Changes in Blood Pressure and in Vasoactive and Volume Regulatory Hormones During Semistarvation in Obese Subjects

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The mechanisms underlying the reduction in blood pressure that occurs with a severe energy-restricted diet were evaluated in 12 obese subjects during 8 days on a very–low-calorie diet (1.67 MJ/d) with a constant intake of 17 mmol sodium per day. The relationship between changes in blood pressure, sodium balance, plasma volume, renin-aldosterone and sympathetic nervous system activities, plasma C-terminus and N-terminus of the atrial natriuretic factor (ANF) prohormone, brain natriuretic peptide (BNP), and endothelin-1 (ET-1) concentrations was investigated. A negative sodium balance was present throughout the diet and was associated with a moderate reduction in plasma volume, a marked activation of the renin-aldosterone system, and a concomitant reduction in C- and N-terminal ANF prohormone levels. Moreover, the postural changes in N-terminal proANF and ANF secretion documented before the diet, disappeared after 8 days of dieting, in contrast to a greater postural stimulation of aldosterone and renin. A negative correlation was found between the changes of C- and N-terminal ANF prohormone levels and those of aldosterone. Urinary catecholamine excretion, BNP, and ET-1 remained unchanged. These results indicate that the decrease in blood pressure occurring during severe caloric restriction was essentially due to the reduction in the effective blood volume, as reflected by the stimulation of the renin-aldosterone system and the decrease in ANF levels. The lack of any changes in catecholamine excretion and endothelin levels suggests that peripheral vascular resistance did not change significantly in these circumstances.

THE DECREASE in blood pressure occurring concomitantly with a loss of weight with severe caloric restriction is a well-known phenomenon.[1-4] However, the mechanism involved in the hypotensive effect of an energy-restricted diet is not entirely elucidated. Several studies[5-8] suggested that the hypotensive effect of the diet is due essentially to the reduction in sympathetic nervous system activity, such as observed during total starvation. Since Andersson et al[9] demonstrated that a significant reduction in sympathetic nervous system activity occurs only after several weeks of dieting, other factors are probably involved in blood pressure regulation during the early period of severe caloric restriction. The observation that the decrease in blood pressure already present during the first days of starvation or a severe diet is associated with an activation of the renin-aldosterone system suggests that the decrease in blood volume may represent an underlying mechanism.[10]

Although the natriuretic and vasodilating properties of atrial natriuretic factor (ANF) are now well established,[11-14] the possible involvement of this peptide in the mechanism of the hypotensive response to dieting has never been demonstrated. ANF is in fact stored in atrial granules as a 126–amino acid prohormone, which on secretion is split into an N-terminal fragment called N-terminal proANF [ANF (1-98)] and a C-terminal fragment [ANF (99-126)] commonly termed ANF. The latter terminology will be used in the text. N-terminal proANF differs from ANF by a longer half-life and a better in vitro stability. During the first week of starvation[10] or during severe caloric restriction,[15] a decrease in ANF concentrations has been observed. McMurray and Vesely[16] showed that N-terminal proANF levels are also reduced after 1 week of semistarvation. Another natriuretic hormone, brain natriuretic peptide (BNP), a 32–amino acid peptide mainly produced by the ventricle in response to ventricular distension,[17-20] has not yet been studied during a very–low-calorie diet. A decreased activity of vasoconstrictive systems might also be involved in the hypotensive effect of diet. In this respect, changes in the production of endothelin-1 (ET-1), a potent endothelial vasoconstrictor, would offer new insight.[21-22] This peptide was investigated in one study showing that its concentrations may be elevated in obese subjects.[23] However, no data are available as to possible changes in ET-1 levels during a severe hypocaloric diet.

The present investigation was therefore designed to provide some additional insight into the hemodynamic and hormonal mechanisms underlying the decrease in blood pressure occurring during severe caloric restriction. To this end, the changes in blood pressure and in sodium balance, plasma volume, renin-aldosterone, and sympathetic nervous system activity together with changes in plasma N-terminal proANF, ANF, BNP, and ET-1 concentrations were evaluated in obese patients during an 8-day period of a very–low-calorie diet.

SUBJECTS AND METHODS

Subjects

Twelve obese subjects (10 women and two men) aged 18 to 63 years (mean, 45) were studied. Their body mass index (BMI) was 31 to 59.3 kg/m^2 (mean, 39.6). Systolic (SBP) and diastolic (DBP) blood pressure determined by 24-hour continuous monitoring (Space Labs Medical) using a large thick cuff, ranged, respectively, from 116 to 161 mm Hg (mean, 134.3) and from 64 to 93 mm Hg (mean, 79.5). Heart rates were between 55 and 103 beats per minute (mean, 78.5). None of the patients were taking any medication that could influence the sodium and water balance, renin-angiotensin-aldosterone system, or sympathetic nervous

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system (no diuretics, antihypertensive or antiarrhythmic drugs, or glucocorticoids). All subjects had normal circulating concentrations of urea nitrogen, creatinine, electrolytes, fasting glucose, thyrotropin, and cortisol. The study was approved by the Ethics Committee of the institution.

Protocol

All subjects were submitted during 8 days to a very–low-calorie diet (1.67 MJ/d, 50% of energy as protein and 17 mmol sodium/d; Equiline, Roussel, France). The diet was administered in three divided portions per day, and only a sodium-free fluid intake was allowed.

Before the diet and on the last day of dieting (day 8), the patients underwent several measurements. SBP, DBP, and heart rate were determined by a 24-hour continuous monitoring recording each variable every 30 minutes and giving the 24-hour averages. Blood samples were taken in the supine position at 8 AM (subjects lying down from at least midnight) and in the standing position (after 2 hours of standing) for measurement of plasma renin activity, aldosterone, cortisol, N-terminal proANF, ANF, BNP, and ET-1. Renin activity (Sorin Biomedica [Saluggia, Vercelli, Italy] Ren-CTK-Renin) and cortisol (Sorin Biomedica Cortisol) and aldosterone (DPC [Los Angeles, CA] aldosterone-RIA) concentrations were determined by characterized radioimmunoassays. The methods for ANF and ET-1 measurements using sensitive and specific radioimmunoassays after plasma extraction have been previously described in great detail by our group.[21,24] N-terminal proANF and BNP were measured using specific antibodies and synthetic peptides from Peninsula (Belmont, CA) after plasma extraction on Sep-Pak C18 cartridges. The N-terminal proANF assay used antibodies to proANF 1-30, which immunologically recognize the 98–amino acid N-terminus and proANF 1-30 as a separate entity.[25] The 24-hour urine samples were collected on chlorhydric acid for determination of epinephrine, norepinephrine, dopamine, and vanilyl mandelic acid (VMA) excretion. These catecholamine levels were measured after extraction by high-performance liquid chromatography and electrochemical detection. Plasma volume was evaluated by isotopic dilution after at least 1 hour in the lying position in fasting subjects between 8 and 11 AM. Plasma volume was determined with human serum albumin labeled with iodine 125. Labeled albumin (10 μc iodinated (^{125}I) human albumin; Amersham International, Amersham, UK) was injected with the use of a 10- and 20-minute equilibration sample.

Body weight, lying and standing blood pressure, and 24-hour urinary sodium excretion were measured daily.

Urea nitrogen, creatinine, electrolytes, and uric acid concentrations were determined every 3 days using standard methods of clinical biology.

Statistical Analysis

All results are presented as the mean ± SEM. Statistical significance was evaluated by paired T test or Wilcoxon's signed-rank test when required. A P value less than .05 was considered significant. Correlations were tested by the correlation coefficient of Pearson (r).

RESULTS

Body Weight and Sodium Balance

The cumulative loss of weight was 3.9 ± 0.7 kg for the 8-day period of semistarvation. A negative sodium balance was present in all subjects, averaging 215.4 ± 30.7 mmol sodium lost during the whole 8-day period of diet with a constant sodium intake of 17 mmol/d.

Blood Pressure and Heart Rate

SBP and DBP, recorded on each day in the lying position, decreased progressively during the 8-day period of diet without any significant postural decrease in blood pressure values (Table 1).

Significant decreases in SBP and DBP were observed at the end of the diet. When measured by a continuous 24-hour monitoring before and at the end of the diet, the 24-hour mean SBP and DBP decreased, respectively, from 134.3 ± 4.1 mm Hg to 120.1 ± 3.5 mm Hg ($P < .001$) and from 79.5 ± 2.6 mm Hg to 74.2 ± 2.2 mm Hg ($P = .03$).

Heart rate did not vary significantly during the diet, since the 24-hour mean heart rate was 78.5 ± 3.2 beats/min before and 75.3 ± 3.1 beats/min at the end of the diet.

Plasma Urea Nitrogen, Creatinine, Electrolytes, and Uric Acid

Plasma urea nitrogen, creatinine, and electrolyte concentrations measured on day 1, day 4, and day 7 remained unchanged. Plasma uric acid measured in the same conditions increased moderately (data not shown).

Plasma Volume, Renin Activity, and Aldosterone

The plasma volume before and at the end of diet was, respectively, 3,042 ± 182 mL and 2,834 ± 176 mL. This decrease in blood volume was of only borderline statistical significance ($P = .057$).

Before the start of the diet, plasma renin activity in the supine and standing position was 3.2 ± 2.2 ng/mL/h (normal, 0.2 to 2.8) and 4.0 ± 2.1 ng/mL/h (normal, 1.5 to 5.7), respectively. At the end of diet, supine and upright plasma renin activity increased to 6.9 ± 3.7 ($P = .016$) and 11.5 ± 5.6 ng/mL/h ($P = .01$), respectively (Fig 1). There was a significant postural stimulation of renin activity before ($P = .002$) and after ($P = .002$) the diet. This postural stimulation was greater ($P = .01$) after the diet.

Before the diet, supine and upright plasma aldosterone levels were within the normal range, respectively, 0.23 ± 0.05 nmol/L (normal, 0.03 to 0.44) and 0.44 ± 0.08 nmol/L (normal, 0.11 to

Table 1. Changes in SBP and DBP Measured in Lying and Upright Position During 8 Days of Very-Low-Calorie Diet (mean ± SEM)

Parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
SBP (mm Hg)								
Lying	138.7 ± 6.9	136.7 ± 4.9	131.7 ± 5.6	130.4 ± 4.2	130.4 ± 4.8	127.9 ± 3.6	127.9 ± 3.5	122.5 ± 4.1
Upright	137.9 ± 5.5	135.0 ± 4.7	130.0 ± 6.6	128.3 ± 4.2	127.1 ± 4.9	125.8 ± 5.7	125.4 ± 3.2	121.7 ± 3.3
DBP (mm Hg)								
Lying	81.7 ± 2.4	77.9 ± 2.4	77.1 ± 3.2	78.3 ± 3.7	77.5 ± 2.5	72.1 ± 1.7	72.5 ± 2.5	73.3 ± 2.8
Upright	80.4 ± 2.3	77.9 ± 2.1	77.9 ± 3.7	78.5 ± 3.5	75.8 ± 2.9	70.0 ± 6.0	75.4 ± 2.7	73.7 ± 3.0

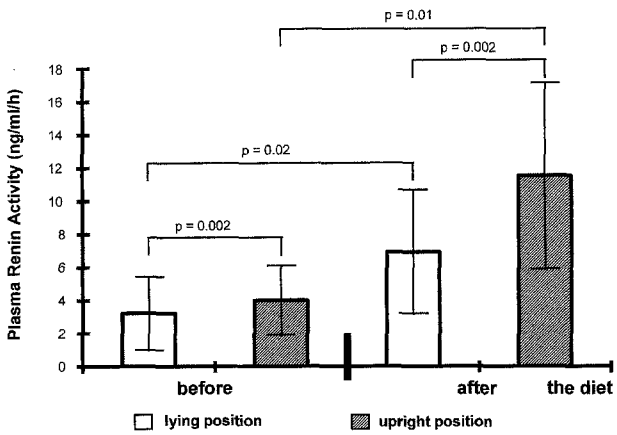


Fig 1. Plasma renin activity determined in lying and upright position in 12 obese subjects before and after 8 days of the very low calorie diet (mean ± SEM). Normal values in supine position: 0.2 – 2.8 ng/mL/h; in standing position, 1.5 – 5.7 ng/mL/h.

0.86). At the end of diet, these levels increased, respectively, to 0.65 ± 0.20 nmol/L (P = .011) and 1.17 ± 0.14 nmol/L (P = .004) (Fig 2). A significant postural stimulation of aldosterone secretion was observed before (P = .011) and after the diet (P = .004), the increase being more important in the latter condition (P = .006).

Plasma Cortisol

The 8 AM and 10 AM plasma cortisol levels (thus determined in the supine and upright position) were, respectively, 443 ± 55 and 312 ± 22 nmol/L before the diet and 454 ± 33 and 349 ± 42 nmol/L after the diet. In the face of increased aldosterone levels, a significant decrease in cortisol was documented between 8 and 10 AM both before (P = .006) and after (P = .026) the diet. There was no significant influence of the diet on 8 and 10 AM plasma cortisol levels.

Urinary Catecholamine Excretion

The 24-hour urinary epinephrine, norepinephrine, dopamine, and VMA excretion before and at the end of diet did not vary significantly. Indeed, the free-catecholamine excretion before and after the diet was 8.94 ± 1.39 and 9.15 ± 1.96 μg/24 h for epinephrine and 40.38 ± 5.7 and 36.98 ± 6.74 μg/24 h for norepinephrine. Dopamine excretion was 256.2 ± 28.4 μg/24 h before the diet and 241.1 ± 29.4 μg/24 h at the end of diet, while the corresponding values for VMA excretion were 3.27 ± 0.29 mg/24 h before and 3.33 ± 0.43 mg/24 h after the 8-day diet.

ANF

Before starting the diet, supine and upright ANF concentrations were, respectively, 43.7 ± 5 (normal, 43 ± 4.6) and 36.3 ± 4.6 pg/mL (normal ,10% to 20% decrease from supine values). After the 8-day period of semistarvation, ANF levels decreased to 29.1 ± 2.7 pg/mL in the lying position (P = .011) and to 25.4 ± 1.8 pg/mL (P = .042) in the upright position (Fig 3). Supine and upright N-terminal proANF concentrations were, respectively, 111.3 ± 17.9 and 79.9 ± 18.3 pg/mL before the diet, and also decreased, respectively, to 67.3 ± 10 pg/mL (P = .008) and 62.1 ± 10.4 pg/mL after the diet (P = .051) (Fig 3).

Thus, there was a significant postural decrease in ANF levels

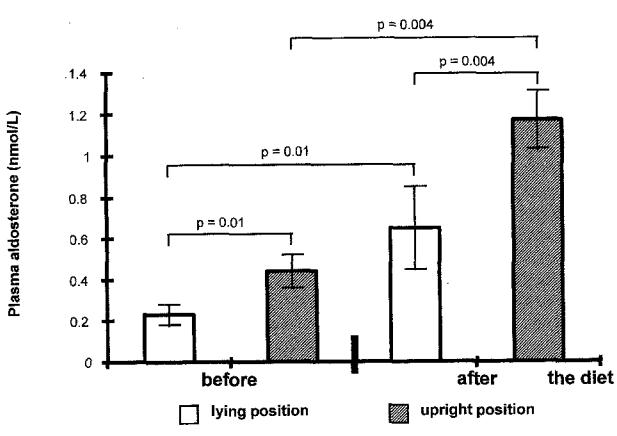
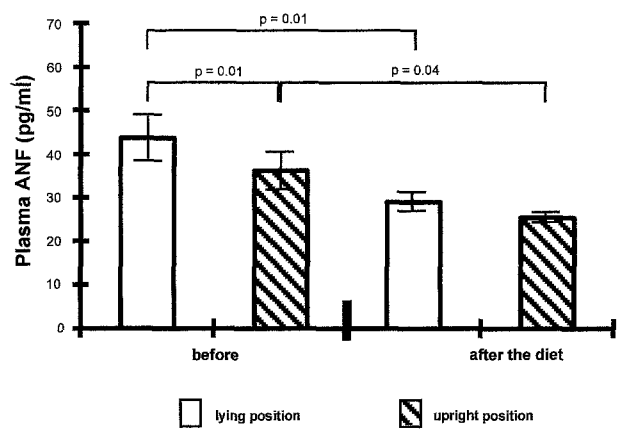


Fig 2. Plasma aldosterone concentrations determined in lying and upright position in 12 obese subjects before and after 8 days of a very-low-calorie diet (mean ± SEM). Normal values in supine position: 0.03 – 0.44 nmol/L; in standing position: 0.11 – 0.86 nmol/L.



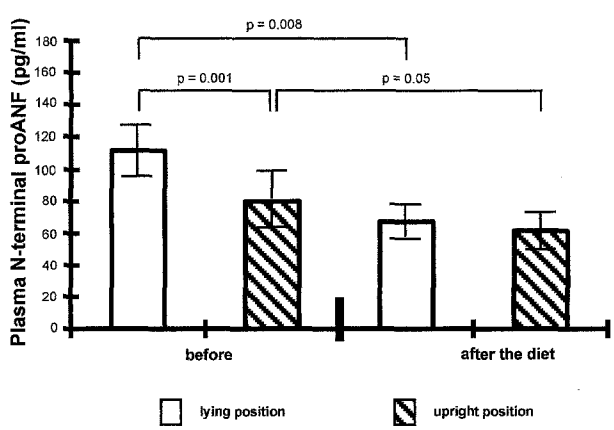


Fig 3. Plasma N-terminal proANF and ANF concentrations determined in lying and upright position in 12 obese subjects before and after 8 days of a very-low-calorie diet (mean ± SEM). Normal values of ANF are in supine position 43 ± 4.6 pg/mL with a 10%—20% decrease in standing position.

after standing, evident both for C-terminal ($P = .014$) and for N-terminal ($P = .0014$) ANF prohormone levels. While ANF and N-terminal proANF decreased significantly at the end of the diet in the lying position, no such postural variation was found after dieting.

Plasma BNP

BNP levels did not vary significantly during the diet. Supine and upright BNP concentrations were, respectively, 7.3 ± 0.9 and 9.1 ± 1.3 pg/mL before the diet and 7 ± 0.7 and 6.9 ± 0.7 pg/mL at the end of diet.

Plasma ET-1

Plasma ET-1 levels in the lying and upright position were, respectively, 3.7 ± 0.3 and 4 ± 0.4 pg/mL before the diet. These ET-1 levels did not change significantly at the end of diet, reaching, respectively, 4.6 ± 0.3 and 4.9 ± 0.2 pg/mL. There was no postural variation for plasma ET-1 levels.

Correlations Between Parameters

At the beginning of the diet, significant positive correlations were found between plasma ANF and N-terminal proANF concentrations ($r = .80$, $P < .01$ in lying position and $r = .81$, $P < .01$ in standing position) and between ANF and 24-hour sodium excretion ($r = .66$, $P < .05$). Moreover, lying plasma ANF correlated negatively with plasma ET-1 ($r = -.63$, $P < .05$). These correlations were lost at the end of diet.

At the end of the diet, whereas lying plasma ANF correlated negatively with renin activity ($r = -.59$, $P < .05$), positive correlations were observed between lying plasma ANF and BNP ($r = .72$, $P < .01$).

Throughout the diet, correlations were found between the changes of lying plasma ANF and N-terminal proANF ($r = .80$, $P < .01$). The changes of lying plasma aldosterone negatively correlated with those of ANF ($r = -.65$, $P < .05$) and of N-terminal proANF ($r = -.67$, $P < .05$).

DISCUSSION

The present study confirms the previously reported observations[1-4] that a significant decrease in SBP and DBP occurs in obese patients undergoing a very–low-calorie diet. This reduction in blood pressure was documented in this study by the 24-hour continuous monitoring recorded before and on the last day of diet. As demonstrated in other trials,[26,27] this decrease in blood pressure occurred already during the first days of diet, thus even before a significant reduction in body weight was evidenced. Thus, factors other than adiposity and the degree of overweight are probably involved in the reduction in blood pressure occurring during severe caloric restriction.[28]

This decrease in blood pressure was concomitant with the enhancement in natriuresis, which usually occurs at the beginning of a very–low-calorie diet.[15,16,26,29,30] The mechanism of this marked natriuresis remains unknown. Studies[10,31,32] in subjects submitted to a total starvation led to the proposal that an enhanced organic anion excretion (mainly ketoacids) could partly explain the natriuresis during the first days of fasting, while the reduction of natriuresis observed after 3 or 4 days of starvation was considered secondary to the increase in ammonium excretion.[31] However, it seems unlikely that such a mechanism could explain the enhancement in urinary sodium excretion in our patients, since during this type of diet urinary ketoacid excretion does not increase sufficiently to interfere with renal sodium handling.[26] It also seems unlikely that the decreased insulin secretion that obviously occurs with a severe energy-restricted diet is involved in the natriuretic and hypotensive response to dieting.[32] Indeed, insulin is devoid of a direct effect on renal sodium handling,[33] and instead of promoting hypertension, it exerts a vasodilatory and hypotensive effect.[34] Whatever the mechanism responsible for this negative sodium balance, the amount of sodium lost during the period of dieting suggests that the water lost during the diet originates mainly from the extracellular space. This conclusion is supported by our recent observation on a relationship between the loss of sodium and of total body water in obese subjects undergoing semistarvation.[35] This loss of extracellular fluid may explain the reduction in plasma volume observed in the present study.

It is now well established that ANF is responsive to changes in intravascular volume[36,37] and in sodium intake.[38] In this study, a significant reduction in circulating N-terminal proANF and ANF levels was observed at the end of diet, as demonstrated in other trials.[15,16] The loss of sodium documented in this investigation during severe caloric restriction probably did induce a decrease in plasma volume that may be responsible, as well as the low sodium intake, for this decreased release of ANF. The abolition of N-terminal proANF and ANF postural changes observed at the end of diet could also be due to this hypovolemic state, as previously observed for ANF.[10] It is noteworthy that both in the lying and standing position, ANF correlated with N-terminal proANF at the beginning of diet, and that changes of both parameters also correlated throughout the diet. This only reflects a common processing from the same ANF precursor. More interestingly, ANF correlated with sodium excretion at the beginning of diet but not at the end, which can be explained by interference of other factors.

No significant variation of BNP plasma levels was noted in this study. Thus, BNP is probably not involved in the hypotensive effect of diet. As previously shown by others,[39] BNP secretion is not responsive to an acute volume change like ANF.

Hypovolemia is the main stimulus of the renin-aldosterone system. In this study, plasma renin activity was higher after a week-long diet. An increase in aldosterone release was also observed while plasma sodium, potassium, and cortisol levels remained unchanged. Moreover, these changes in renin and aldosterone levels were probably not related to a variation in sympathetic nervous system activity, as reflected by unchanged heart rate and catecholamine excretion. So, the activation of the renin-aldosterone system observed in our patients was probably consecutive to the hypovolemic state. While ANF is known to inhibit the renin-aldosterone system at several levels,[40,41] significant inverse correlations were found in the present study between ANF and renin activity at the end of diet and between changes of ANF and aldosterone throughout the diet. Thus, both hypovolemia and the associated decrease in ANF could account for this increase in renin and aldosterone secretion. So, despite the only slight reduction in plasma volume documented in this study, the decrease in ANF levels and the activation of the renin-aldosterone system suggest a biologically relevant de-

crease in effective circulating volume. Whether the negative sodium balance with ensuing reduction in the effective blood volume and the decrease in blood pressure, such as observed in the present study was induced solely by the energy restriction or was mainly due to the restricted sodium intake cannot be answered on the basis of the data presented here. That the severe reduction of energy intake rather than that of sodium represents the underlying mechanism is strongly suggested by the observation reported by Tuck et al[42] that the energy-restricted diet produced a similar reduction in blood pressure when sodium intake was kept normal or severely reduced such as in the conditions of the present study. In addition, as concluded from the Intersalt Study,[43] the reduction of sodium intake by 100 mmol/d produces a much less marked reduction in blood pressure than the hypotensive effect of the very–low-calorie diet reported here.

In the present study, the decrease in blood pressure was not associated with a reduced sympathetic nervous system activity, given the unchanged heart rate and urinary catecholamine excretion and the absence of postural hypotension (Table 1). Neither was there any significant variation in ET-1 concentrations, which remained within the normal range. These observations could lead to the proposal that blood pressure reduction occurring during a very low calorie diet is probably not associated with a decreased peripheral vasoconstriction but is mainly due to hypovolemia, thus to reduced preload.

ET-1 concentrations did not change during semistarvation, but the interpretation of the data should be made with caution because of the paracrine action of ET-1 on the smooth muscular cells. Tissue concentrations of this peptide are therefore more reliable. In the present study, no postural stimulation of ET-1 was observed while it was demonstrated by others[42] during an acute tilting test. Degranulation of cells localized in the neuropituitary gland in response to an information from the baroreceptors has been suggested to induce this postural release of ET-1.[44] In our experimental set-up, this postural stimulation was not present, probably because the blood samples, collected 2 hours after standing are not representative of an acute postural change.

The results of the study are therefore in keeping with the hypothesis that the decrease in blood pressure occurring during a very–low-calorie diet is mainly induced by a reduction in extracellular volume leading to a reduced preload. Knowing that both obese hypertensive and normotensive subjects present an increased intravascular volume, a reduction in volemia, occurring already during the first days of a severe diet, would contribute to the decrease in blood pressure.

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REFERENCES

1. Fletcher AP: The effect of weight reduction upon the blood pressure of obese hypertensive women. Q J Med 23:331-345, 1954

2. Singh RB, Rastogi SS, Mehta PJ, et al: Effect of diet and weight reduction in hypertension. Nutrition 6:297-302, 1990

3. Singh RB, Niaz MA, Bishnoi I, et al: Effect of low energy diet and weight loss on major risk factors, central obesity and associated disturbances in patients with essential hypertension. J Hum Hypertens 9:355-362, 1995

4. McCarron D, Reusser M: Body weight and blood pressure regulation. Am J Clin Nutr 63:423S-425S, 1996 (suppl)

5. Landsberg L, Young JB: Fasting, feeding and regulation of the sympathetic nervous system. N Engl J Med 298:1295-1300, 1978

6. Jung RT, Shetty PS, Barrand M, et al: Role of catecholamines in hypotensive response to dieting. BMJ 1:12-13, 1979

7. Landsberg L: Pathophysiology of obesity-related hypertension: Role of insulin and the sympathetic nervous system. J Cardiovasc Pharmacol 23:51-58, 1994

8. Brands M, Hall J, Van Vliet B, et al: Obesity and hypertension: Roles of hyperinsulinemia, sympathetic nervous system and intrarenal mechanisms. J Nutr 125:1725S-1731S, 1995 (suppl)

9. Andersson B, Elam M, Wallin BG, et al: Effect of energy-restricted diet on sympathetic muscle nerve activity in obese women. Hypertension 18:783-789, 1991

10. Donckier J, Kolanowski J, Berbinschi A, et al: Relationship between natriuresis and changes in plasma atrial natriuretic factor, renin activity and aldosterone levels in fasting obese subjects. Diabete Metab 16:278-283, 1990

11. De Bold AJ, Borenstein HB, Veress AT, et al: A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 28:89-94, 1981

12. Currie MG, Geller DM, Cole BR, et al: Bioactive cardiac substances: Potent vasorelaxant activity in mammalian atria. Science 221:71-73, 1983

13. Maack T, Marion DN, Camargo F: Effects of auriculin on blood pressure, renal function, and the renin-aldosterone system in dogs. Am J Med 77:1069-1075, 1984

14. Garcia R, Thibault G, Cantin M, et al: Effect of a purified atrial natriuretic factor on rat and rabbit vascular strip and vascular beds. Am J Physiol 247:1234-1239, 1984

15. McMurray RW, Vesely DL Jr: Weight reduction decreases atrial natriuretic factor and blood pressure in obese patients. Metabolism 38:1231-1237, 1989

16. McMurray RW, Vesely DL: Calorie-restricted weight reduction, blood pressure, and atrial natriuretic peptides. Nutrition 9:178-182, 1993

17. Yasue H, Yoshimura M, Sumida H, et al: Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 90:195-203, 1994

18. Yoshimura M, Yasue H, Okumura K, et al: Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. Circulation 87:464-469, 1993

19. Wei CM, Heublein DM, Perrella MA, et al: Natriuretic peptide system in human heart failure. Circulation 88:1004-1009, 1993

20. Rubin SA, Levin ER: The endocrinology of vasoactive peptides: Synthesis to function. J Clin Endocrinol Metab 78:6-10, 1994

21. Donckier J, Hanet C, Berbinschi A, et al: Cardiovascular and endocrine effects of endothelin-1 at pathophysiological and pharmacological plasma concentration in dogs. Circulation 84:2476-2484, 1991

22. Vesely D, Chiou S, Douglass M, et al: Atrial natriuretic peptides negatively and positively modulate circulating endothelin in humans. Metabolism 45:315-319, 1996

23. Ferri C, Bellini C, Desideri G, et al: Plasma endothelin-1 levels in obese hypertensive and normotensive men. Diabetes 44:431-436, 1995

24. Donckier J, De Coster PM, Buysschaert M, et al: Effect of exercise on plasma atrial natriuretic factor and cardiac function in men and women. Eur J Clin Invest 18:415-419, 1988

25. Vesely DL, Douglass MA, Dietz JR, et al: Three peptides from the atrial natriuretic factor prohormone amino terminus lower blood pressure and produce diuresis, natriuresis, and/or kaliuresis in humans. Circulation 90:1129-1140, 1994

26. Kolanowski J: Modifications du bilan de sodium et de la tension artérielle au cours de la diète protidique chez les sujets obèses. Cah Nutr Diet 20:47-50, 1985

27. Dustan HP: Obesity and hypertension. Diabetes Care 14:488-504, 1991

28. Kolanowski J: Particularités de l'hypertension artérielle associée à l'obésité: de la physiopathologie à l'approche thérapeutique. Rev Fr Endocrinol Clin 37:475-480, 1996

29. Sigler MH: The mechanism of the natriuresis of fasting. J Clin Invest 55:377-387, 1975

30. Marks P, Wilson B, Delasalle A: Aldosterone studies in obese patients with hypertension. Am J Med Sci 289:224-228, 1985

31. Kolanowski J, Bodson A, Desmecht P, et al: On the relationship between ketonuria and natriuresis during fasting and upon refeeding in obese patients. Eur J Clin Invest 8:277-282, 1978

32. Cooke CR, Turin MD, Whelton A, et al: Studies of marked and persistent sodium retention in previously fasted and sodium deprived obese subjects. Metabolism 36:609-615, 1987

33. Briffeuil P, Huynh-Thu T, Kolanowski J: Reappraisal of the role of insulin on sodium handling by the kidney: Effect of intrarenal insulin infusion in the dog. Eur J Clin Invest 22:523-528, 1992

34. Hall JE: Renal and cardiovascular mechanisms of hypertension in obesity. Hypertension 23:381-394, 1994

35. Wojcik M, Kolanowski J: Changes in body composition and energy expenditure following a short-term very low calorie diet in the obese. Int J Obes 21:571, 1997 (suppl 2, abstr)

36. Lang R, Thocken H, Ganten D, et al: Atrial natriuretic factor—A circulating hormone stimulated by volume loading. Nature 33:363, 1985 (letter)

37. Shenker Y, Sider RS, Ostafin EA, et al: Plasma levels of immunoreactive ANF in healthy subjects and in patients with edema. J Clin Invest 76:1684-1687, 1985

38. Weidmann P, Hellmueller B, Uehlinger D, et al: Plasma levels and cardiovascular endocrine and excretory effects of atrial natriuretic peptide during different sodium intakes in man. J Clin Endocrinol Metab 62:1027-1035, 1986

39. Ogawa T, Linz W, Stevenson M, et al: Evidence for load-dependent and load-independent determinants of cardiac natriuretic peptide production. Circulation 93:2059-2065, 1996

40. Burnett JC, Granger JP, Opgenorth TJ: Effects of synthetic atrial natriuretic factor on renal function and renin release. Am J Physiol 247:F863-F865, 1984

41. Maack T, Marion DN, Camargo F, et al: Effect of auriculin on blood pressure, renal function, and the renin-aldosterone system in dogs. Am J Med 77:1069-1075, 1984

42. Tuck ML, Sowers J, Dernfeld I, et al: The effect of weight reduction on blood pressure, plasma renin activity and plasma aldosterone levels in obese patients. N Engl J Med 304:930-933, 1981

43. Elliott P, Stemler J, Nichols R, et al: Intersalt revisited: Further analyses of 24-hour sodium excretion and blood pressure within and across population. BMJ 312:1249-1253, 1996

44. Kaufmann H, Oribe E, Oliver JA: Plasma endothelin during upright tilt: Relevance for orthostatic hypotension? Lancet 338:1542-1545, 1991