($p < 0.02$). Similarly, plasma noradrenaline rose significantly from 1.8 ± 0.4 nmol/l to 2.8 ± 0.5 nmol/l at R + 15 min ($p < 0.05$).

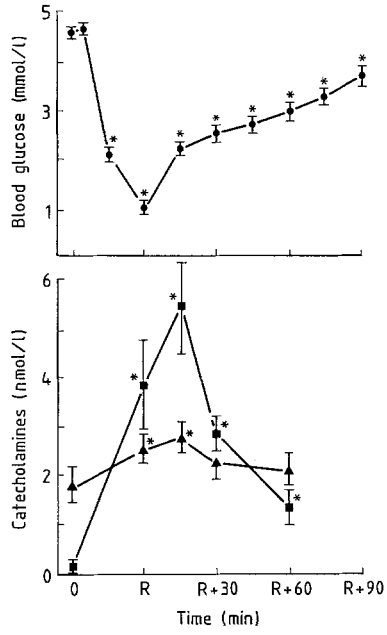

Fig. 1. Mean response (± SEM) to blood glucose (●), plasma adrenaline (■) and noradrenaline (▲) following injection of intravenous insulin (0.15 U/kg) at time 0. (R = autonomic reaction). *$p <$ 0.05 compared to 0

Cardiovascular changes (Figs. 2 and 3)

The placebo injection of saline had no effect on heart rate or blood pressure. No immediate change in the mean heart rate occurred following the bolus injection of insulin, which was 63 ± 4 beats/min basally and 64 ± 3 beats/min 5 min after the injection. This response occurred in all subjects with the exception of one individual, in whom an immediate rise in heart rate was noted, from 52 to 62 beats/min. This rise was transient, and the heart rate returned to the basal value by R + 10 min. At the time of the acute hypoglycaemic reaction (R) a rise in heart rate occurred in all subjects with a mean heart rate of 87 ± 3 beats/min ($p < 0.005$ compared to basal). This increase in heart rate was not sustained, and by R + 30 min the heart rate was similar to basal values.

No change in blood pressure was observed immediately after the insulin injection. The systolic blood pressure increased at the time of onset of the acute reaction, reaching a peak of 127 ± 5 mmHg compared to a basal value of 104 ± 4 mmHg at R + 15 min ($p <$ 0.01 compared to basal). The diastolic blood pressure fell significantly from a basal value of 64 ± 3 mmHg to 52 ± 1 mmHg at R + 15 min ($p < 0.001$). No change in the mean arterial pressure occurred; the mean basal value was 77 ± 3 mmHg, and was 77 ± 1 mmHg at R + 15 mins.

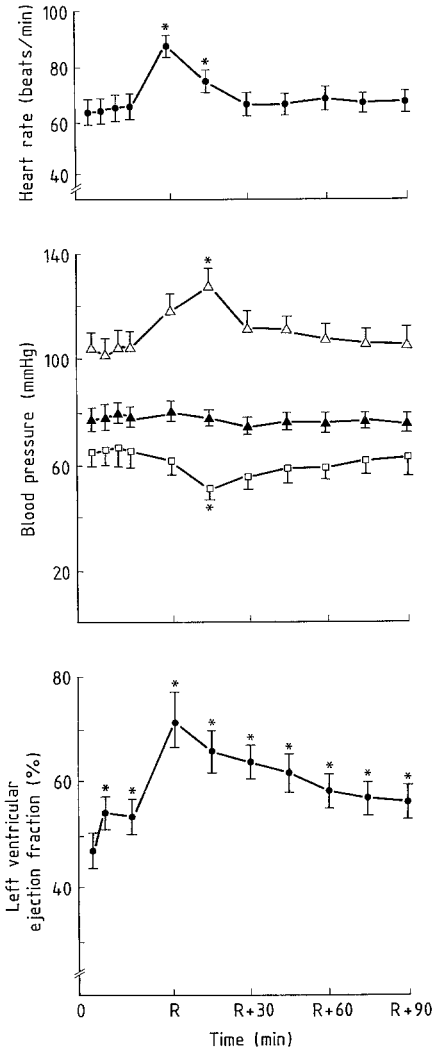

Fig. 2. Mean response (±SEM) of heart rate (●), systolic blood pressure (△), diastolic blood pressure (□), mean arterial blood pressure (▲) and left ventricular ejection fraction (●, lower panel) following intravenous injection of insulin at time 0. (R = autonomic reaction). *$p < 0.05$ compared to 0

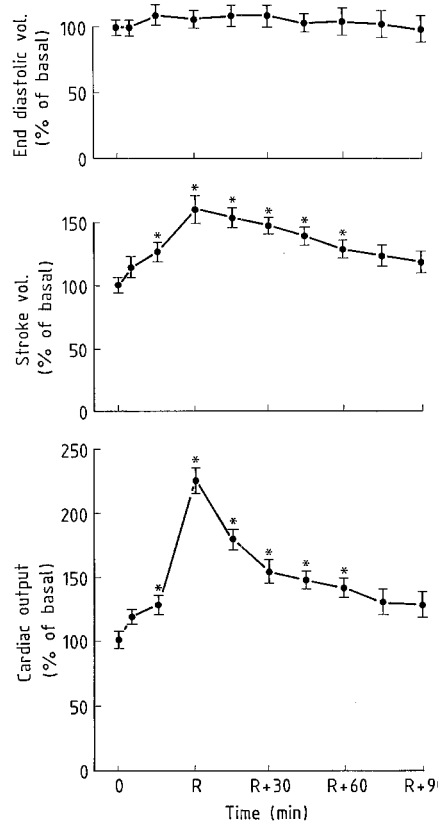

Fig. 3. Mean response (±SEM) of relative end-diastolic volume, stroke volume and cardiac output following intravenous injection of insulin at time 0. (R = autonomic reaction). *$p < 0.05$ compared to 0

The basal left ventricular ejection fraction (LVEF) was 47±3%. This was unchanged following the placebo injection at 46±3%. The LVEF rose briefly to 54±3% in the 5 min immediately after the insulin injection which was a significant increase from the basal value ($p < 0.01$). The LVEF rose significantly to a peak of 72±5% ($p < 0.001$ compared to basal) with the onset of the acute hypoglycaemic reaction (R), and remained significantly elevated at all subsequent times of measurement. No significant change occurred in the relative end-diastolic volume, which rose to a maximum of 109±6% at R+15 min (Fig. 2). Relative stroke volume increased significantly reaching a peak of 159±9% at R ($p < 0.01$). Similarly the relative cardiac output increased significantly reaching a peak of 226±10% at R ($p < 0.005$).

Discussion

Multiple-gated radionuclide ventriculography is an accurate, non-invasive method of assessing cardiac function allowing serial measurements, in contrast to "first pass" radionuclide techniques in which a limited number of measurements of cardiac function are possible [6]. The multiple-gated technique can be used to assess cardiac function at rest and in response to a number of physiological stresses including isometric exercise [9], cold-pressor stimulation [10], and dynamic exercise [11]. Cardiac function was examined immediately after an intravenous bolus injection of insulin in the present study. This was to ascertain whether insulin does have a direct effect on cardiac function, distinct from the autonomic and hormonal changes which accompany acute hypoglycaemia, which has been suggested by earlier studies of normal and diabetic patients [3, 12]. Insulin per se promotes an increase in heart rate, which is most marked in the upright position [3, 12]. This effect occurs within 5–10 min of an intravenous bolus injection of insulin, before any significant fall in blood glucose occurs and has been attributed to changes in circulating blood volume [4]. However, this early increase in heart rate is not prevented by beta-adrenergic blockade [13], and is unlikely to be caused

by compensatory adrenergic changes secondary to a fall in plasma volume.

A direct inotropic effect of insulin on the myocardium has been demonstrated in cats [14], sheep [15] and dogs [16]. In humans a rise in LVEF measured by radionuclide ventriculography has been observed in patients with acute myocardial infarction in response to a therapeutic regimen containing glucose, insulin and potassium given by intravenous infusion [17], although it is not known which constituent provokes the cardiac effect. In the present study a significant rise in left ventricular ejection fraction was observed within 5 min of the intravenous injection of insulin, before any measurable change in the blood glucose concentration had occurred, and confirmed that insulin has a direct effect on the cardiovascular system, which is independent of the development of hypoglycaemia. It was not possible to distinguish any changes which may be caused by a direct positive inotropic effect of insulin on the myocardium, from the peripheral effects of insulin administration, because the methods used to examine cardiac function were indirect. Maintenance of a normal blood glucose during continuous hyperinsulinaemia with a euglycaemic clamp technique has been employed to assess cardiac function using echocardiography [5]. The authors used a protocol for insulin infusion which resulted in an initial overshoot in plasma insulin concentration, which was followed by a plateau in plasma insulin levels. Unfortunately the effect on cardiac function in the 10-min period immediately after commencing the insulin was not reported. No inotropic or chronotopic effects were found with moderate hyperinsulinaemia during the plateau in plasma insulin levels. It is possible that supraphysiological hyperinsulinaemia may have occurred immediately following the injection of the bolus of insulin in the present study.

The effect of acute hypoglycaemia on cardiac output has been measured by Hilsted et al. [2], using the non-invasive technique of acetyline re-breathing to derive cardiac output. In that study [2] the cardiac output increased by 50% in response to hypoglycaemia, reaching its zenith coincidentally with the nadir of blood glucose and the maximal tachycardia. This increase in cardiac output was associated with a later, lesser rise in stroke volume. The authors postulated that the initial rise in cardiac output was caused by the increase in heart rate, whereas the later rise in cardiac output resulted from a presumed increase in myocardial contractility following the increase in sympatho-adrenal activity. The left ventricular ejection fraction bears no direct relationship to these other measurements of cardiac function. The increase in the left ventricular ejection fraction during hypoglycaemia was dramatic in comparison to the slight increase which occurred immediately following the injection of insulin. The pronounced increase in left ventricular ejection fraction which was observed in the present study was not associated with a change in the left ventricular end-diastolic diameter. This demonstrates that the later increase in stroke volume and in cardiac output is a direct result of an increase in myocardial contractility and is not caused by a Frank-Starling mechanism stimulated by an increase in end-diastolic volume.

In acute insulin-induced hypoglycaemia in man the temporal sequence of secretion of counterregulatory hormones following the fall of blood glucose is well defined [18]. Catecholamines are released initially, with a brisk rise in plasma adrenaline and noradrenaline which reach peak levels approximately 50 min after the injection of insulin [18]. The rise in plasma catecholamines provokes some of the acute haemodynamic changes (especially affecting blood pressure) in response to hypoglycaemia [1]. By contrast, the increase in heart rate probably results from direct sympathetic neural stimulation of the heart [19] and precedes the maximal rise in plasma adrenaline. When adrenaline was injected intravenously to achieve plasma concentrations similar to those in the current study [20], a rise in cardiac output was produced which was of similar magnitude to that occurring after hypoglycaemia [2]. An increase both of heart rate and of stroke volume contributed to the increased cardiac output which was observed [20], confirming that in man the major haemodynamic changes following acute hypoglycaemia occur in response to sympatho-adrenal activation.

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