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Hypo- and hypervolemic edema in children with steroid sensitive nephrotic syndrome

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Background/aim: The mechanism of edema formation in nephrotic syndrome is still poorly understood. We aimed to evaluate the volume status in children with steroid-sensitive nephrotic syndrome (SSNS) and to emphasize the importance of echocardiography in demonstrating of volume changes.

Materials and methods: Thirty-two SSNS patients and 30 healthy children were enrolled in this study. The volume statuses of patients were evaluated by clinical and laboratory features, including fractional sodium excretion (FENa) and distal sodium/potassium exchange (UK/UNa+K ratio). Inferior vena cava collapsibility index (IVCCI), left atrial diameter (LAD), aortic diameter (AD), and left ventricular mass index (LVMI) were measured using conventional echocardiographic methods.

Results: FENa was lower in children with NS; however, the distal K/Na ratio of the patient and control groups did not differ. In addition, IVCCI, LAD, AD, and LVMI were not different among groups. When evaluating the volume status of patients, 8 patients (25%) were hypovolemic while 24 patients (75%) were nonhypovolemic (normovolemic or hypervolemic). LAD was significantly lower in hypovolemic patients.

Conclusion: The majority of children with SSNS are normovolemic or hypervolemic and echocardiography is an easy and valuable method for the evaluation of volume status in these patients.

Key words: Children, edema, inferior vena cava collapsibility index, left atrial diameter, nephrotic syndrome, sodium

1. Introduction

Nephrotic syndrome (NS) is a common type of renal disease in childhood. The disease is characterized by massive proteinuria, hypoalbuminemia, and edema. Edema is one of the cardinal features of NS, but its pathogenesis is still not entirely understood (1,2).

By definition, edematous nephrotic patients always have a total body excess of both sodium and water. Edema in NS is usually considered to be due to massive proteinuria, which leads to hypoalbuminemia and retention of sodium and water to compensate for intravascular volume depletion (1–3).

Although patients with nephrotic syndrome have increased total body water and sodium, the intravascular volume status of these patients is somewhat controversial. Two hypotheses have been proposed to explain the intravascular situation in the nephrotic syndrome: the underfill hypothesis and overfill hypothesis (2–5). Assessment of intravascular volume in patients is routinely demonstrated by clinical and biochemical data. However, these data alone are not sufficient for the assessment of blood volume. In addition, vasoactive hormones, renal function tests, and lithium clearances can be used to evaluate the intravascular volume. In recent years, tests that can be performed more quickly and easily are recommended. Examples of these tests are fractional sodium excretion (FENa) and urinary sodium/potassium exchange (U_K/U_{Na+K} ratio) (1). The purpose of this study is to evaluate the intravascular volume status in children with steroid-sensitive nephrotic syndrome (SSNS) and to determine the value of the echocardiographic measurements in assessment of the volume changes.

2. Materials and methods

2.1. Patients and study design

The patients were diagnosed with the presence of edema, massive proteinuria (>40 mg m^{-2} h^{-1} or a urine protein/creatinine ratio of >2.0 mg/mg), and hypoalbuminemia (<2.5 g/dL), with normal serum creatinine and urea levels and without macroscopic hematuria and

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hypocomplementemia. Patients who were in remission in response to corticosteroid treatment alone were defined as SSNS patients.

This was a cross-sectional study of children with new-onset NS. The study began with 33 patients. The patient's weight, height, blood pressure, and pulse rate were measured on admission day. The initial treatment was started as 60 mg m^{-2} day^{-1} (2 mg kg^{-1} day^{-1}) of prednisone for 4 to 8 weeks. After the urine had become protein free, it was followed by 40 mg/m^2 every other day for 4 to 8 weeks and then a gradual taper until it was discontinued. One patient who did not achieve remission following the standard regimen of 4-week daily prednisone was excluded from the study. None of the patients had been administered steroids or immunosuppressive drugs during the previous 3 months. We evaluated the patient's volume status by clinical and laboratory features (levels of blood urea, FENa, and U_K/U_{Na+K} ratio). Thirty age- and sex-matched healthy children served as the control group.

This study was approved by the local research ethics committee (28.05.2009/41). Informed consent was obtained from the parents of all subjects. Our study conformed to good medical and laboratory practices and the Declaration of Helsinki on Biomedical Research.

2.2. Laboratory measurements

Blood samples were obtained in the morning before breakfast. Total protein, albumin, blood urea nitrogen, creatinine, sodium, potassium, cholesterol, triglyceride, and complements (C3 and C4) and in spot urine sodium, potassium, and creatinine were measured at the same time. Although the random urine protein/creatinine ratio correlates highly with daily urinary protein loss, 24-h urine samples were collected for determination of urinary protein excretion in our study.

Serum and urinary concentrations of sodium, potassium, urea nitrogen, and creatinine were measured by standard biochemical methods using an Architect C1600 clinical analyzer (Abbott, Saint-Laurent, Quebec, Canada). Urinary sodium and potassium excretion levels were measured by a potentiometric method and creatinine in urine was analyzed with flame photometry.

Fractional sodium excretion (FENa, %) was calculated by following the standard formula: (Urinary Na × Plasma Cr)/(Urinary Cr × Plasma Na) × 100. The quotient of distal K-Na was taken as an indicator for sodium/potassium exchange in the distal tubule. This quotient was calculated using the following formula: distal K-Na= (U_K/U_{Na+K}) × 100.

2.3. Echocardiographic examination

Echocardiographic examinations were done by the same pediatric cardiologist to determine the volume load of all patients after the patient had taken a 10-min rest. All of the measurements were performed at least 3 times. Inferior vena cava (IVC) diameter during expiration and maximal inspiration was measured from 1 to 2 cm under the diaphragm with color Doppler echocardiography. The IVC collapsibility index (IVCCI) was measured by the following formula: [(maximal diameter of IVC on expiration – minimal diameter on inspiration)/(maximal diameter on expiration)] × 100 (6).

Left atrium diameter (LAD) at the parasternal position was measured. LAD was determined as diameter of left atrium (mm)/body surface area (m^2). Aortic annulus diameter (AD) was measured independently from the two-dimensional parasternal long axis view (7). Left ventricular mass (LVM) was calculated using measurements made according to the recommendations of the American Society of Echocardiography (CAC1 12): $LVM = 0.8\{1.04([LVEDD + PWT + IVSDT]^3 - [LVEDD]^3)\} + 0.6$ g, where LVEDD is left ventricular diameter in end diastole, PWT is posterior wall thickness in diastole, and IVSDT is interventricular septum thickness in end diastole. The calculated mass correlates well with necropsy values for LVM (8). Left ventricular mass index (LVMI) was calculated as LVM divided by height $(m)^{2.7}$. Correcting LVM for height$^{2.7}$ minimizes the effect of sex, race, age, and obesity (9). A routine echocardiographic examination was also performed to diagnose other cardiac pathologies.

2.4. Statistical analyses

The analysis was performed using the SPSS for Windows 15.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as means ± standard deviations or medians, depending on the distribution. Student's t-tests, Mann–Whitney U-tests, and chi-squared tests were used for comparison between patients and controls. Correlations were assessed using Spearman's correlations matrix. Stepwise linear regression analysis was performed to assess the independent predictors of urinary sodium and potassium changes. P-values of less than 0.05 were accepted as statistically significant.

3. Results

Thirty-two children with newly diagnosed SSNS were included in this study. The patients were admitted to our clinic in 1–4 days (median: 2 days) after the onset of edema. The demographic characteristics of the study groups are summarized in Table 1. Average weight at presentation (actual weight) was 9% higher than the posttreatment (dry) weight (respectively, 32.36 ± 20.18 kg vs. 29.21 ± 19.22 kg).

Serum urea, creatinine, sodium, potassium, and complements of the patients were normal and there was no statistically significant difference among patient and control groups ($P > 0.05$). As expected, serum total protein and albumin were lower while total cholesterol and triglyceride were higher in children with SSNS. Urine

Table 1. Comparison of demographic characteristics of the study groups.

	Patients (n = 32)	Controls (n = 30)	P
Age (years)	7.78 ± 5.17	9.47 ± 4.17	>0.05
Sex (M/F)	24/8	23/7	>0.05
Height (cm)	120.9 ± 29.2	129.6 ± 23.0	>0.05
Weight (kg)	32.36 ± 20.18*	28.81 ± 14.07	>0.05

*Mean posttreatment (dry) weight was 29.21 ± 19.22 kg.

sodium and potassium concentrations were lower in patients than controls (Table 2). In addition, FENa was significantly lower in patients with SSNS, but the mean distal K-Na was similar in both groups (Table 3).

When the echocardiographic indices of nephrotic and healthy children were compared not regarding volume status, there was no difference between the two groups (Table 4). We did not detect a correlation between echocardiographic parameters and urine indicators (FENa and distal K-Na).

Afterwards, NS patients were divided into two groups as hypovolemic and nonhypovolemic according to their clinical and laboratory characteristics**.** Tachycardia, dizziness, orthostatic hypotension, muscular cramps, and delayed capillary refill were considered as clinical signs of hypovolemia. Accompanied by clinical signs of hypovolemia, the patients with FENa levels below 1% and/or distal tubular K/Na ratios above 60% were defined as hypovolemic [1]. Based on this definition, 8 (25%) of 32 patients with nephrotic syndrome were hypovolemic, while 24 (75%) of them were nonhypovolemic (normovolemic or hypervolemic). Pulse rates were higher and systolic and diastolic blood pressures were lower in hypovolemic patients than nonhypovolemic patients (Table 5). In the hypovolemic group, there was dizziness in 3 patients and muscle cramps in 2 patients. One

Table 2. Biochemical parameters of study groups.

	Patients (n = 32)	Controls (n = 30)	P
Urea (mg/dL)	24.6 ± 9.8	24.2 ± 7.3	>0.05
Creatinine (mg/dL)	0.46 ± 0.15	0.53 ± 0.08	>0.05
Sodium (mmol/L)	137.2 ± 3.92	137.7 ± 2.09	>0.05
Potassium (mmol/L)	4.26 ± 0.38	4.23 ± 0.38	>0.05
Total protein (g/dL)	4.06 ± 0.53	7.21 ± 0.39	<0.001
Albumin (g/dL)	1.92 ± 0.62	4.37 ± 0.42	<0.001
Total cholesterol (mg/dL)	359 ± 156	154 ± 18	<0.001
Triglyceride (mg/dL)	272 ± 239	126 ± 71	0.001
Complement-3 (g/L)	128 ± 26	122 ± 47	>0.05
Complement-4 (g/L)	22.5 ± 5.3	21.9 ± 5.5	>0.05
Spot urine Na (mmol/L)	59.4 ± 59.3	155.3 ± 58.3	<0.001
Spot urine K (mmol/L)	35.2 ± 27.6	83.6 ± 37.5	0.001

Table 3. Renal tubular sodium and potassium excretion.

	Patients (n = 32)	Controls (n = 30)	P
FENa (%)	0.84 ± 0.25	1.25 ± 0.29	0.001
Distal K-Na (%)	42 ± 23	36 ± 17	>0.05

FENa, Fractional sodium excretion; Distal K-Na, sodium/potassium exchange in the distal tubule.

Table 4. Echocardiographic parameters of the intravascular volume.

	Patients (n = 32)	Controls (n = 30)	P
LVMI (g/m^2)	40.33 ± 15.95	38.25 ± 8.37	>0.05
AD (mm)	21.54 ± 4.76	20.82 ± 4.31	>0.05
LAD (mm/m^2)	27.7 ± 8.45	22.96 ± 7.37	>0.05
IVCCI (%)	14.32 ± 5.89	11.26 ± 3.76	>0.05

LVMI, Left ventricular mass index; AD, aortic diameter; LAD, left atrium diameter; IVCCI, inferior vena cava collapsibility index.

Table 5. Pulse rates, blood pressures, and echocardiographic findings according to volume status in SSNS patients.

	Hypovolemic (n = 8)	Nonhypovolemic (n = 24)	P
Pulse rate (/s)	93.67 ± 6.66	81.09 ± 4.41	0.012
SBP (mmHg)	80.7 ± 5.1	97.6 ± 9.9	0.005
DBP (mmHg)	46.7 ± 4.5	62.7 ± 6.1	0.025
LVMI (g/m^2)	36.92 ± 8.61	41.26 ± 17.65	>0.05
AD (mm)	26.53 ± 5.92	20.17 ± 3.60	>0.05
LAD (mm/m^2)	23.01 ± 12.69	28.98 ± 7,23	0.03
IVCCI (%)	12.35 ± 8.55	14.85 ± 5.38	>0.05

SBP, Systolic blood pressure; DBP, diastolic blood pressure, LVMI, left ventricular mass index; AD, aortic diameter; LAD, left atrium diameter; IVCCI, inferior vena cava collapsibility index.

patient's capillary refill time was prolonged (>2 s). When comparing echocardiographic parameters of patients with and without hypovolemia, the mean LAD values of hypovolemic patients were significantly lower than the values of nonhypovolemic patients. LVMI, AD, and IVCCI values were similar in both groups (Table 5).

4. Discussion

NS is a disease characterized by massive urinary protein losses, resulting in hypoalbuminemia and edema formation (1–4). This prospective study was planned to evaluate the volume status using clinical and laboratory methods in children with SSNS.

The balance between capillary hydrostatic pressure and capillary oncotic pressure prevents edema formation in healthy subjects. The status of intravascular volume in patients with nephrotic syndrome is somewhat controversial. Two hypotheses, he underfill and overfill hypotheses, have been suggested to explain the intravascular state in nephrotic syndrome (1,2,5). Underfill hypothesis refers to the reduced effective circulating blood volume, while overfill hypothesis indicates the expanded intravascular volume (4,5,10,11).

Detection of intravascular volume is very important for a patient's therapeutic management in NS. Clinical symptoms alone are often unreliable for an assessment of blood volume. For this purpose, vasoactive hormones, renal function tests, and lithium clearances can be used. However, these tests are relatively expensive and time-consuming. The measurements of FENa and U_K/U_{Na+K} ratio correlate well with plasma aldosterone levels and provide useful tests for detecting hypovolemia (1–4). Therefore, we evaluated the intravascular volume state of nephrotic patients by measurements of FENa and U_K/U_{Na+K} in addition to their clinical findings.

In this study, FENa was significantly lower in patients than that of the control group. However, there was no statistically significant difference among patient and control groups regarding distal K-Na (U_K/U_{Na+K}), which is an indicator for sodium/potassium exchange in the distal tubule. The results were similar to those of Donmez et al. (12) and Gurgoze et al. (13), whereby severe sodium retention was described in children with edematous NS.

The notion of sodium reabsorption related to the RAA system activated by hypovolemia in cases of edematous NS is easier to explain. However, determination of probable intrarenal sodium reabsorption in nonhypovolemic patients is a more critical issue. In our study, the important contribution of sodium reabsorption to the formation of edema has been demonstrated in accordance with the results of previous studies. Sodium reabsorption, a contributor to the formation of edema, is accomplished in renal tubules. It mostly occurs in the proximal renal tubule. Many studies demonstrating proximal tubular sodium reabsorption in the formation of edema are available (12–15).

In patients with NS, urinary potassium-sodium exchange rate (U_K/U_{Na+K} ratio) is investigated in order to demonstrate the role of sodium reabsorption of the distal tubule on the pathogenesis of edema (16,17). In our study, FENa was lower in NS patients than controls, while mean distal K-Na was similar to that of controls. In other words, no significant difference in distal tubular potassium-sodium exchange parameter was found. Based on this, we concluded that the distal tubules did not have a significant impact on sodium reabsorption. Our results confirmed the studies that demonstrated the importance of sodium reabsorption in proximal tubuli for the development of edema. Gurgoze et al. (13) identified intrarenal sodium reabsorption in the pathogenesis of edema in NS. Vande Welle et al. (14) detected that the rate of distal tubular potassium-sodium exchange is markedly higher in favor of sodium retention in cases of hypovolemic NS, while in nonhypovolemic patients they did not detect such a significant impact of the distal tubule, in accordance with our results. They also suggested that the main determinant of sodium reabsorption is the proximal tubule, as in previous studies. In the early phase of NS, urinary indices reveal an overlap of primary and secondary sodium retention (18). FENa alone cannot be used to differentiate between primary and secondary sodium retention. However, in children with NS, strong positive correlations were found between U_K/U_{Na+K} ratio and plasma aldosterone (19). It can be useful in differentiating primary sodium retention from secondary sodium retention in NS patients (18).

Our patients were divided into two groups as hypovolemic and nonhypovolemic according to the above-mentioned clinical and laboratory criteria. Kapur et al. (20) defined as hypovolemic the patients who had FENa of <1%. However, in phase 2 of their study, the FENa criterion for the volume status was modified and patients with FENa of <0.2% were identified with volume contraction. We thus have not decided on the basis of urine indicators alone. According to these definitions, we identified that the majority of children with SSNS (75%) were nonhypovolemic.

Plasma rennin activity, vasoactive hormones like aldosterone, and ANP are indirect indicators of the circulating volume. The concept of sodium reabsorption associated with the RAA system, which is activated with hypovolemia in edematous cases of SSNS, can be explained more readily (13). The most important limitation of our study is that these indicators have not been investigated.

The second aim of our study was to determine the value of echocardiographic measurements (LAD, IVCCI, LVMI, and AD) on volume changes. For the estimation of circulating blood volume, IVCCI and LAD have been reported as valuable predictive factors. Decreased IVCCI and/or increased LAD indicate the increased volemic status in patients (12,13,21,22). Increased LVMI is defined as an increase in the mass of the left ventricle, which can be secondary to an increase in wall thickness, an increase in cavity size, or both. This increase in mass predominantly results from a chronic increase in the afterload of the left ventricle caused by hypertension and/or by chronic volume load (23–25). Aortic annulus diameter enlargement has been reported in children with hypertension other than Turner and Marfan syndromes (26,27). However, neither LVMI nor AD has been studied in children with NS to date.

Donmez et al. (12) reported that the IVCCI of edematous NS patients was significantly lower and LAD values were not different from the controls. The study by Gurgoze et al. (13) did not include a control group, and NS subgroups were compared among themselves. They found no difference between groups in terms of both the IVCCI and LAD. In our study, echocardiographic measurements of our patients did not differ from controls.

We reevaluated the echocardiographic parameters of patients after separating them into two groups according to volume status. LAD measurements of hypovolemic patients were found to be significantly lower than in nonhypovolemic patients ($P = 0.03$). Other echocardiographic findings were similar between these two groups in our study (Table 5).

In conclusion, the majority of children with SSNS are normovolemic or hypervolemic rather than hypovolemic. LAD is the best echocardiographic parameter that shows the volume status of these patients. Lastly, we suggest that there is a weak impact of the distal tubule on sodium reabsorption, because distal K-Na exchange of nephrotic patients is not different from that of healthy children.

References

1. Van de Walle JG, Donckerwolcke RA. Pathogenesis of edema formation in the nephrotic syndrome. Pediatr Nephrol 2001; 16: 283–293.
2. Doucet A, Favre G, Deschenes G. Molecular mechanism of edema formation in nephrotic syndrome: therapeutic implications. Pediatr Nephrol 2007; 22: 1983–1990.
3. Dorhout Mees EJ, Geers AB, Koomans HA. Blood volume and sodium retention in the nephrotic syndrome: a controversial pathophysiological concept. Nephron 1984; 36: 201–211.
4. Geers AB, Koomans HA, Boer P, Dorhout Mees EJ. Plasma and blood volumes in patients with the nephrotic syndrome, Nephron 1984; 38: 170–173.
5. Schrier RW, Fassett RG. A critique of the overfill hypothesis of sodium and water retention in the nephrotic syndrome. Kidney Int 1998; 53: 1111–1117.
6. Pepi M, Tamborini G, Galli C, Barbier P, Doria E, Berti M, Guazzi M, Fiorentini C. A new formula for echo-Doppler estimation of right ventricular systolic pressure. J Am Soc Echocardiogr 1994; 7: 20–26.
7. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58: 1072–1083.
8. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. J Am Coll Cardiol 1986; 57: 450–458.
9. De Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992; 20: 1251–1260.
10. Usberti M, Gazzotti RM, Poiesi C, D'Avanzo L, Ghielmi S. Considerations on the sodium retention in nephrotic syndrome. Am J Nephrol 1995; 15: 38–47.
11. Ichikawa I, Rennke HG, Hoyer JR, Badr KF, Schor N, Troy JL, Lechene CP, Brenner BM. Role for intrarenal mechanisms in the impaired salt excretion of experimental nephrotic syndrome. J Clin Invest 1983; 71: 91–103.
12. Donmez O, Mir S, Ozyurek R, Cura A, Kabasakal C. Inferior vena cava indices determine volume load in minimal lesion nephrotic syndrome. Pediatr Nephrol 2001; 16: 251–255.
13. Gurgoze MK, Gunduz Z, Poyrazoglu MH, Dursun I, Uzum K, Dusunsel R. Role of sodium during formation of edema in children with nephrotic syndrome. Pediatr Int 2011; 53: 50–56.
14. Van de Walle JG, Donckerwolcke RA, Greidanus TB, Joles JA, Koomans HA. Renal sodium handling in children with nephrotic relapse: relation to hypovolemic symptoms. Nephrol Dial Transplant 1996; 11: 2202–2208.
15. Allon M, Pasque CB, Rodriguez M. Sodium and water excretion in nephrotic patients. Effects of changes in renal haemodynamics. Clin Sci 1990; 79: 123–129
16. Donckerwolcke RA, France A, Raes A, Walle JV. Distal nephron sodium-potassium exchange in children with nephrotic syndrome. Clin Nephrol 2003; 59: 259–266.
17. Van de Walle JG, Donckerwolcke RA, van Isselt JW, Derkx FH, Joles JA, Koomans HA. Volume regulation in children with early relapse of minimal change nephrosis with or without hypovolemic symptoms. Lancet 1995; 346: 148–152.
18. Iyengar AA, Kamath N, Vasudevan A, Phadke KD. Urinary indices during relapse of childhood nephrotic syndrome. Indian J Nephrol 2011; 21: 172–176.
19. Matsumoto H, Miyaoka Y, Okada T, Nagaoka Y, Wada T, Gondo A, Esaki S, Hayashi A, Nakao T. Ratio of urinary potassium to urinary sodium and the potassium and edema status in nephrotic syndrome. Intern Med 2011; 50: 551–555.
20. Kapur G, Valentini RP, Imam AA, Mattoo TK. Treatment of severe edema in children with nephrotic syndrome with diuretics alone--a prospective study. Clin J Am Soc Nephrol 2009; 4: 907–913.
21. Moreno FLL, Hagan JR, Pryor TA, Strickland RD, Castle CH. Evaluation of size and dynamics of the inferior vena cava as an index of right-sided cardiac function. Am J Cardial 1984; 53: 579–585.
22. Cheriex EC, Leunissen KML, Janssen HA, Mooy JMV, van Hooff JP. Echography of the inferior vena cava is a simple and reliable tool for estimation of 'dry weight' in haemodialysis patients. Nephrol Dial Transplant 1989; 4: 563–568.
23. Mitsnefes MM. Cardiovascular complications of pediatric chronic kidney disease. Pediatr Nephrol 2008; 23: 27–39.
24. Sladowska-Kozłowska J, Litwin M, Niemirska A, Wierzbicka A, Wawer ZT, Janas R. Change in left ventricular geometry during antihypertensive treatment in children with primary hypertension. Pediatr Nephrol 2011; 26: 2201–2209.
25. Civilibal M, Caliskan S, Oflaz H, Sever L, Candan C, Canpolat N, Kasapcopur O, Bugra Z, Arisoy N. Traditional and "new" cardiovascular risk markers and factors in pediatric dialysis patients. Pediatr Nephrol 2007; 22: 1021–1029.
26. Jakrapanichakul D, Chirakarnjanakorn S. Comparison of aortic diameter in normal subjects and patients with systemic hypertension. J Med Assoc Thai 2011; 94 (Suppl. 1): S51–56.
27. Cuspidi C, Meani S, Fusi V, Valerio C, Sala C, Zanchetti A. Prevalence and correlates of aortic root dilatation in patients with essential hypertension: relationship with cardiac and extracardiac target organ damage. J Hypertens 2006; 24: 573–580.