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Changes in blood pressure and plasma catecholamine levels during prolonged hyperinsulinemia

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Abstract

Hyperinsulinemia has been shown to induce activation of the sympathetic nervous system and vasodilatation. Whether these effects result in changes in blood pressure (BP) is discussed controversially. We measured BP and plasma catecholamine levels in 30 healthy men during a 60-minute baseline phase and 360-minute period of insulin infusion. In a double-blind, between-subject comparison, insulin was infused at a low rate (1.5 mU insulin/kg per minute) in one half of the subjects and at a high rate (15 mU/kg per minute) in the other half. Throughout the experiments, blood glucose levels were held constantly within the normal range by a simultaneous infusion of glucose. Serum insulin levels increased to a plateau of 543 ± 34 pmol/L during low rate and to 24 029 ± 1595 pmol/L during high rate of insulin infusion. Compared with baseline, insulin infusion of either rate significantly increased systolic BP, BP amplitude, and heart rate (all $P < .05$). In comparison with the low rate of insulin infusion, the high rate provoked a more pronounced increase in heart rate ($P < .02$) and systolic BP ($P < .05$) but tended to decrease diastolic BP ($P < .08$) summing up to a distinctly more increased BP amplitude ($P < .05$). Plasma norepinephrine as well as epinephrine levels did not significantly change during the low-rate insulin infusion but significantly increased during high-rate insulin infusion (both $P < .05$). By showing a dose-dependent increasing influence of insulin on systolic BP and circulating catecholamine levels, the present study provides experimental evidence for the notion that hyperinsulinemia contributes to the development of hypertension.

1. Introduction

Since more than 30 years, hyperinsulinemia as a consequence of insulin resistance has been related to hypertension [1,2]. Numerous experimental studies in healthy subjects and clinical as well as epidemiological trials in patients with diabetes, obesity, or hypertension addressed the question as to whether insulin per se can induce hypertension. An association between chronic hyperinsulinemia and increased blood pressure (BP) was revealed in some clinical and epidemiological studies [3-9], whereas others failed [10-12]. Interestingly, hyperinsulinemia is often even found in nondiabetic patients with hypertension [3,13,14]. Whether hyperinsulinemia can cause hypertension is still a matter of debate [15,16]. The main problem of disentangling a link between hyperinsulinemia and elevated BP in clinical populations derives from the fact that typically these symptoms are concerted with several other risk factors such as old age, male sex, little exercise, obesity, type 2 diabetes, alcohol consumption, family history of hypertension, increased dietary salt intake, and nephropathy [14]. To control for such contaminating factors, foregoing experimental studies [17-24] assessed acute effects of insulin infusion on cardiovascular parameters and sympathetic nervous activity in healthy subjects while blood glucose concentration was kept within the normal range (euglycemic clamp). In some of those studies, hyperinsulinemia was found to stimulate sympathetic nervous activity as indicated by increased muscle sympathetic nerve activity [19,20] as well as by increased plasma norepinephrine levels [17-20,25]. Yet, other studies did not confirm these effects [21,22], and BP increased [18], decreased [25], or remained unchanged [17,23,24].

A major problem in the interpretation of those previous results appears to stem from the fact that influences of exogenous insulin infusion were compared with conditions

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of placebo infusion without any supply of glucose to prevent the fasting-associated decrease in plasma glucose concentration. In addition to decreasing plasma glucose levels, fasting induces numerous other metabolic and neuroendocrine alterations [26,27], which may per se affect sympathetic activity and cardiovascular parameters. Another important methodological problem in this regard is that the clamp procedure itself likely evokes a stress response which increases BP and catecholamine release [21]. On this background, comparing the effects of different doses of insulin infusion with simultaneous infusion of glucose appears to be a more appropriate strategy to evaluate the effects of insulin.

Here we tested the hypothesis that hyperinsulinemia dose-dependently increases blood pressure and circulating catecholamine levels in healthy men. Two different rates of insulin infusion were used with simultaneous infusion of glucose at a variable rate to keep plasma glucose levels within a narrow normal range. To sensitively detect potential effects of insulin on blood pressure and catecholamine levels, 2 markedly different degrees of hyperinsulinemia were induced, the higher of which being clearly supraphysiological. A similar approach has previously been successfully used to establish insulin effects on the receptor and postreceptor level [28,29].

2. Subjects and methods

2.1. Subjects

Subjects were 30 healthy men (aged 22-32 years) of normal body weight (body mass index, 20-25 kg/m^2) and without personal and family history of diabetes or hypertension. All subjects were nonsmokers and not under current medication. Ten hours before testing they had to fast and abstain from coffee and alcoholic beverages. The study was approved by the local Ethics Committee on Research Involving Human Subjects, and written informed consent was obtained from all subjects.

2.2. Procedure

The 30 subjects were assigned randomly and in a single blind manner to 2 groups each including 15 subjects. Each subject was tested during a baseline phase followed by a euglycemic clamp, with 15 subjects being infused with a low rate of insulin infusion (1.5 mU/kg per minute), and the remaining 15 subjects with a high rate of insulin infusion (15 mU/kg per minute) for 360 minutes (regular human insulin: Insuman rapid, Aventis, Bad Soden, Germany). Experiments took place in a sound-attenuated room between 8:00 AM and 4:00 PM with the subject sitting with the trunk in supine position (about 60°) and the legs in horizontal position in a bed. One hour before testing, a catheter was inserted into a vein of the dorsal hand, which was warmed up to 55°C to sample arterialized blood for blood glucose monitoring and for determination of serum insulin, epinephrine, and norepinephrine levels. A second intravenous catheter at the opposite arm was used to infuse insulin and glucose. Blood samples were collected every 5 minutes for determination of blood glucose (by a Beckman glucose analyser II, Fullerton, Calif) and every 30 minutes for determination of serum insulin and catecholamines.

After the 60-minute baseline period, an initial bolus of insulin (30 mU/kg) was intravenously administered. Thereafter, insulin was infused at a constant rate of 1.5 or 15 mU/kg per minute. The individual fasting blood glucose concentration was maintained by an additional manually controlled glucose infusion (20 % solution) for 360 minutes. All infusions were administered via an intravenous catheter connected to a long thin tube (volume, 1.5 ml), which enabled adjustments in the rate of glucose infusion from an adjacent room without notice of the subject. One of the 2 investigators staying with the subject did not know either the actual glucose infusion rate and whether insulin was infused at the high or low rate so that this investigator was unaware of the treatment condition. Blood samples for determination of blood glucose, serum insulin, and catecholamine concentrations were likewise collected via

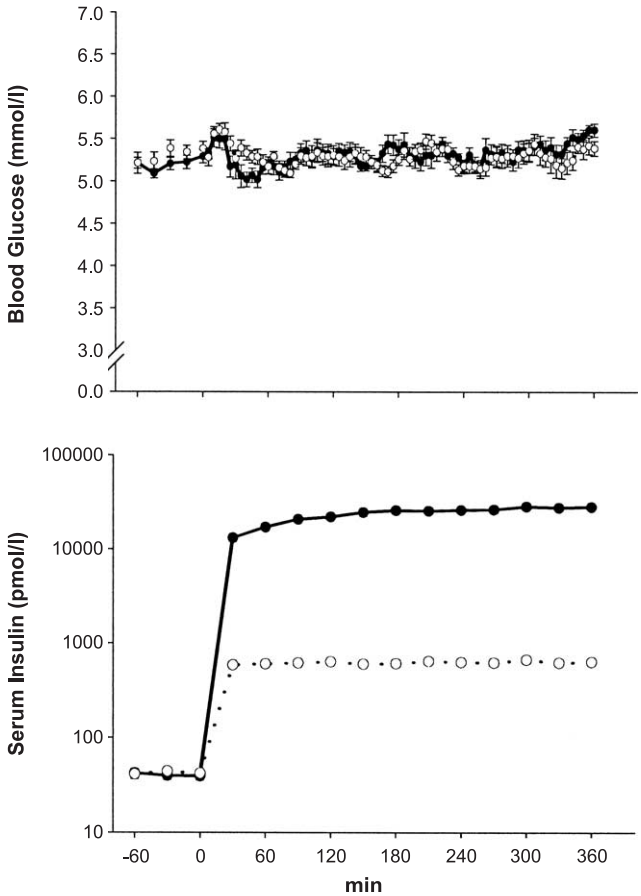

Fig. 1. Mean (±SE) blood glucose (top) and serum insulin concentrations (bottom) during the baseline phase and during infusion of 1.5 mU/kg per minute insulin (open circles) and 15 mU/kg per minute insulin (black circles) for 360 minutes. Standard errors of serum insulin concentrations for all points in time were smaller than the size of the circles.

another long thin tube from the adjacent room without disturbing the subject. The second investigator measuring and clamping the blood glucose concentration had no personal contact with the subject. With this procedure, the subject was completely blinded to the experimental treatment condition, and feelings of disturbance and discomfort were reduced to a minimum.

2.3. Recordings and apparatus

Systolic and diastolic BP as well as heart rate were measured oscillometrically with a Boso blood pressure monitor (Boso Prestige, Bosch und Sohn GmbH, Jungingen, Germany), which is a manual electronic system. The investigator performing the measurements was unaware of the treatment condition. Measures were equally spaced every 90 minutes across the baseline period and the interval of the insulin infusion. At each point, measures were performed in duplicate with an interval of 5 minutes. Final data analysis was performed on collapsed values representing BP and heart rate during baseline and after 90, 180, 270, and 360 minutes of insulin infusion.

Serum insulin was determined by radioimmunoassay (Pharmacia Insulin RIA 100, Pharmacia Diagnostics, Uppsala, Sweden) with an interassay error, measured as coefficient of variation (CV), below 5.4%. Intra-assay variation was below 4.5% in all cases. The same kit was used for all samples of an individual. Plasma epinephrine and norepinephrine were measured in duplicate by standard high-performance liquid chromatography with electrochemical detection (Chromosystems, Munich, Germany). Intra-assay and interassay CV was below 2.9% and 4.2% for epinephrine and below 2.6% and 3.9% for norepinephrine. Plasma glucose was measured in duplicate with a Beckman glucose analyser II (Beckman Instruments, Inc, Fullerton, Calif) with a CV of less than 1.1%.

2.4. Statistical analysis

Data analysis was generally based on analyses of covariance for a repeated measure design including the factors “treatment” for high-rate vs low-rate insulin infusion and “time” for the repeated measures during the clamps. In these analyses, baseline values served as covariate. In addition, changes in cardiovascular parameters and catecholamine levels during insulin infusion with reference to baseline values were assessed separately for the 2 treatment conditions by paired t test. A Greenhouse-Geisser corrected P value less than .05 was considered significant.

3. Results

Baseline blood glucose concentrations were nearly identical in both groups and remained essentially un-

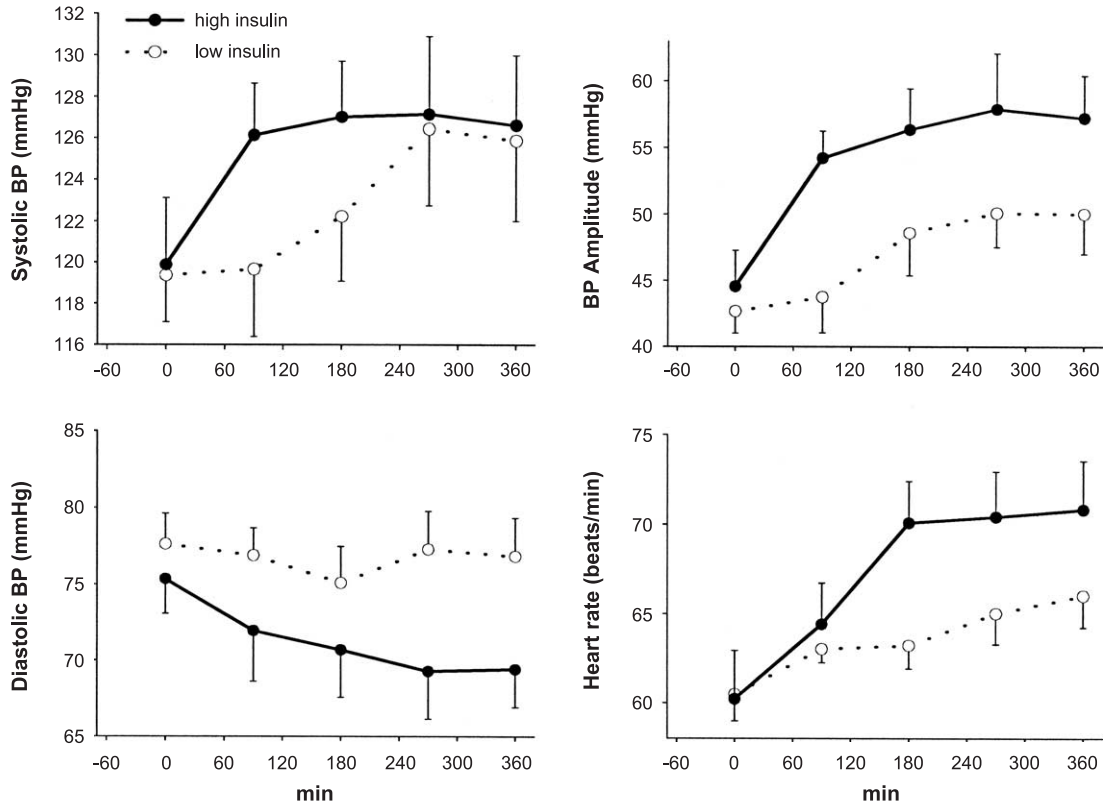

Fig. 2. Mean (± SE) systolic blood pressure (BP) (left panel, top), diastolic BP (left panel, bottom), BP amplitude (right panel, top) and heart rate (right panel, bottom) at the end of the baseline phase and during infusion of 1.5 mU/kg per minute insulin (open circles) and 15 mU/kg per minute insulin (black circles) for 360 minutes.

changed during insulin infusion (Fig. 1). Serum insulin concentrations rapidly increased from 42 ± 4 to 543 ± 34 pmol/L after starting the low-rate insulin infusion, and from 45 ± 7 to 24 029 ± 1595 pmol/L after starting the high-rate insulin infusion ($P < .0001$ for low-rate vs high-rate insulin infusion).

Heart rate ($P < .005$), BP amplitude ($P < .07$), plasma concentrations of norepinephrine ($P < .0001$), and epinephrine ($P < .01$) progressively increased with duration of the hyperinsulinemic clamp, with these increases being more pronounced during the high than low rate of insulin infusion (all $P < .05$; Figs. 2 and 3). In contrast, systolic BP was well comparable between the low-rate and high-rate insulin infusion condition at the end of the clamp (Fig. 2). However, during the high-rate insulin infusion the increase in BP occurred distinctly earlier than during the low-rate insulin infusion ($P < .05$).

Compared with baseline values, infusion of insulin at the lower rate increased on average systolic BP by 4.2 ± 1.8 mm Hg ($P < .05$), BP amplitude by 5.5 ± 1.8 mm Hg ($P < .01$), and heart rate by 3.8 ± 1.2 beats/min ($P < .01$).

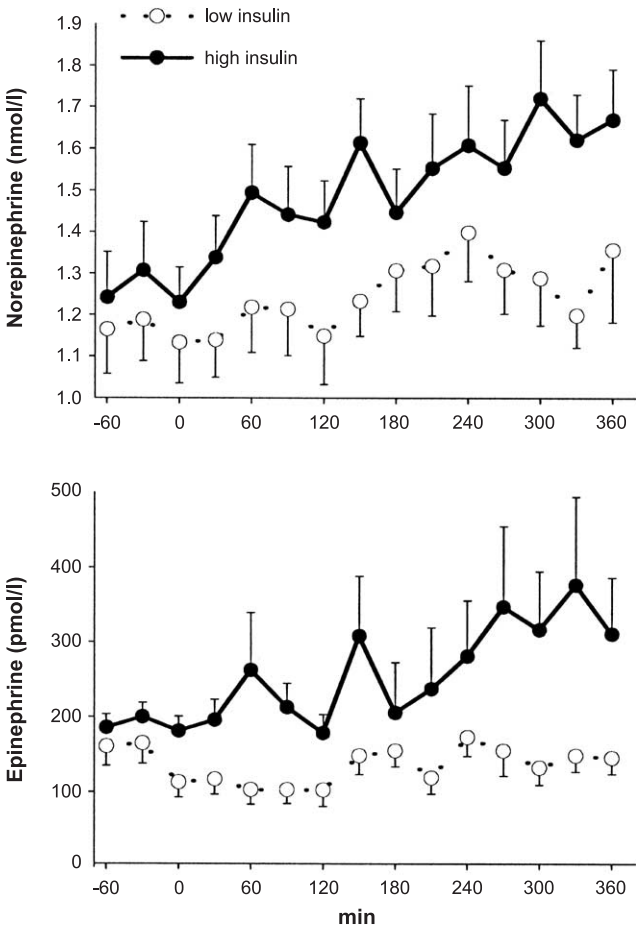

Fig. 3. Mean (± SE) concentrations of norepinephrine (top) and epinephrine (bottom) during the baseline phase and during infusion of 1.5 mU/kg per minute insulin (open circles) and 15 mU/kg per minute insulin (black circles) for 360 minutes.

Diastolic BP as well as plasma levels of norepinephrine and epinephrine did not significantly change during the low rate insulin infusion.

The high rate of insulin infusion in comparison to baseline values increased on average systolic BP by 6.9 ± 3.3 mm Hg ($P < .05$), BP amplitude by 11.9 ± 3.0 mm Hg ($P < .001$), heart rate by 8.7 ± 2.2 beats/min ($P < .01$), and plasma norepinephrine levels by 0.28 ± 0.06 nmol/L ($P < .001$), whereas it decreased diastolic BP by 5.0 ± 2.3 mm Hg ($P < .05$).

4. Discussion

Present data show that insulin dose-dependently increases systolic BP, BP amplitude, heart rate, and plasma catecholamine levels, which strongly supports the previous notion of a stimulatory influence of insulin on the sympathetic nervous system. Although the effects of insulin infusion on BP amplitude, heart rate, and plasma catecholamine were clearly dose-dependent as well as time-dependent, the extent of the increasing influence on systolic BP appeared to be similar after 360 minutes of infusion of insulin at the 2 different rates suggesting a satiability of this influence.

It should be pointed out that by using rather high rates of insulin infusion in the present study, we clearly induced supraphysiological serum concentrations of insulin. Although the degree of hyperinsulinemia resulting from the low rate of insulin infusion can be found in subjects with severe insulin resistance such as patients with type 2 diabetes, the degree of hyperinsulinemia achieved with the higher infusion rate cannot. In an attempt to distinguish clear insulin effects, we infused these standard doses of insulin, which have previously been used by Kolterman et al [28,29] to establish dose responses on the receptor and postreceptor level. Considering that the bioactivity of insulin follows a sigmoid dose response, the observed effects may even be of greater importance for differences in insulin levels within the physiological range [30].

The mechanism by which insulin increases norepinephrine levels is not known. Evidence suggests several possibilities: first, an activation of ventromedial hypothalamic neurons [31-34]; second, an indirect mediation via reduced stimulation of baroreceptors [25]; and, third, a direct effect of insulin on muscle norepinephrine metabolism [35]. However, the latter mechanism is unlikely as insulin infused locally into the forearm failed to change norepinephrine release and uptake by the surrounding muscle tissue [36]. Also, the view that the increased norepinephrine concentration during insulin infusion resulted from baroreceptor reflex stimulation receives little support from findings indicating that this increase develops already before any significant decrease in diastolic BP emerges [37].

Epinephrine levels were also higher during infusion of high- than low insulin concentrations. Results from previous studies in this regard remained inconclusive [22,25,38]. However, it is noteworthy that several studies reported on

elevated epinephrine levels under basal conditions in patients with type 1 [12,39-41] and type 2 [42] diabetes. In one of those studies in patients with type 1 diabetes, multivariate analysis suggested that increased epinephrine levels considerably contribute to the high nocturnal BP in those patients [12].

Performing hyperinsulinemic-euglycemic clamp of rather long duration (ie, 360 min) enabled us to evaluate the time course of changes in the respective parameters. The high-rate insulin infusion induced a rapid increase in systolic BP within 90 minutes, which persisted till the end of the clamp. With time spent in hyperinsulinemia, the lower rate of insulin infusion also gradually increased systolic BP, reaching values identical to those of the high-rate condition toward the end of the infusion (Fig. 2). The differential time course of these changes during high-rate and low-rate insulin infusion fits well with the notion of a mediation of these insulin effects via an action on the brain [43,44]. Because insulin crosses the blood-brain barrier via a receptor-mediated transport [45,46], brain insulin concentration is indeed expected to rise faster during the high- than low insulin condition [45]. However, in the low insulin condition this difference was compensated with continuing time spent in hyperinsulinemia. In line with this view are results of a foregoing study indicating a time course of changes in evoked brain potentials and in subjective symptoms very similar to that of systolic BP in the present study [47]. Moreover, in animals, infusion of insulin selectively to brain vessels distinctly increased systolic and diastolic BP, heart rate, and catecholamine levels as compared with the effects of insulin infused at the same rate to a peripheral vessel [48,49]. Together, these data suggest that the observed effects of insulin on systolic blood pressure and catecholamine levels could, at least in part, be mediated via central nervous mechanisms.

On the other hand, it should be pointed out that in the present study diastolic BP slightly decreased during insulin infusion, which is in line with previous observations [19,25]. This decreasing influence of insulin on diastolic BP has been attributed to a direct dilatory effect on blood vessels [25,50]. Epidemiological studies, however, did not provide any evidence that chronic hyperinsulinemia could be associated with decreased diastolic BP [15]. In this context, it is worth mentioning that there is evidence that in the condition of chronic hyperinsulinemia the hormone loses its vasodilatory action [32,51,52], whereas its stimulatory influence on the sympathetic nervous systems remains preserved [17-19,25].

The crucial question of this experiment was whether the net outcome of changes during systemic hyperinsulinemia becomes manifest in a distinct increase in BP. Based on the present data, it is tempting to conclude that hyperinsulinemia likely contributes to an elevation of systolic BP, which is a hallmark of hypertension, but decreases rather than increases diastolic BP. However, considering that during chronic hyperinsulinemia blood vessels likely become resistant to the dilatative effect of the hormone so that the sympathostimulatory effect becomes predominate and thus contributes to hypertension.

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