Effects of euglycaemic and hypoglycaemic hyperinsulinaemia on sympathetic and parasympathetic regulation of haemodynamics in healthy subjects

Tomi Laitinen*, Hanna Huopio†, Ilkka Vauhkonen‡, Cyril Camaro§, Juha Hartikainen‡, Markku Laakso‡ and Leo Niskanen‡

*Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital and University of Kuopio, P.O. Box 1777, FIN-70211, Kuopio, Finland, †Department of Paediatrics, Kuopio University Hospital and University of Kuopio, P.O. Box 1777, FIN-70211, Kuopio, Finland, ‡Department of Medicine, Kuopio University Hospital and University of Kuopio, P.O. Box 1777, FIN-70211, Kuopio, Finland, and §University Medical Centre, University of Nijmegen, P.O. Box 9102, 6500 HC Nijmegen, The Netherlands

ABSTRACT

The effects of hypoglycaemia during hyperinsulinaemia, occurring under various pathophysiological conditions, on the cardiovascular regulatory system and vasculature are largely unknown. The aim of the present study was to investigate regulatory and haemodynamic responses to acute hyperinsulinaemia and consequent hypoglycaemia in 18 healthy subjects. Blood sampling and 5 min ECG and blood pressure recordings were performed at baseline and during the euglycaemic and hypoglycaemic phases of a hyperinsulinaemic clamp. Heart rate variability (HRV) and blood pressure variability (BPV) were assessed by using power spectral analysis, and baroreflex sensitivity (BRS) was assessed using the cross-spectral method. Stroke volume was assessed from the non-invasive blood pressure signal by the arterial pulse contour method. Euglycaemic hyperinsulinaemia did not change plasma catecholamine concentrations, HRV, BPV, BRS, heart rate, blood pressure, stroke volume, cardiac output or peripheral resistance. However, hyperinsulinaemic hypoglycaemia resulted in an 11.7-fold increase in the plasma adrenaline concentration (from 0.19±0.03 to 1.68±0.32 nmol/l; P<0.001), and a modest 1.3-fold increase in the plasma noradrenaline concentration (from 1.74±0.22 to 2.02±0.19 nmol/l; P<0.05) compared with baseline. Furthermore, we observed significant decreases in diastolic blood pressure (from 68±3 to 60±3 mmHg; P<0.05) and peripheral resistance (from 24.1±1.2 to 18.5±1.1 mmHg·min⁻¹·l⁻¹; P<0.01). Stroke volume and cardiac output increased markedly from the euglycaemic to the hypoglycaemic period only (P<0.01 for both). Hypoglycaemia did not influence HRV, BPV or BRS. Our findings indicate that hyperinsulinaemic hypoglycaemia is characterized by a significant increase in the plasma adrenaline concentration and by decreases in peripheral resistance and blood pressure. Counter-regulation during hyperinsulinaemic hypoglycaemia involves selective adrenomedullary sympathetic activation, and does not influence cardiac parasympathetic regulation or baroreflex control of heart rate.

Key words: adrenaline, autonomic nervous system, counter-regulation, hypoglycaemia, insulin, noradrenaline.

Abbreviations: BPV, blood pressure variability; BRS, baroreflex sensitivity; HF, high frequency; HRV, heart rate variability; LF, low frequency.

Correspondence: Dr Tomi Laitinen, Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, P.O. Box 1777, FIN-70211 Kuopio, Finland (e-mail Tomi.Laitinen@kuh.fi).
INTRODUCTION

Autonomic dysregulation is closely involved in metabolic and cardiovascular complications associated with hypoglycaemia. In patients with Type I diabetes or advanced Type II diabetes, recent antecedent hypoglycaemia may result in hypoglycaemia unawareness, characterized by reduced symptomatic responses to hypoglycaemia and autonomic failure [1]. On the other hand, hypoglycaemia has been suggested to trigger arrhythmic events and myocardial ischaemia in diabetic patients by mechanisms possibly related to sympathetic overactivation and increased catecholamine secretion [2–5]. The underlying mechanisms in hypoglycaemia-associated autonomic dysregulation and its consequences are not well described.

Hypoglycaemia is known to activate counter-regulatory mechanisms, resulting in increases in the plasma adrenaline (epinephrine) concentration, systemic noradrenaline (norepinephrine) spillover and the plasma noradrenaline concentration; concomitant hyperinsulinaemia causes additional activation of sympathetic postganglionic nerve function [6–8]. However, the involvement of parasympathetic nervous function in the response to hypoglycaemia remains unclear. As there are complicated central and peripheral interactions between the sympathetic and parasympathetic systems, information from studies concentrating only on one system at a time is incomplete.

The present exploratory study was conducted in order to investigate both sympathetic and parasympathetic regulatory responses to acute hyperinsulinaemia and hypoglycaemia in healthy subjects by assessing changes in plasma catecholamine concentrations as markers of sympathetic hormonal regulation, heart rate variability (HRV) as a marker of cardiac parasympathetic regulation, blood pressure variability (BPV) as a marker of sympathetic vasomotor regulation, baroreflex sensitivity (BRS) as a marker of parasympathetic reflex control of heart rate, and haemodynamics during euglycaemic and hypoglycaemic hyperinsulinaemic clamp. According to a concept of antagonistic functions of the sympathetic and parasympathetic systems, we hypothesized that sympathetic activation in response to hypoglycaemia is accompanied by parasympathetic deactivation.

METHODS

Subjects

The study population has been described in detail previously [9]. The subjects for the present study were 18 healthy subjects who fulfilled the following criteria: (1) age between 30 and 40 years; (2) no diabetes; (3) no first-degree relatives with a history of diabetes; (4) no drug treatment or any disease that could potentially modify carbohydrate metabolism; and (5) strenuous physical activity on no more than three occasions per week. Eight subjects were parents of patients with congenital hyperinsulinaemia who were homozygous for the SUR1 mutation V187D. All of them had a normal glucose tolerance, insulin sensitivity and appropriate insulin secretion, as well as normal counter-regulatory system function, as reported previously [9]. According to a subgroup analysis (results not shown), the regulatory responses to hyperinsulinaemia and hypoglycaemia of these subjects were comparable with the responses of the other healthy subjects in the present study. The clinical and biochemical characteristics of the study population are shown in Table 1.

Study protocol

The study protocol was approved by the Ethics Committee of Kuopio University Hospital. Informed consent was given by all subjects. The subjects were admitted to the metabolic ward of the Department of Medicine, Kuopio University Hospital, where the intravenous glucose tolerance test was performed, followed by the hyperinsulinaemic euglycaemic and hypoglycaemic clamp studies.

Procedures

Subjects were placed in the supine position and instrumented for the recordings. Intravenous catheters were placed in the right and left antecubital fossae for insulin/glucose infusion and for obtaining blood for glucose and hormonal analyses.

Euglycaemic and hypoglycaemic clamps

The degree of insulin resistance was evaluated using the euglycaemic hyperinsulinaemic clamp technique [10]. In the euglycaemic clamp, a priming dose of intravenous insulin (Actrapid®; 100 i.u./ml; Novo Nordisk, Gentofte,
Denmark) was administered during the initial 10 min to acutely raise plasma insulin to the desired level, where it was maintained by a continuous intravenous insulin infusion at a rate of 80 m-units·m\(^{-2}\)·body surface area·min\(^{-1}\). Blood glucose was clamped at 5.0 mmol/l for the next 120 min (the euglycaemic clamp: 0–120 min) and then at 3.0 mmol/l for the next 120 min (the hypoglycaemic clamp: 120–240 min) by intravenous infusion of 20 % (w/v) glucose at a variable rate according to blood glucose measurements performed at 5-min intervals (mean coefficient of variation of blood glucose < 3 % during the euglycaemic clamp and 3 % during the hypoglycaemic clamp). The steady-state phase was defined as the period when blood glucose was maintained at the desired level by a constant glucose infusion. At the steady state of the euglycaemic clamp, the plasma insulin concentration was 999 ± 57 pmol/l, and during the hypoglycaemic clamp it was 862 ± 33 pmol/l. The rates of whole-body glucose uptake (\(M\)-values) were measured according to the mean value for the period from 60 to 120 min during the euglycaemic clamp and from 180 to 240 min during hypoglycaemic clamp.

**Symptoms of hypoglycaemia**

The symptoms of hypoglycaemia were recorded using a questionnaire that has been described previously [11]. The subjects were asked to evaluate the severity of autonomic symptoms (such as sweating, shaking, nervousness and pounding of the heart) and the neuroglycopenic symptoms (such as blurred vision, weakness, hunger, tiredness, dizziness, difficulty in thinking, faintness and tingling) on a visual scale from 0 (absent) to 10 (severe). In the present study, the severity of hunger was used in further analyses.

**Blood sampling**

The blood samples for measurements of plasma insulin, plasma adrenaline and plasma noradrenaline were drawn at baseline, at 90 min during the euglycaemic clamp (normoglycaemic state) and again at 240 min during the hypoglycaemic clamp.

**Assays and calculations**

Blood glucose was measured using the glucose oxidase method (Glucose & Lactate Analyzer 2300 Stat Plus; Yellow Springs Instrument Co., Yellow Springs, OH, U.S.A.). For the determination of plasma insulin, blood was collected into EDTA tubes. After centrifugation, the plasma for the determination of insulin was stored at −20 °C until analysis. Plasma insulin was determined by RIA (Phadeseph Insulin RIA 100; Pharmacia Diagnostics AB, Uppsala, Sweden). This insulin assay also detects proinsulin and proinsulin conversion products, with a cross-reactivity of 47 %. The counter-regulatory adrenalineline and noradrenaline responses were analysed by HPLC with electrochemical detection [12].

**Recordings**

Electrodes were placed for ECG recordings. Continuous blood pressure recording was performed using a Finapres digital plethysmograph (Ohmeda Inc., Englewood, CO, U.S.A.) placed on the middle finger of the right hand. Self-adjustment of the Finapres device was performed just before the recordings, and it was disconnected during the recordings. We recorded 5-min ECG and blood pressure signals at baseline and during the steady-state periods of the euglycaemic hyperinsulinaemic clamp and the hypoglycaemic hyperinsulinaemic clamp. During the recordings, the subjects were in the supine position and were asked to breathe according to a metronome at 0.2 Hz frequency with their normal tidal volume. Recorded signals were analogue-to-digital converted with a temporal resolution of 200 Hz/channel and an amplitude resolution of 12 bits. Data acquisition was performed with an IBM PC-compatible microcomputer with CAFTS software (Medikro Ltd., Kuopio, Finland).

**Assessment of haemodynamics and cardiovascular autonomic regulation**

Stroke volume was assessed from the non-invasive blood pressure signal by using the arterial pulse contour method, which is modified from the model flow method [13]. Cardiac output was calculated from the equation: cardiac output = (heart rate) × (stroke volume). Peripheral resistance was calculated as: total peripheral resistance = (mean arterial pressure)/(cardiac output). Mean heart rate, systolic, diastolic and mean arterial blood pressure, stroke volume, cardiac output and total peripheral resistance were assessed during the 5-min periods. Cardiovascular variability was analysed following the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [14]. Spectral estimates of R-R interval and systolic blood pressure were obtained from stationary regions free of ectopic beats and technical artifacts. Fast Fourier Transform was used to obtain power spectral estimates of HRV and BPV. Total power in the frequency range 0–0.40 Hz was divided into low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.40 Hz) bands. Signal powers of each band were calculated as integrals under the respective power spectral density functions, and expressed in absolute units (ms\(^2\) or mmHg\(^2\)). BRS was calculated as the square root of the ratio between HRV and systolic BPV over the ranges with coherence > 0.50 and negative phase angle in the 0.04–0.15 Hz (\(\alpha_{LF}\)) and 0.15–0.40 Hz (\(\alpha_{HF}\)) bands [15,16]. Data analyses were performed with an IBM PC-compatible microcomputer.
with WINCPRS software (Absolute Aliens Oy, Turku, Finland).

**Statistical analysis**

Because parameters of cardiovascular variability and hormone levels were not normally distributed, the data were analysed using tests for non-parametric distribution. Friedman’s test over three-point time trends was performed, and significant changes were analysed further by Wilcoxon’s matched-pairs signed-rank test for the effects of hyperinsulinaemia and hypoglycaemia on all regulatory, hormone and haemodynamic parameters. Calculations were performed using SPSS for Windows software (SPSS Inc., Chicago, IL, U.S.A.). Data are shown as means ± S.E.M.

**RESULTS**

Time-related (baseline to euglycaemic hyperinsulinaemia to hypoglycaemic hyperinsulinaemia) statistically significant changes were observed in plasma adrenaline \((P < 0.001)\) and noradrenaline \((P < 0.05)\) concentrations, diastolic blood pressure \((P < 0.01)\), stroke volume \((P < 0.05)\), peripheral resistance \((P < 0.01)\) and cardiac output \((P < 0.05)\).

During euglycaemic hyperinsulinaemia, no statistically significant changes in plasma catecholamine concentrations, HRV, BPV, heart rate, blood pressure, stroke volume, cardiac output or peripheral resistance occurred (Figures 1 and 2; Table 2). BRS was comparable during baseline and euglycaemic hyperinsulinaemia, according to \(a_{LF}\) (10.1 ± 1.5 and 10.4 ± 1.2 ms/mmHg respectively) and \(a_{HF}\) (21.1 ± 4.0 and 18.8 ± 2.4 ms/mmHg respectively).

In response to hyperinsulinaemic hypoglycaemia, we observed an 11.7-fold increase in the plasma adrenaline concentration \((P < 0.001)\) and with euglycaemic hyperinsulinaemia and a 1.3-fold increase in plasma noradrenaline concentration \((P < 0.05)\) compared with baseline; \(P < 0.01\) compared with euglycaemic hyperinsulinaemia) and a 1.3-fold increase in plasma noradrenaline concentration \((P < 0.05)\) compared with baseline; \(P < 0.01\) compared with euglycaemic hyperinsulinaemia) and a 1.3-fold increase in plasma noradrenaline concentration \((P < 0.05)\) compared with baseline; \(P < 0.01\) compared with euglycaemic hyperinsulinaemia and peripheral resistance \((P < 0.01\) compared with baseline and with euglycaemic hyperinsulinaemia) in response to hyperinsulinaemic hypoglycaemia (Figure 2). Heart rate tended to increase from its baseline level of 68 ± 3 to 71 ± 3 beats/min during hyperinsulinaemic hypoglycaemia, but this response was not statistically significant. Stroke volume

![Figure 1](image1.png)  
**Figure 1** Catecholamine responses to euglycaemic and hyperinsulinaemic hypoglycaemia

Epinephrine and norepinephrine are adrenaline and noradrenaline respectively. Significance of differences: * \(P < 0.05\), **\(P < 0.001\) compared with baseline; ## \(P < 0.01\), ### \(P < 0.001\) compared with euglycaemic clamp.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Euglycaemia</th>
<th>Hypoglycaemia</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power (ms²)</td>
<td>2430 ± 601</td>
<td>2332 ± 599</td>
<td>2421 ± 652</td>
<td>0.66</td>
</tr>
<tr>
<td>LF power (ms²)</td>
<td>649 ± 273</td>
<td>630 ± 196</td>
<td>488 ± 133</td>
<td>0.39</td>
</tr>
<tr>
<td>HF power (ms²)</td>
<td>1178 ± 296</td>
<td>1057 ± 335</td>
<td>1182 ± 400</td>
<td>0.59</td>
</tr>
<tr>
<td>LF/HF ratio (%)</td>
<td>59 ± 10</td>
<td>75 ± 9</td>
<td>81 ± 18</td>
<td>0.94</td>
</tr>
<tr>
<td>Systolic BPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power (mmHg²)</td>
<td>24.5 ± 3.8</td>
<td>34.9 ± 10.0</td>
<td>23.2 ± 3.1</td>
<td>0.94</td>
</tr>
<tr>
<td>LF power (mmHg²)</td>
<td>7.4 ± 1.8</td>
<td>6.1 ± 0.9</td>
<td>6.3 ± 1.1</td>
<td>0.42</td>
</tr>
<tr>
<td>HF power (mmHg²)</td>
<td>4.1 ± 0.9</td>
<td>3.0 ± 0.6</td>
<td>4.2 ± 0.7</td>
<td>0.06</td>
</tr>
<tr>
<td>LF/HF ratio (%)</td>
<td>312 ± 77</td>
<td>323 ± 78</td>
<td>218 ± 52</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic BPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power (mmHg²)</td>
<td>7.7 ± 1.2</td>
<td>6.9 ± 0.7</td>
<td>6.5 ± 0.8</td>
<td>0.94</td>
</tr>
<tr>
<td>LF power (mmHg²)</td>
<td>3.1 ± 0.7</td>
<td>2.8 ± 0.4</td>
<td>2.8 ± 0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>HF power (mmHg²)</td>
<td>1.1 ± 0.4</td>
<td>0.7 ± 0.1</td>
<td>1.3 ± 0.2</td>
<td>0.08</td>
</tr>
<tr>
<td>LF/HF ratio (%)</td>
<td>605 ± 148</td>
<td>522 ± 84</td>
<td>334 ± 72</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Figure 2  Haemodynamic responses to euglycaemic and hyperinsulinaemic hypoglycaemia
Significance of differences: *P < 0.05, **P < 0.01 compared with baseline; ##P < 0.01 compared with euglycaemic clamp.

Catecholamines stimulate glycogenolysis and gluconeogenesis, but also control the rate of glucose delivery by modulating vascular tone and blood flow, and thus are capable of mediating the metabolic as well as the haemodynamic responses to hypoglycaemia [17]. In response to hyperinsulinaemic hypoglycaemia, we found a marked increase in the plasma concentration of adrenaline and a slight increase in that of noradrenaline, which is in line with previous studies indicating activation of the sympathoadrenal system. Because we did not measure muscle sympathetic nerve activity or any other index of sympathetic activity to the heart or blood vessels, we cannot evaluate the sympathetic activation of the cardiovascular organs. However, although the plasma concentration of noradrenaline is a compromised indicator of general sympathetic activity, one might expect a more pronounced response of its concentration to hyperinsulinaemic hypoglycaemia, in line with the response of adrenaline, unless the sympathetic response to hyperinsulinaemia and hypoglycaemia is non-uniform.

The sympathetic and parasympathetic systems often act as physiological antagonists, but under some circumstances physiological interventions have been shown to cause parallel changes in vagal and sympathetic nerve activity [18]. Thus sympathoadrenal activation during hypoglycaemia may be accompanied by changes in parasympathetic regulation, characterized either by accentuated antagonism or by a reciprocal excitation-type response. Moreover, the processes by which the brain regulates energy homoeostasis are complex, and
involve brain regions that are closely associated with the central autonomic network. There is evidence that glucose-sensing neurons are located in the hypothalamus, and also in the nucleus of the solitary tracts of the medulla oblongata [19]. Because the nucleus of the solitary tracts is a central synapse of the baroreceptor loop, and some of its efferents distributed with the vagus nerves synapse directly with parasympathetic fibres carried to the heart [20], it is possible that parasympathetic control of the heart is involved in hypoglycaemic counter-regulation.

We planned in the present study to explore for the first time the cardiac autonomic responses to hyperinsulinaemic hypoglycaemia by assessing cardiovascular variability and baroreflex control of heart rate during the hypoglycaemic hyperinsulinaemic clamp. We did not find any changes either in cardiac parasympathetic regulation during hyperinsulinaemic hypoglycaemia or in the baroreflex control of heart rate. This suggests that the response to hypoglycaemia in autonomic nervous regulation involves just adrenomedullary sympathetic activation, and not changes in cardiac parasympathetic regulation or the baroreflex control of heart rate. On the other hand, it is possible that, since the non-uniform sympathetic response does not include cardiac sympathetic activation, the reciprocal cardiac parasympathetic response does not occur. We may also speculate whether stimulation of the autonomic nervous system by hyperinsulinaemia and hypoglycaemia was powerful enough to evoke significant responses. There is some evidence indicating that the strength of the stimulus is relevant. We found an 8 mmHg decrease in diastolic blood pressure and an 11 ml increase in stroke volume on average, which can evoke significant cardiovascular autonomic responses in normal circumstances. Another fact that emphasizes the relevance of the stimulus is that the subjects experienced marked hypoglycaemic symptoms.

The effects of catecholamines on haemodynamics depend on the relative excitation of $\alpha$- and $\beta$-adrenoceptors in the heart and blood vessels. Fisher and co-workers [21] have shown that blood pressure responses to hypoglycaemia are mediated by excitation of both $\alpha$- and $\beta$-adrenoceptors. In their study, $\beta$-adrenergic blockade during hypoglycaemia resulted in an increase in blood pressure, whereas $\alpha$-adrenergic blockade caused the opposite effect. Furthermore, these workers showed that increases in heart rate and ejection fraction in response to hypoglycaemia could be abolished by $\beta$-adrenergic blockade, suggesting that cardiac influences are selectively mediated by $\beta$-adrenoceptors [21]. We observed a decrease in diastolic blood pressure in response to hyperinsulinaemic hypoglycaemia, which was accompanied by a decrease in peripheral resistance, indicating peripheral vasodilatation. According to previous studies, the haemodynamic reaction during hyperinsulinaemic hypoglycaemia is also characterized by increases in heart rate [6,21–24] and cardiac function (stroke volume, cardiac output, left ventricular ejection fraction and peak filling rate) [21,22,24].

It has been shown previously that insulin-mediated vasodilatation increases skeletal muscle blood flow, and may also increase glucose uptake [25], although the physiological significance of this observation remains disputed [26]. It is possible that, during hypoglycaemia, the delivery of glucose and non-esterified fatty acids is rate-limiting for energy metabolism, and thus vasodilatation accompanied by an increase in cardiac output promotes the uptake of these fuels by peripheral tissues. On the other hand, Hoffman and co-workers [17] have shown that, during hypoglycaemia with intra-arterial administration of propranolol, forearm blood flow was unchanged, whereas peripheral glucose uptake decreased, suggesting that adrenergic activation decreases glucose uptake by muscle. Accordingly, during hypoglycaemia more alternative fuels, such as non-esterified fatty acids, become available for skeletal muscles, and glucose is spared for utilization in the brain. In our present study, the rates of whole-body glucose uptake were significantly lower during hypoglycaemia than during euglycaemia, which probably reflects catecholamine-induced insulin resistance.

In our present study, responses to hypoglycaemia were measured during a hyperinsulinaemic clamp in which the plasma insulin concentration was supra-physiological. This should be taken into consideration when interpreting our results, because insulin may contribute to both regulatory and haemodynamic responses to hypoglycaemia. Davis and co-workers [27,28] have shown that hyperinsulinaemia can amplify the counter-regulatory secretion of catecholamines, cortisol and growth hormone in healthy men and women. Furthermore, hyperinsulinaemia has been found to modulate haemodynamic responses to catecholamines, but the results from different studies have been conflicting. Gans and co-workers [29] found that the circulating level of noradrenaline required to elevate diastolic blood pressure by 20 mmHg was lower during euglycaemic hyperinsulinaemia than during a saline infusion, suggesting an increase in cardiovascular responsiveness to noradrenaline. In contrast, in another study by Baron et al. [30], hyperinsulinaemia was accompanied by a rightward shift of the noradrenaline pressor dose–response curve and an increase in the metabolic clearance of noradrenaline.

Our study population consisted of 18 healthy men and women aged 30–40 years. Eight of them were carriers of an inactivating $\beta$-cell ATP-sensitive $K^+$-channel mutation, but they had normal glucose tolerance and insulin sensitivity and appropriate insulin secretion [9], which justifies their inclusion in the study. There were some methodological limitations in our study. First, because the plasma concentrations of catecholamines
represent a balance between release and clearance, changes in concentration may be due to changes in either or both of these parameters. However, it is likely that an increase in the plasma adrenaline concentration in response to hyperinsulinaemic hypoglycaemia reflects predominantly increased adrenal secretion of adrenaline. Secondly, cardiovascular variability is an indirect reflection of autonomic regulation, and cannot be interpreted unambiguously irrespective of the prevailing circumstances. Although all blood sampling and recordings were performed under steady-state conditions, the results of the present study regarding cardiovascular variability should be interpreted with caution. Thirdly, stroke volume was assessed using the arterial pulse contour method, based on solid physical principles and less solid physiological models, which involve substantial computations [31]. However, it has been shown that the pulse contour method suffices for tracking changes in stroke volume and cardiac output, but is not reliable for absolute values [32]. Our study setting is founded on the assessment of individual changes, and thus the interpretation of our results is still well grounded.

In summary, the results of the present study suggest that hyperinsulinaemic hypoglycaemia induces a significant increase in the plasma adrenaline concentration, as well as decreases in peripheral resistance and blood pressure. The novel aspect of our study was that counter-regulation during hyperinsulinaemic hypoglycaemia seems to involve adrenomedullary sympathetic activation, but not changes in cardiac parasympathetic regulation or the baroreflex control of heart rate. This observation may be of clinical importance with regard to the adverse cardiovascular effects of hypoglycaemia.

ACKNOWLEDGMENTS

This work was supported financially by the Kuopio University Hospital (EVO 403019).

REFERENCES


