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Urinary cortisol is inversely associated with capillary recruitment in women and statistically explains part of the cortisol-blood pressure relationship

Short title: cortisol and microvascular function

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Author Disclosure Summary

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Abstract

The relationships of cortisol with elevated blood pressure and insulin resistance are likely to be the result of a complex interplay of different mechanisms. We hypothesized that cortisol is associated with impaired microvascular function and that this contributes to cortisol-associated high blood pressure and insulin resistance. We examined 24h urinary free cortisol excretion in 56 healthy adults (26 women). Blood pressure was assessed by 24h ambulatory measurements. Insulin sensitivity was determined by the hyperinsulinaemic euglycaemic clamp technique. Skin capillary recruitment after arterial occlusion was visualized with videomicroscopy and endothelium-(in)dependent vasodilation was evaluated with iontophoresis of acetylcholine and sodium nitroprusside combined with laser Doppler fluxmetry. Men were characterized by higher urinary cortisol excretion (median (interquartile range), 162 (130-194) vs. 118 (99-156) nmol/24h, $P < 0.05$). In women, but not in men, urinary cortisol excretion was associated with impaired capillary recruitment ($r = -0.66$, $P < 0.001$), higher systolic blood pressure ($r = 0.64$, $P < 0.001$) and lower insulin sensitivity ($r = -0.43$, $P < 0.05$). Urinary cortisol excretion was not associated with endothelium-(in)dependent vasodilation in men or women. Regression analysis demonstrated that capillary recruitment statistically explained 37% of the association between urinary cortisol and blood pressure in women. Capillary recruitment did not explain part of the association between urinary cortisol and insulin sensitivity. In conclusion, urinary cortisol excretion is inversely associated with capillary recruitment in women, but not in men, and explains part of the cortisol-blood pressure relationship. These data suggest that, in women, impairment of capillary function mediates some of the adverse effects of cortisol and thus may provide a target to prevent such adverse effects.

Introduction

Cortisol excess is characterized by a cluster of cardiovascular risk factors consisting of hypertension, insulin resistance and obesity [1;2]. The aetiology of cortisol-induced hypertension is complex and multiple mechanisms have been proposed to play a role, such as a cortisol-induced increase in peripheral vascular resistance possibly in part by direct inhibition of endothelial NO synthesis [3-5]. In turn, cortisol-induced insulin resistance may result of altered insulin-binding and intracellular signalling, reduced translocation of glucose transporters or increased lipolysis in adipose tissue [2]. Alternatively, cortisol may decrease the availability of glucose and insulin to muscle cells by effects on total blood flow or intramuscular blood flow patterns. Indeed, administration of corticosteroids inhibits insulin-induced increases in total skeletal muscle blood flow [6]. Thus, associations of cortisol with elevated blood pressure and insulin resistance are likely to be the result of a complex interplay of different mechanisms. However, cortisol-induced effects on muscle blood flow may explain part of both associations.c

Numerous studies have shown associations between defects in skin microvascular function and cardiovascular risk factors, such as hypertension, insulin resistance and obesity [7-12]. In addition, impairment of skin microvascular function is related to increased coronary heart disease risk as estimated by the Framingham risk score [13]. Furthermore, recent studies have proposed that insulin-mediated effects on microvascular blood flow distribution regulate peripheral muscle glucose uptake [14;15]. Also, defects in skin microvascular function are not only associated with, but also may precede, elevation of blood pressure [16-18]. Moreover, large epidemiological studies have shown that retinal microvascular defects are predictive for the development of hypertension and diabetes mellitus [19-21]. Therefore, alterations in microvascular function seem to be particularly important in the development of insulin resistance and hypertension and it's associated cardiovascular risk.

To our knowledge, data on associations of cortisol with microvascular function have hitherto been limited. Previous studies in isolated cells and vessels have shown that corticosteroids impair angiogenesis [22-24] and that corticosteroids are able to disrupt microvascular architecture, leading to loss of functional capillaries [23]. Also, corticosteroids inhibit the insulin-induced proliferation of capillary endothelium in

animal muscle, indicating an opposite effect of insulin and corticosteroids on capillary networks [25]. In addition, Walker and colleagues have previously demonstrated that locally applied corticosteroids induce blanching of human skin, which has been suggested to be due to a vasoconstrictive response in the skin microvasculature [26]. Thus, previous studies suggest that corticosteroids may influence both structure and function of the microvasculature.

On the basis of these data, we hypothesized that higher cortisol levels are associated with defects in microvascular function. Furthermore, we hypothesized that these defects may link increased cortisol levels with elevated blood pressure and insulin resistance.

Methods

Subjects

This study is part of a larger project in which vascular and metabolic variables were studied in prepubertal children and their parents [27;28]. In the present study only data of the parents are reported. Couples were contacted by letter and telephone. All participants were of Caucasian origin. After exclusion of individuals with vasoactive medication, diabetes mellitus type 2, rheumatoid arthritis and incomplete data for cortisol measurements (2 individuals), 26 women and 30 men, containing 26 couples, participated in this study. The study was undertaken with approval of the local Ethics Committee and performed in accordance with the Declaration of Helsinki. Informed consent was obtained from each individual before start of the study.

Microvascular measurements

The microvascular measurements were conducted in the morning after 30 minutes of acclimatisation in a quiet, temperature-controlled room ($T=23.4\pm 0.4^{\circ}\text{C}$), with individuals in the sitting position and the investigated, non-dominant hand at heart level. All individuals had abstained from caffeine-containing drinks overnight. Nailfold and iontophoresis studies were performed on the same day and by a single experienced investigator (RGJ). Perfused nailfold capillaries in the dorsal skin of the third finger were visualised by a capillary microscope, as described previously [10;27;28]. Briefly, nailfold capillaries of the non-dominant hand were recorded before and after 4 minutes of arterial occlusion with a digital cuff. This procedure was performed twice and the mean of both measurements was used for analyses. The number of capillaries at baseline and directly after release of the cuff were counted off-line for respectively 15 and 30 seconds from a freeze-framed reproduction of the videotape and from the running videotape when it was uncertain whether a capillary was present or not. Post-occlusive capillary recruitment was calculated as the absolute and relative increase in number of capillaries. The intrasubject coefficient of variation of relative post-occlusive capillary recruitment was $17.2\pm 12.1\%$, as determined in 7 individuals on two occasions.

Endothelium-dependent and -independent vasodilatation of skin microcirculation was evaluated by iontophoresis of acetylcholine and sodium nitroprusside in combination with laser Doppler fluxmetry as previously described in more detail

[10;27]. Acetylcholine dissolved in mannitol 3% in water (1% acetylcholine; Miochol, Bournonville Pharma, The Netherlands) was delivered using an anodal current (7 doses of 0.1 milliamps (mA) for 20 s with a 60-s interval). Nitroprusside dissolved in water for injection (0.1% sodium nitroprusside; Nipride, Roche, The Netherlands) was delivered using a cathodal current (9 doses of 0.2 mA for 20 s with a 90-s interval). Acetylcholine-dependent and nitroprusside-dependent vasodilation were measured on the middle phalanx of the third and fourth finger, respectively. Approximately 15 minutes elapsed between these two measurements. The responses to acetylcholine and sodium nitroprusside were calculated as the absolute and relative increase from baseline to the plateau phase (during the final two iontophoretic deliveries). Intrasubject coefficients of variation of the relative increase were $13.5\pm 7.7\%$ for acetylcholine and $18.7\pm 23.4\%$ for sodium nitroprusside, as determined in 7 individuals on two occasions.

Anthropometrical, blood pressure and insulin sensitivity measurements

Anthropometrical measurements were performed twice and the mean of two measurements was used for analyses. Weight and height were determined barefoot and wearing light clothing. Waist and hip circumference were measured as the horizontal circumference at the level of the umbilicus and both great trochanters, respectively.

Ambulatory monitoring (Spacelabs 90207, Redmond, Washington, USA) was used to obtain 24-hour recordings of blood pressure and heart rate. The non-dominant arm was used with an appropriately sized cuff. The monitors were programmed to take blood pressure and heart rate readings every 20 minutes from 7.00 – 22.00 and every 30 minutes from 22.00 – 7.00.

Insulin-mediated glucose disposal was assessed by the hyperinsulinaemic, euglycaemic clamp technique, as previously described [10]. Briefly, insulin (Velosulin; Novo Nordisk, Bagsvaerd, Denmark) was infused in a primed continuous manner at a rate of $60 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ for 2 h. Normoglycaemia was maintained by adjusting the rate of a 20% D-glucose infusion based on plasma glucose measurements performed at 5-minute intervals. Whole body glucose uptake (M) was calculated from the glucose infusion rate during the last 60 minutes and expressed per unit of plasma insulin concentration (M/I). For convenience the M/I ratio was multiplied by 100.

Biochemical methods

Fasting blood samples were drawn and samples were stored frozen (-20°C) until analyses. Plasma glucose, serum total cholesterol, HDL cholesterol and triglyceride concentrations were measured by enzymatic techniques (Hitachi 747 model 100, Roche diagnostics, Mannheim, Germany). LDL cholesterol was calculated by the Friedewald formula. Plasma insulin concentrations were measured by radioimmunoassay techniques (Immunoradiometric Assay, Medgenix Diagnostics, Fleurus, Belgium). Urinary free cortisol was measured by radioimmunoassay (Coat-A-Count, DPC, Los Angeles, USA) with inter-assay and intra-assay coefficients of variation of 6% and 9% in 100 and 190 samples, respectively.

Statistical methods

Variables are presented as mean \pm standard deviation (SD), or, in case of a nonparametric distribution, as median and interquartile range. Triglycerides, urinary cortisol showed a skewed distribution and the log transformed variables were used in statistical analyses. The independent samples t-test was used to study differences between men and women. Analysis of covariance was used to examine gender differences after adjustment for other variables. Partial correlation analyses were used to investigate relationships among urinary cortisol, capillary recruitment, blood pressure, insulin sensitivity and measures of adiposity. Multiple regression analysis was used to analyse whether the cortisol-blood pressure and the cortisol-insulin sensitivity associations could statistically be explained by differences in skin capillary recruitment or measures of adiposity. Correlation and multiple regression analysis require that, for each variable, measurements are independent. Because our study of 56 adults includes 26 couples and cortisol levels may correlate positively among spouses, we examined the correlation of this variable between men and women. Partial correlation analysis demonstrated plasma cortisol and urinary cortisol were not positively associated between men and women within the couples ($r=0.10$, $p=0.6$ and $r=-0.06$, $p=0.8$). A two-tailed P-value of <0.05 was considered significant. All analyses were adjusted for age. All analyses were performed on a personal computer using the statistical software package SPSS version 11.0 (SPSS, Chicago, IL, USA).

Results

Characteristics of the study population

Characteristics are presented for men and women separately (Table 1). Men were older and characterized by higher body mass index (BMI), waist circumference, waist-to-hip-ratio (WHR), systolic blood pressure (SBP), total cholesterol and triglycerides, and by lower acetylcholine-mediated vasodilation and nitroprusside-mediated vasodilation. In addition, men were characterized by higher levels of urinary cortisol excretion and creatinine excretion. Adjustment for age or BMI did not change these findings (data not shown).

Relationships among cortisol, microvascular function, blood pressure, insulin sensitivity and measures of adiposity

Partial correlation analyses demonstrated that greater urinary cortisol excretion was associated with less capillary recruitment in women, but not in men. In addition, in women, urinary cortisol was positively associated with SBP and measures of adiposity, and negatively associated with insulin sensitivity (Table 2 and Figure 1). Urinary cortisol was not associated with acetylcholine-mediated vasodilation in women or men ($r=0.17$, $P=0.4$ and $r=0.12$, $P=0.6$, respectively) or nitroprusside-mediated vasodilation ($r=-0.25$, $P=0.2$ and $r=0.21$, $P=0.3$, respectively). Adjustment for BMI or WHR did not materially affect these associations, except that the association of urinary cortisol with insulin sensitivity in women was no longer significant after adjustment for BMI or WHR ($r=-0.19$, $p=0.4$ and $r=-0.24$, $P=0.3$, respectively).

Interaction analyses demonstrated significant gender differences in the associations of urinary cortisol with capillary recruitment ($P=0.01$ for the interaction variable), SBP ($P=0.007$), BMI ($P=0.02$) and WHR ($P=0.03$). Interaction with gender for the association of urinary cortisol with insulin sensitivity tended to be significant ($P=0.1$). Correction of urinary cortisol for creatinine levels did not significantly change these findings.

Similar conclusions were reached if absolute increases in capillary recruitment, acetylcholine-mediated vasodilation and nitroprusside-mediated vasodilation were used instead of relative increases.

The contribution of capillary recruitment and anthropometrical measures to the cortisol-blood pressure and the cortisol-insulin sensitivity relationship in women

We used multiple regression analyses to investigate whether impaired capillary recruitment could statistically explain (part of) the association of urinary cortisol levels with SBP in women (Table 3). Model 1 demonstrates that cortisol (independent variable) was positively associated with SBP (dependent variable). The regression coefficient of the association between urinary cortisol and SBP decreased by approximately 37% and was no longer significant when capillary recruitment was entered into the regression analysis (model 2). The regression coefficient decreased by 24% but remained significant after introduction of BMI into the regression model (model 3). This suggests that, at least statistically, capillary recruitment and to a lesser extent BMI partly explain the relationship between urinary cortisol and SBP. If capillary recruitment was entered to the model in addition to BMI, the regression coefficient further decreased by 31% indicating that capillary recruitment, at least statistically, explained part of the relationship independently of BMI (model 4). If WHR instead of BMI was added to model 1, the regression coefficient decreased by 12% (β 19.0, 95%-CI 5.3 to 32.7) and remained significant ($P=0.009$), suggesting that WHR plays a less important role in the relationship between urinary cortisol and blood pressure than BMI. In order to examine the contribution of capillary recruitment and measures of adiposity to the relationship between urinary cortisol and insulin sensitivity in women, we used insulin sensitivity as dependent variable. Indeed, urinary cortisol was inversely associated with insulin sensitivity in women (β -0.90, 95%-CI -1.78 to -0.02, $P<0.05$). Addition of capillary recruitment did not decrease the regression coefficient (β -1.09, 95%-CI -2.24 to 0.07, $P=0.06$) indicating that capillary recruitment cannot explain the association between urinary cortisol and insulin sensitivity. Addition of BMI or WHR did reduce the regression coefficient with 68% (β -0.29, 95%-CI -1.12 to 0.55, $P=0.5$) and 47% (β -0.47, 95%-CI -1.39 to 0.44, $P=0.3$), respectively, indicating a potential role for BMI and WHR in the association between urinary cortisol and insulin sensitivity in women.

Discussion

The main finding of the present study is an association between urinary free cortisol excretion and capillary recruitment in healthy women and the absence of this relationship in healthy men. Subsequent regression analysis demonstrated that part of the relationship between urinary cortisol excretion and blood pressure in women can, at least statistically, be explained by impaired capillary recruitment.

In the present study we found striking gender differences. Higher urinary cortisol excretion rates in men than in women are in agreement with most [29-33], but not all previous studies [34-36]. These gender differences may, at least partly, be explained by differences in cortisol binding. Earlier studies have reported higher concentrations of cortisol binding globulin in women compared to men [37-39]. To our knowledge, gender differences in relationships between urinary free cortisol and blood pressure or insulin sensitivity have not previously been reported. However, in line with our findings, Stolk and colleagues have previously shown a relationship between plasma free cortisol, assessed by the ratio of fasting cortisol over cortisol binding globulin, and fasting insulin levels, as a measure of insulin resistance, in women, but not in men [38]. There are several explanations for our finding of gender differences in the association of cortisol with capillary recruitment. Firstly, in our study, men were more, in particular centrally, obese than women. Associations among cortisol and other variables may differ within different strata of obesity. Unfortunately, our study population was not large enough to perform analyses stratified for measures of adiposity. Secondly, a sexual dimorphism in activity of 11 β -hydroxysteroid dehydrogenase (11 β -HSD), which regulates the interconversion of inactive cortisone to active cortisol in several tissues, has been shown in humans [40;41]. 11 β -HSD is also present in vascular endothelial and smooth muscle cells [42;43], which suggests that local 11 β -HSD expression may play a role in regulation of local glucocorticoid activity and its effect on vascular function. Gender differences in local vascular 11 β -HSD activity might explain differences in associations between urinary cortisol and variables related to vascular function such as capillary recruitment, blood pressure and insulin sensitivity.

Cortisol inhibits endothelium-dependent vasodilation in the human forearm [44] and inhibition of cortisol production prevents stress-related endothelial dysfunction in

human resistance vessels [45]. We did not find an association between cortisol and impaired endothelium-dependent vasodilation in the skin microvasculature of the hand. This discrepancy may be due to different study designs. We studied cross-sectional data in healthy humans, whereas studies on macrovascular function used interventions to induce cortisol elevation. Another explanation is that hand and forearm (micro)vascular beds may differ in their responses to pharmacological stimuli [46].

Several earlier findings suggest that impairment of tissue capillary perfusion contributes to and precedes the development of hypertension. Hypertension is characterized by increased capillary pressure [47;48], while venous pressure is normal [49]. This implicates that capillary or postcapillary vascular resistance is increased and explains part of the increase in total peripheral vascular resistance in hypertension. Also, mathematical modeling of in vivo capillary networks shows an exponential relationship between capillary number and network resistance [50]. Furthermore, capillary rarefaction has been observed before the development of overt hypertension [16-18] and, moreover, muscle capillary rarefaction predicts the increase in mean arterial pressure in two decades [51], suggesting a pathogenic role. Thus, our findings of an inverse association between capillary recruitment and cortisol in women are in line with a role of impaired capillary perfusion in the development of corticosteroid-induced hypertension in women. However, at this point, it should be emphasized that cause and effect cannot be distinguished in our study because of its cross-sectional design. Therefore, it cannot be excluded that (part of the) impaired capillary recruitment is a result of the cortisol-induced increase in blood pressure or related mechanisms instead of a pathophysiological link. To further elucidate these issues, intervention studies and studies on the temporal relationships of cortisol-induced hypertension and microvascular defects are warranted.

Previous studies have shown that impairment of capillary recruitment is associated with a reduction of muscle glucose uptake and that physiological coupling between both is plausible [14;15]. However, in the present study, capillary recruitment did not mediate the association between cortisol and insulin sensitivity. A possible explanation for this phenomenon may be that effects of cortisol on nutritive capillary blood flow and concomitant insulin and glucose delivery are overruled by effects on other mechanisms that determine peripheral glucose uptake. Corticosteroids inhibit

insulin-induced translocation of glucose transporters [52;53] and influence insulin receptor binding and intracellular second messenger signaling [2]. Thus, our finding that capillary recruitment does not mediate the relationship between cortisol and insulin sensitivity may indicate that effects of cortisol on other determinants of peripheral glucose uptake than amount of nutritive flow may be rate-limiting.

A limitation of the present study was that a single 24-hour urine collection was used instead of an average of several collections. 24-Hour urinary sampling may not be practical and may be characterized by low compliance [32;36]. In order to minimize sampling errors in the present study all participants were provided with collection bottles and clear instructions and were questioned afterwards about their compliance. Also, there is uncertainty whether urinary cortisol can best be expressed in term of cortisol/creatinine ratio or total cortisol excretion [54]. Correction for the amount of creatinine excreted corrects for urine collection errors. However, it is dependent on diet and muscle mass and therefore is likely to underestimate true urinary cortisol excretion in men compared to women [54]. In the present study, correction for urinary creatinine excretion did not change the main findings.

In the present study we examined the contribution of different measures of adiposity to relationships among cortisol, insulin sensitivity and blood pressure. However, it may be argued whether it is legitimate to consider measures of adiposity as confounder, because different scenarios for the role of adiposity in these relationships can be depicted. There is considerable evidence that elevated cortisol causes fat accumulation at the level of the adipocyte by enhancing lipoprotein lipase activity [55]. In such a scenario, adiposity is not a confounder of the cortisol – insulin resistance relationship, but rather an intermediary variable. Secondly, adiposity may lead to inappropriately elevated cortisol levels through enhanced responsiveness of the hypothalamic-pituitary-adrenal axis to various stimuli and through peripheral alterations of cortisol production and metabolism [56]. In this scenario adiposity is the pathophysiological first step leading to increased cortisol levels and therefore again should not be considered a confounder. Finally, adiposity may lead to hypercortisolism on the one hand and both insulin resistance and hypertension on the other through non-related pathophysiological mechanisms. Only in this scenario adiposity is a true

confounder. These issues are controversial and more work is obviously needed to disentangle these complex interrelationships.

In conclusion, our present data provide the first evidence of an inverse association between urinary cortisol and skin capillary recruitment in healthy women, but not in men. Furthermore, in women, capillary recruitment explains part of the cortisol-blood pressure relationship. However, additional studies are necessary to examine whether capillary recruitment is a true pathophysiological link in this relationship in women. Also, the gender differences remain unexplained in the present study and studies on gender differences in particularly local vascular 11 β -hydroxysteroid dehydrogenase activity would of considerable interest. Nevertheless, our findings in healthy women suggest that, on the one hand, any impairment of capillary recruitment may predispose women to develop high blood pressure when exposed to excess cortisol concentrations. On the other hand, improvement of capillary function may partly protect women from the development of cortisol-associated high blood pressure. Therefore, interventions directed at preservation or improvement of microvascular function may be worthwhile in women in whom cortisol excess is to be expected.

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Legends to Figures

Figure 1.

Correlations among capillary recruitment, urinary cortisol and systolic blood pressure in 26 women (left panels) and 30 men (right panels).

Table 1. Baseline characteristics of the study population

	Men	Women
N	30	26
Age (years)	45.7±4.9	42.4±4.0*
BMI (kg/m ²)	26.1±2.5	23.8±4.4*
Waist (cm)	92.6±7.9	82.5±12.0 [‡]
WHR	0.90±0.06	0.83±0.07 [‡]
24h systolic blood pressure (mmHg)	125±9	119±13*
24h diastolic blood pressure (mmHg)	76±9	74±9
Heart rate (beats per minute)	69±11	74±9
Insulin sensitivity (mg/kg/min per pmol/L)*100	1.5±1.1	1.6±0.8
Plasma glucose (mmol/L)	4.8±0.7	4.7±0.5
Total cholesterol (mmol/L)	5.5±1.0	4.9±0.9*
Triglycerides (mmol/L)	1.2 (0.9-1.9)	0.9 (0.6-1.5)*
Urinary cortisol (nmol/24h)	162 (130-194)	118 (99-156)*
Urinary creatinine (mmol/24h)	16.3±2.6	10.7±1.9 [‡]
Urinary volume (ml/24h)	1598±533	1763±668
<i>Post-occlusive capillary recruitment</i>		
Capillary density in the resting state (n/mm ²)	42.3±9.5	48.2±13.2
Absolute increase in capillary density (n/mm ²)	13.4±9.1	17.6±8.5
Relative increase in capillary density (%)	32.0±22.8	39.6±24.8
<i>Endothelium-dependent vasodilation</i>		
Baseline skin perfusion (PU)	34.6±12.1	32.2±10.2
Absolute Ach-mediated vasodilation (PU)	107.1±50.3	157.1±110.4*
Relative Ach-mediated vasodilation (%)	342±212	508±325*
<i>Endothelium-independent vasodilation</i>		
Baseline skin perfusion (PU)	33.4±12.0	37.1±14.5
Absolute SNP-mediated vasodilation (PU)	85.9±75.0	149.2±139.4*
Relative SNP-mediated vasodilation (%)	314±410	451±473

Data are presented as mean±SD, or as median (interquartile range). PRH = peak reactive hyperaemia, Ach = acetylcholine, SNP = sodium nitroprusside, PU = perfusion units, *P<0.05, [†]P<0.01, [‡]P<0.001 men vs. women

Table 2. Correlations between urinary and plasma cortisol, post-occlusive skin capillary recruitment, 24h systolic blood pressure and anthropometrical measures in 26 women and 30 men

	Log urinary cortisol	Capillary recruitment	24h SBP	Insulin sensitivity
26 women				
Capillary recruitment	-0.66 [‡]	-	-	-
24h SBP	0.64 [‡]	-0.51*	-	-
Insulin sensitivity	-0.43*	0.21	-0.48*	-
WHR	0.48*	-0.38	0.41	-0.53 [†]
BMI	0.46*	-0.46*	0.50*	-0.66 [‡]
30 men				
Capillary recruitment	0.01	-	-	-
24h SBP	-0.01	-0.17	-	-
Insulin sensitivity	0.08	0.40*	-0.52 [†]	-
WHR	-0.14	-0.10	0.57 [†]	-0.52 [†]
BMI	-0.05	-0.21	0.53 [†]	-0.70 [‡]

Correlation coefficients are adjusted for age, *P<0.05, [†]P<0.01, [‡]P<0.001

Table 3. Regression analysis with 24h systolic blood pressure as dependent variable in 26 women

	β	95%-CI	P	R square	P model
1. Log urinary cortisol (nmol/24h)	21.5	9.2 to 33.6	0.001	0.35	0.001
2. Log urinary cortisol (nmol/24h)	13.5	-1.7 to 28.7	0.08	0.43	0.002
Capillary recruitment (%)	-0.18	-0.40 to 0.03	0.1		
3. Log urinary cortisol (nmol/24h)	16.4	3.2 to 29.5	0.03	0.43	0.001
BMI (kg/cm ²)	0.9	-0.1 to 2.0	0.09		
4. Log urinary cortisol (nmol/24h)	11.3	-4.0 to 26.6	0.1	0.47	0.002
Capillary recruitment (%)	-0.14	-0.36 to 0.08	0.2		
BMI (kg/cm ²)	0.7	-0.4 to 1.8	0.2		

All models are adjusted for age

Figure 1.

