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ORIGINAL ARTICLE

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Elevated Plasma Homocysteine Level as a Risk Factor for Hypertension

Podwyższone stężenie homocysteiny w osoczu jako czynnik ryzyka nadciśnienia tętniczego

Streszczenie

Wstęp Celem pracy była ocena związku pomiędzy stężeniem homocysteiny a występowaniem nadciśnienia tętniczego.

Materiał i metody W badaniu uczestniczyło 88 pacjentów z nadciśnieniem tętniczym (62 mężczyzn i 26 kobiet, w wieku 18–72 lat) i 120 zdrowych ochotników (87 mężczyzn i 33 kobiety, w wieku 32–81 lat). Stężenie homocysteiny w osoczu na oznaczono metodą FPI (*Fluorescence Polarization Immunoassay*), stężenie kwasu foliowego i witaminy B12 oznaczono metodą chemiluminescencji.

Wyniki Stężenie homocysteiny było większe w grupie pacjentów niż w grupie kontrolnej (12,07 ± 5,1 *vs.* 10,72 ± ± 2,13 μmol/l, $p < 0,001$, skorygowane względem wieku). Podwyższone stężenie homocysteiny — definiowane jako stężenie powyżej 90 percentyla rozkładu w grupie kontrolnej (≥ 13,52 μmol/l) — zaobserwowano u 24% pacjentów i u 10% osób z grupy kontrolnej. Iloraz szans (OR, *odds ratio*) wystąpienia nadciśnienia tętniczego u osób z podwyższonym stężeniem homocysteiny wyniósł 2,8 (95-procentowy przedział ufności 1,3–6,1, $p < 0,01$). W analizie wieloczynnikowej, po uwzględnieniu innych czynników ryzyka (wiek, płeć, wskaźnik masy ciała, palenie tytoniu, występowanie chorób układu krążenia w rodzinie, hiperlipidemia), podwyższone stężenie homocysteiny pozostało niezależnym czynnikiem ryzyka nadciśnienia tętniczego (OR 6,6, 95-procentowy przedział ufności 2,3–19,1, $p < 0,001$). Iloraz szans wystąpienia nadciśnienia tętniczego przy wzroście stężenia homocysteiny o 5 μmol/l wyniósł 1,7 (95-procentowy przedział ufności 1,1–2,6, $p < 0,001$), a w analizie wieloczynnikowej 3,8 (95-procentowy przedział ufności 1,7–8,2, $p < 0,001$).

Wnioski Podwyższone stężenie homocysteiny jest ważnym czynnikiem ryzyka nadciśnienia tętniczego. Wzrost stężenia homocysteiny o 5 μmol/l może wiązać się z co najmniej 2-krotnym wzrostem ryzyka nadciśnienia tętniczego.

słowa kluczowe: homocysteina, nadciśnienie tętnicze, kwas foliowy, witamina B12

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Introduction

The importance of hyperhomocysteinemia in the pathogenesis of atherosclerosis was recognised in 1969, when McCully [1] reported evidence of atherosclerosis in children with homocysteinuria and elevated plasma homocysteine concentrations. Since then, prospective and retrospective studies, like the Physicians' Health

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Study [2] or the European Concerted Action Project [3], confirmed the association between hyperhomocysteinemia and cardiovascular disease. In many clinical trials subjects with elevated homocysteine levels had increased risk of coronary artery disease [4, 5], stroke [6] and intima-media thickness [7] or peripheral vascular disease (PVD) [8, 9]. The role of homocysteine in atherogenesis remains unclear. Hyperhomocysteinemia may be associated with endothelial-cell injury and dysfunction [10–12], followed by platelet activation and thrombus formation, lipid peroxydation, LDL-oxydation [13–14] and proliferation of vascular smooth-muscle cells [15]. Homocysteine makes a prothrombotic environment in the vessel, by activating factors V and XII [16], and by depressing protein C [17]. Another hypothesis is that homocysteine may be a risk factor for hypertension and accelerate the atherosclerotic process through increasing blood pressure. The animal model shows that hyperhomocysteinemia may be a reason for hypertension [18]. The minipigs fed with a methionine-based diet developed hyperhomocysteinemia after 4 months. They also presented with systolic-diastolic hypertension and extended reactive hyperaemia as well as mega-artery syndrome in hyperpulsatile arteries due to expanded volumetric compliance, curtailed stiffness, strengthened vascular tension and prevalence of the viscous wall component. In their arterial tree hypertrophic endothelial cells covered a thickened subendothelial space. Similarly, in fructose-fed rats, elevated blood pressure was observed with an elevation of homocysteine level [19]. Also in human study with hypertensive patients, homocysteine correlated with aortic stiffness, measured as the carotid-femoral pulse wave velocity [20]. So the aim of this study was to assess the potential association between the prevalence of essential hypertension and total homocysteine concentrations.

Material and methods

Patients and controls

88 consecutive patients (62 men and 26 women, aged 18 to 72 years) with essential hypertension and 120 healthy controls (87 men and 33 women, aged 32–81 years) were studied. Informed consent was obtained from all patients and controls. Questionnaires providing information about all risk factors, such as smoking, hyperlipidemia, diabetes mellitus and family history of premature cardiovascular disease, were completed.

Definitions

The Body Mass Index was calculated using the standard formula. Hypertension was defined as blood pressure ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic) or if patient was taking any antihypertensive medications because of previously diagnosed hypertension.

Hyperlipidemia was defined if the total cholesterol level was > 200 mg% or LDL-cholesterol level was > 130 mg% or if patient was taking a lipid-lowering drug.

Smokers were defined as those currently smoking any tobacco or those who had stopped smoking less than 6 months before study.

Family history of cardiovascular disease (CVD) was considered present if the coronary artery disease or hypertension was documented in first-degree relative before 65 years.

Diabetes mellitus was diagnosed if patient was taking oral hypoglycaemic agents or insulin, or if the fasting serum glucose level was greater than 140 mg%.

Elevated homocysteine level was defined as a level greater than 90th percentile for control subjects (level ≥ 13,52 μmol/L). Plasma folate and vitamin B12 deficiencies were defined as the levels below 10th percentile of the control distribution (≤ 7,4 nmol/L and ≤ 143,48 pmol/L, respectively).

Biochemical Measurements

The blood was drawn in the fasting state. Plasma total homocysteine level, including protein-bound and free homocysteine, was measured using Fluorescence Polarisation Immunoassay (FPIA) on the IMx Analyser, made by Axis Biochemicals.

Plasma folate and plasma vitamin B12 were assayed with chemiluminescency and IMMULITE Automated Analyser made by Diagnostic Products Corporation.

Concentrations of total fasting cholesterol, high-density lipoprotein, triglycerides and glucose were measured using standard laboratory techniques. Low density-lipoprotein cholesterol was calculated by the formula of Friedewald for patients with serum triglyceride concentrations below 354 mg%.

Statistical Analysis

All continuous variables are reported as mean plus or minus one standard deviation. Differences in cardiovascular risk factors between patients and controls were tested with Student's T-test for continuous variables and χ^2–test for comparison of frequencies. A two-sided 5% level of significance was considered significant.

Logistic regression was used to examine the risk for hypertension conferred by elevated homocysteine level and 5 μmol/L homocysteine increment. Pearson's correlation of the vitamins and plasma homo-

Table I. Demographic characteristics and risk factor profiles of patients and controls
Tabela I. Porównanie czynników ryzyka w grupie badanej i kontrolnej

Variable	Cases	Controls	P
No.	88	120	
Mean age (y)	45.93 ± 11.92	47.26 ± 8.69	NS
Male (%)	70.5	72.5	NS
BMI [kg/m^2]	27.5 ± 3,8	25.8 ± 3.7	< 0.01
Obesity (%)	26	12.5	< 0.05
Current smoker (%)	12	41	< 0.05
Hyperlipidemia (%)	67	41	0.001
Family history of CVD (%)	30	17.5	0.05
Cholesterol (mean ± SD) (mg%)	221.27 ± 44.32	211.37 ± 43.35	NS
LDL-cholesterol (mean ± SD) (mg%)	137.6 ± 33.67	127.84 ± 40.16	NS
HDL-cholesterol (mean ± SD) (mg%)	51.33 ± 11.86	54.23 ± 12.64	NS
Triglycerides (mean ± SD) (mg%)	145.44 ± 74.33	144.92 ± 105.66	NS

BMI, body mass index, indeks masy ciała; LDL, low-density lipoprotein, lipoproteina o niskiej gęstości; HDL, high-density lipoprotein, lipoproteina o wysokiej gęstości; CVD, cardiovascular disease, choroba układu sercowo-naczyniowego

cysteine levels was calculated. The comparison of homocysteine and vitamins levels, according to the levels of diastolic blood pressure, was made using analysis of variance (Duncan's multiple range test). The statistical analysis was performed using SAS System 6.12.

Results

Characteristics of the studied group

There were no differences between patients and controls as for age, gender and lipid concentrations. Patients had higher body mass index and more often family history of CVD. In 10% of patients diabetes mellitus was diagnosed, 12% of patients were smokers. The characteristics of the studied group are presented in Table I.

Total plasma homocysteine concentrations

Total plasma homocysteine concentrations were higher in patients than in controls (12,07 ± 5,1 *vs.* 10,72 ± 2,13 μmol/L, p< 0,05). Male patients had also significantly higher homocysteine levels than male controls (12,47 ± 5,24 *vs.* 10,81 ± 2,07 μmol/L, p < 0,05). This difference was not observed between female patients and controls (11,12 ± 4,54 *vs.* 10,47 ± ± 2,31 μmol/L, p = ns). The subjects with obesity had higher homocysteine than subjects with normal weight (12,86 ± 4,46 *vs.* 11,18 ± 3,58 μmol/L, p < 0,05). The mean levels of homocysteine in particular subgroups of patients are presented in Table II.

Homocysteine slightly correlated with BMI in all subjects (r = 0,15, p < 0,05), and did not correlate with age and vitamin B12 level. In all subjects an inverse correlation between homocysteine and folic acid was noted (r = –0,22, p < 0,01). This correlation was much stronger in hypertensive patients (r = –0,34, p < 0,01) than in the controls (r = –0,27, p < 0,05).

Elevated homocysteine level was seen in 24% of patients, compared with 10% of the controls (p < 0,01).

The odds ratio (OR) for hypertension in subjects with elevated homocysteine level was 2,8 (95% CI 1,3–6,1, p < 0,01). In male subjects this OR was even higher — 3,0 (95% CI 1,2–7,4, p < 0,05).

After adjustment for other risk factors (age, BMI, smoking, family history of CVD, hyperlipidemia), elevated homocysteine level remained an independent risk factor for hypertension — the OR in all the studied group was 6,6 (95% CI 2,3–19,1, p < 0,001) and in the male subgroup 8,4 (95% CI 2,4–28,9, p < 0,001).

When homocysteine was considered as a continuous variable, the odds ratio for hypertension of 5 μmol/L increment in plasma homocysteine level was 1,7 (95% CI 1,1–2,6, p < 0,001) in all subjects and 1,9 (95% CI 1,1–3,2, p < 0,05) in males. In multivariate analysis the OR for hypertension was 3,8 (95% CI 1,7–8,2, p < 0,001) in all the studied group and 7,4 (95% CI 2,6–21,3, p < 0,001) in the male subgroup.

Vitamin concentrations in patient population

There were no significant differences in vitamin levels between patients and controls. Mean plasma folate level in patients was 17,16 ± 7,87 nmol/L com-

Table II. Plasma total homocysteine, folate and vitamin B12 levels in particular subgroups of subjects

Tabela II. Stężenia homocysteiny, kwasu foliowego i witaminy B12 w poszczególnych podgrupach badanych osób

	Mean tHcy (μmol/L)	SD	Mean folic acid (nmol/L)	SD	Mean B12 (pmol/L)	SD
Men	11.50	3.80	15.33	9.87	251.12	118.36
Women	10.76	3.45	20.05	13.22	251.26	111.83
Obese patients	12.86*	4.46	15.64	8.48	248.72	133.58
Non-obese patients	11.18	3.58	16.38	11.41	253.77	115.23
Smokers	11.54	3.77	12.54**	5.48	245.06	134.09
Non-smokers	11.47	3.75	17.61	12.22	254.63	112.48
With hyperlipidemia	11.79	3.91	15.44	6.83	240.11	106.89
Without hyperlipidemia	11.05	2.83	16.33	12.63	267.26	131.23
With family history of CVD	11.58	2.79	18.76	14.13	248.91	141.14
Without family history of CVD	11.25	3.37	15.64	10.47	258.31	113.84

*p < 0.05, **p < 0.01, in other p = NS. Thcy, total homocysteine, całkowite stężenie homocysteiny; CVD, cardiovascular disease, choroba układu sercowo-naczyniowego

pared with 15,86 ± 12,39 nmol/L in control group. Folate deficiency was found in 5,4% of patients and 10,6% of controls. All males had non-significantly lower folate level than females (15,33 ± 9,87 *vs*. 20,05 ± ± 13,22 nmol/L). This difference was observed in smoking subjects, who had a much lower level of folate than non-smokers (12,54 ± 5,48 compared with 17,61 ± 12,22 nmol/L). Patients with elevated homocysteine level had much lower folate concentrations than patients with normal homocysteine concentration (12,42 ± 6,12 *vs.* 17,27 ± 11,47, p < 0,01).

Plasma folate level did not correlate with age or vitamin B12. The correlation between folate and BMI was significant only in the control group (r = –0,29, p < 0,01), but in all studied subjects this correlation was weak (r = –0,15, p = 0,07).

Vitamin B12 in patients and controls were 259,78 ± ± 127,13 and 245,7 ± 109,8 pmol/L, respectively. Vitamin B12 deficiency was seen in 7,3% of patients and 10,3% of controls. Plasma vitamin B12 concentrations did not correlate with age or BMI, either in hypertensive or healthy subjects. The concentrations of vitamins in particular subgroups of subjects are presented in Table II.

Analysis of correlation of homocysteine and vitamins with blood and pulse pressure

Homocysteine tended to be correlated with systolic (SBP) and diastolic blood pressure (DBP), although most patients had been pharmacologically treated. Although the correlation with SBP (r = 0,21, p = 0,07) and with DBP (r = 0,2, p = 0,09) was not significant, homocysteine concentration was related to DBP level. Patients with higher DBP had much higher homocysteine levels and much lower folic acid concentrations, as presented in Table III. Folate and vitamin B12 strongly correlated with systolic and diastolic blood pressure, as is shown in Table IV.

Homocysteine and folate were not associated with pulse pressure, in contrast to vitamin B12, which correlated significantly (r = –0,29, p < 0,05).

Table III. Mean homocysteine and vitamin levels according to the diastolic blood pressure

Tabela III. Stężenia homocysteiny i witamin w zależności od rozkurczowego ciśnienia tętniczego w grupie pacjentów

Diastolic blood pressure [mm Hg]	Mean tHcy (μmol/L)	Mean folic acid (nmol/L)	Mean B12 (pmol/L)
≤ 90	11.93	19.81	292.62
91–105	12.29	15.58	238.69
> 105	16.77	11.63	215.19
P	0.06	< 0.05	NS

Table IV. Correlations (r-Pearson) between homocysteine, vitamins and blood pressure. SBP, systolic blood pressure; DBP, diastolic blood pressure

Tabela IV. Korelacje pomiędzy stężeniem homocysteiny, witamin a ciśnieniem tętniczym. SBP, skurczowe ciśnienie tętnicze; DBP, rozkurczowe ciśnienie tętnicze

	SBP	DBP
Homocysteine	0.21	0.2
Folic acid	–0.31*	–0.31*
Vitamin B12	–0.48**	–0.33*

*p < 0.05, **p < 0.001

Discussion

The definition of an elevated homocysteine level is still being discussed. In most studies it is determined as the 80th, 90th or 95th percentile of the homocysteine distribution in control population. In this study, a level over the 90th percentile was chosen arbitrarily. Then we observed that subjects with an elevated homocysteine level had a more than twofold increase of risk for hypertension, compared with those with values in the bottom 90% of the controls (OR 2,88, 95% CI 1,1–7,8).The OR in men was even higher — 3,7. An elevated homocysteine level remained an independent risk factor after adjustment for other risk factors. These odds ratios were not significant in women, most probably because of the small number of females included in the trial. Homocysteine tended to be correlated with systolic and diastolic blood pressure, despite the majority of patients having taken antihypertensive drugs.

Nevertheless, the results of studies assessing the relationship between blood pressure or prevalence of hypertension and hyperhomocysteinemia are equivocal both in cohort studies with healthy subjects and in case-control studies.

A significant positive association between homocysteine and blood pressure was observed in the Hordaland Homocysteine Study [21]. In this study, including over 16 000 healthy subjects, homocysteine correlated with diastolic blood pressure (DBP), especially in middle-aged men. Male subjects with DBP over 100 mm Hg had almost 1 μmol/L higher homocysteine level than those with DBP below 70 mm Hg. The relationship was graded and significant after adjustment for other risk factors like age, sex, smoking status, physical activity and lipids levels. However, homocysteine was determined in non-fasting state.

Also Bates et al. [22], who determined homocysteine in almost one thousand UK people aged over 65 years, found the association between homocysteine and DBP.

A positive correlation between homocysteine and blood pressure was noted in non-insulin-dependent diabetes mellitus (NIDDM) patients, both normo- and hypertensive. Normotensive patients with elevated homocysteine levels had significantly higher diastolic blood pressure and mean arterial pressure. In that study, Fiorina et al. [23] extrapolate the results and conclude that a twofold increase in homocysteine level (from 6 to 12 μmol/L) is associated with a 4,5 mm Hg rise in DBP values and this means three more strokes per ten patients. When homocysteine increased threefold, they observed an increase of 8 mm Hg in DBP values. In the study performed by Stabler et al. [24], including 452 subjects with NIDDM and mean diastolic blood pressure 80 mm Hg or higher, total homocysteine level correlated with systolic blood pressure and duration of hypertension.

Verhoef et al. [25] investigated almost six hundred subjects participating in the Physicians' Health Study: 109 subjects who developed ischaemic stroke and 427 controls. Although she did not show the relationship between homocysteine and stroke, she found that hypertensive controls had a much higher homocysteine level than normotensive ones (11,8 compared with 10,3 μmol/L). This difference was not observed in the patients' group.

The results of case-control studies including hypertensive patients are very interesting. In the study performed by Sutton-Tyrrell et al. [26], including 179 patients aged over 60 years with isolated systolic hypertension and 171 healthy subjects, homocysteine remained an independent risk factor for systolic hypertension. Each 10 μmol/L increment in homocysteine level increased twofold the risk of systolic hypertension. Moreover, when all subjects were classified according to JNC V criteria, homocysteine values increased with each stage.

Similarly, Chambers et al. [27] investigated homocysteine in 299 hypertensive males and 715 age-matched normotensive controls. Hypertensive subjects had a higher homocysteine level both in the fasting state and after methionine load. The relationship between elevated homocysteine level and hypertension was graded and independent of body-mass index, waist-hip ratio, glucose, triglicerydes and HDL-cholesterol.

Also Sheu and Mendis observed an association between homocysteine level and prevalence of hypertension in their Chinese and Sri Lankan studies, including similar groups of subjects. Sheu [28] investigated 90 Chinese hypertensive patients and they had a higher homocysteine level than 86 age- and

sex-matched controls (8,1 *vs.* 6,8 μmol/L, $p < 0,05$). In the Sri Lanka study [29], subjects with homocysteine concentration above 18 μmol/L had an almost threefold increase of risk for hypertension.

Malinow et al. found [30] that hypertension was more common among patients with peripheral vascular disease (PVD) and high plasma homocysteine levels than in subjects with PVD but with normal homocysteine levels. In contrast, this author with other colleagues [31] showed that high levels of homocysteine were indeed related to cerebral infarcts but were unrelated to the presence of elevated blood pressure.

The relationship between homocysteine and hypertension was observed also in studies with black Americans. In one study [32], a positive correlation between homocysteine and systolic and diastolic blood pressure was found in female subjects ($r = 0,54$, $r = 0,69$, respectively).

In another case-control study, Sharabi and colleagues [33] studied the potential relationship between homocysteine level and history of cardiac or cerebral events in 100 patients with hypertension. Although homocysteine did not appear to be the predictor of atherothrombotic events, its mean concentration in all hypertensive patients was much higher than determined in the same laboratory in 250 healthy subjects.

Alternatively, it is possible that there is no association between hypertension and plasma homocysteine and they are unrelated risk factors with no synergic or additive effects.

Several studies did not confirm the hypothesis that homocysteine promotes atherosclerosis through elevated blood pressure. No correlation between homocysteine and blood pressure was found in almost six hundred healthy French Canadians and 150 subjects with coronary artery disease [34].

Whincup et al. [35] determined homocysteine concentrations in almost four hundred middle-aged men after myocardial infarction and 454 age-matched controls but the association between systolic or diastolic blood pressure and homocysteine was not observed. Similarly, Brattstrom et al. [36] did not find any relationship between homocysteine and hypertension in patients with stroke. Furthermore, hypertensive stroke survivors had an even lower homocysteine level than those without hypertension.

Also methylenetetrahydrofolate reductase gene polymorphism and its homozygous Val/Val genotype, which may result in an elevated homocysteine level, does not seem to be a risk factor for hypertension. The study of Nakata [37] on a Japanese population gave amazing results. The frequency of Val/Val genotype was significantly lower in hypertensive patients than in controls. Subjects with the Ala allele had an almost twofold increased risk for hypertension, suggesting that Val allele may be associated with lower blood pressure.

In contrast, Wilken et al. [38] observed weak correlation between Val allele and hypertension in male patients. Val/val homozygotes were more prevalent in patients with hypertension (13,3%) than in those without (9,8%). The Val allele frequency was also significantly higher among hypertensive patients than normotensive ones. Wilken in a log-linear analysis observed a significant three-way interaction among sex, hypertension and MTHFR genotypes. The association between MTHFR and hypertension was especially significant in male patients.

In conclusion, the results of published studies are still not definitive. Our study suggests that an elevated homocysteine level may cause hypertension but large cohort prospective studies are needed to explain whether an elevated homocysteine level is a risk factor or may be a result of hypertension.

Summary

Background The aim of the study was to assess the significance of association between hypertension (Ht) and circulating homocysteine concentrations.

Material and methods 88 consecutive hypertensive patients (62 men and 26 women, aged 18 to 72 years) and 120 healthy controls (87 men and 33 women, aged 32–81 years) were investigated. Homocysteine was assayed using Fluorescence Polarisation Immunoassay on the IMx Analyser made by Axis Biochemicals. Plasma folate and plasma vitamin B12 were assayed with chemiluminescency and IMMULITE Automated Analyser made by the Diagnostic Products Corporation.

Results Homocysteine concentrations were higher in patients than in controls (12,07 $\pm$ 5,1 *vs.* 10,72 $\pm$ $\pm$ 2,13 μmol/L, $p < 0,001$, adjusted for age). Elevated homocysteine level -defined as a level above the 90th percentile of the control distribution ($\geq$ 13,52 μmol/L) — was seen in 24% of the patients compared with 10% of the control group ($p < 0,05$).

The odds ratio (OR) for Ht in persons with an elevated homocysteine level was 2,8 (95% CI 1,3–6,1, $p < 0,01$). After adjustment for conventional risk factors (age, gender, body mass index, smoking, family history of cardiovascular disease, hyperlipidemia), an elevated homocysteine level remained an independent risk factor for Ht (OR 6,6, 95% CI 2,3–19,1,

$p < 0,001$). The OR for Ht of 5 μmol/L increment in homocysteine level was 1,7 (95% CI 1,1–2,6, $p < 0,001$), and in multivariate analysis OR was 3,8 (95% CI 1,7–8,2, $p < 0,001$).

Conclusion An elevated plasma homocysteine level is a strong risk factor for hypertension. A 5 μmol/L increment in total homocysteine level may be associated with at least a twofold increase of risk for hypertension.

key words: homocysteine, hypertension, folic acid, vitamin B12

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References

1. McCully K.S. Vascular pathology of homocysteinemia: implication for pathogenesis of arteriosclerosis. Am. J. Pathol. 1969; 56: 111–128.
2. Stampfer M.J., Malinow M.R., Willett W.C., Newcomer L.M., Upson B., Ullmann D. et al. A prospective study of plasma homocyst(e)ine and risk of myocardial infarction in US Physicians. JAMA 1992; 268: 877–881.
3. Graham I.M., Daly L.E., Refsum H., Robinson K., Brattstrom L., Ueland P.M. et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. JAMA 1997; 277: 1775–1781.
4. Boushey C.J., Beresford S.A., Omenn G.S., Motulsky A.G. A Quantitative Assessment of Plasma homocysteine as a Risk Factor for Vascular Disease. JAMA 1995; 274: 1048–1057.
5. Robinson K., Mayer E.L., Miller D.P. Hyperhomocysteinemia and low pyridoxal phosphate: common and independent reversible risk factors for coronary artery disease. Circulation 1995; 92: 2825–2830.
6. Perry I.J., Refsum H., Moris R.W., Ebrahim S.B., Ueland P.M., Shaper A.G. Prospective study of serum total homocysteine concentration and risk of stroke in middle-aged British men. Lancet 1995; 346: 1395–1398.
7. Malinow M.R., Nieto F.J., Szklo M., Chambless L.E., Bond G. Carotid intima-media wall thickening and plasma homocysteine in asymptomatic adults — The Atherosclerosis Risk in Communities Study. Circulation 1993; 87: 1107–1113.
8. Cheng S.W., Ting A.C., Wong J. Fasting total plasma homocysteine and atherosclerotic peripheral vascular disease. Ann. Vasc. Surg. 1997; 11: 217–223.
9. Aronow W.S., Ahn C. Association between plasma homocysteine and peripheral vascular disease in older persons. Coron. Artery Dis. 1998; 9: 49–50.
10. De Groot P.G., Willems C., Boers G.H., Gonsalves M.D., van Aken W.G., van Mourik J.A. Endothelial cell dysfunction in homocystinuria. Eur. J. Clin. Invest. 1983; 13: 405–410.
11. Starkebaum G., Harlan J.M. Endothelial cell injury due to copper-catalyzed hydrogen peroxide generation from homocysteine. J. Clin. Invest. 1986; 77: 1370–1376.
12. Wall R.T., Harlan J.M., Harker L.A., Striker G.E. Homocysteine induced endothelial cell injury in vitro: a model for the study of vascular injury. Throm. Res. 1980; 18: 113–121.
13. Heinecke J.W. Superoxide-mediated oxydation of low density liporotein by thiols. In: Cerrutti P.A., Fridovich I., McCord J.M. (eds) Oxy-radicals in molecular biology and pathology. New York: Allan R. Liss; 1988. 443–457.
14. Loscalzo J. The oxidant stress of hyperhomocyst(e)inemia. J. Clin. Invest. 1996; 98: 5–7.
15. Welch G.N., Upchurch G.R. Jr, Farivar R.S., Pigazzi A., Vu K., Brecher P. et al. Homocysteine induced nitric oxide production in vascular smooth muscle cells by NF-κB dependent transcriptional activation of Nos2. Proc. Assoc. Am. Phys. 1998; 110: 22–31.
16. Rodgers G.M., Kane W.H. Activation of endogenous factor V by a homocysteine-induced vascular endothelial cell activator. J. Clin. Invest. 1986; 77: 1909–1916.
17. Rodgers G.M., Conn M.T. Homocysteine, an atherogenic stimulus, reduces protein C activation by arterial and venous endothelial cells. Blood 1990; 75: 895–901.
18. Rolland P.H., Friggi A., Barlatier A., Piquet P., Latrille V., Faye M.M. et al. Hyperhomocysteinemia — induced vascular damage in the minipig. Circulation 1995; 92: 1161–1174.
19. Erlich Y., Doolman R., Sela B.A. Hyperhomocysteinemia in the fructose-induced hypertensive-hyperinsulinemic rat. J. Hypertens. 1997; 15 (suppl. 4): 31.
20. Bortolotto L.A., Safar M.E., Billaud E., Lacroix C., Asmar R., London G.M. et al. Plasma homocysteine, aortic stiffness and renal function in hypertensive patients. Hypertension 1999; 34 (4, Pt 2): 837–842.
21. Nygard O.,Vollset S.E., Refsum H., Stensvold I., Tverdal A., Nordrehaug J.E. et al. Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. JAMA 1995; 274: 1526–1533.
22. Bates C.J., Mansoor M.A., van der Pols J., Cole T.J., Finch S. Plasma total homocysteine in a representative sample of 972 British men and women aged 65 and over. Eur. J. Clin. Nutr. 1997; 51: 691–697.
23. Fiorina P., Lanfredini M., Montanari A., Peca M.G., Veronelli A., Mello A. et al. Plasma homocysteine and folate are related to arterial blood pressure in type II diabetes mellitus. Am. J. Hypertens. 1998; 11: 1100–1107.
24. Stabler S.P., Estacio R., Jeffers B.W., Cohen J.A., Allen R.H., Schrier R.W. Total homocysteine is associated with nephropathy in non-insulin-dependent diabetes mellitus. Metabolism: Clinical & Experimental 1999; 48: 1096–1101.
25. Verhoef P., Hennekens C.H., Malinow M.R., Kok F.J., Willet W.C., Stampfer M.J. A prospective study of plasma homocysteine and risk of ischemic stroke. Stroke 1994; 25: 1924–1930.
26. Sutton-Tyrrell K., Bostom A., Selhub J., Zeigler-Johnson Ch. High homocysteine levels are independently related to isolated systolic hypertension in older adults. Circulation 1997; 96: 1745–1749.
27. Chambers J., Obeid O.A., Thomson A., Kooner J.S. Hyperhomocysteinemia is a novel risk factor for hypertension. Eur. Heart J. 1999; 20 (suppl.): 660.
28. Sheu W.H., Lee W.J., Chen Y.T. Plasma homocysteine concentrations and insulin activity in hypertensive subjects. Am. J. Hypertens. 2000; 13: 14–20.
29. Mendis S., Athauda S.B.P., Naser M., Takahashi K. Association between hyperhomocysteinemia and hypertension in Sri Lankans. J. Int. Med. Res. 1999; 27: 38–44.
30. Malinow M.R., Kang S.S., Taylor L.M., Wong P.W.K., Coull B., Inahara T. et al. Prevalence of hyperhomocysteinemia in patients with peripheral arterial occlusive disease. Circulation 1989; 79: 1180–1188.
31. Malinow M.R., Levenson J., Giral P., Nieto F.J., Ravazian M., Segond P. et al. Role of blood pressure, uric acid and hemor-

heological parameters on plasma homocysteine concentration. Atherosclerosis 1995; 114: 175–183.
32. Sherif K., Summer A.E., Majors A., Kushner H., Pyeritz R., Falkner B. Plasma homocysteine and cardiovascular risk factors in African-American women. Am. J. Hypertens. 1998; 11: 25A–26A.
33. Sharabi Y., Doolman R., Rosenthal T., Grossman E., Rachima-Maoz C., Nussinovitch N. et al. Homocysteine levels in hypertensive patients with a history of cardiac or cerebral atherothrombotic events. Am. J. Hypertens. 1999; 12: 766–771.
34. Dalery K., Lussier-Cacan S., Selhub J., Davignon J., Latour Y., Genest J. Homocysteine and coronary artery disease in French Canadian subjects: relation with vitamins B12, B6, pirydoxal fosfate and folate. Am. J. Cardiol. 1995; 75: 1107–1111.
35. Whincup P.H., Refsum H., Perry I.J., Morris R., Walker M., Lennon L. et al. Serum total homocysteine and coronary heart disease: prospective study in middle-aged men.
36. Brattstrom L., Lindgren A., Israelsson B., Malinow M.R., Norrving B., Upson B. et al. Hyperhomocysteinemia in stroke: prevalence, cause and relationships to type of stroke and stroke risk factors. Eur. J. Clin. Invest. 1992; 22: 214–221.
37. Nakata Y., Katsuya T., Takami S., Sato N., Fu Y., Ishikawa K. et al. Methylenetetrahydrofolate reductase gene polymorphism - relation to blood pressure and cerebrovascular disease. Am. J. Hypertens. 1998; 11: 1019–1023.
38. Wilken D.E.L., Vang X.L., Sim A.S., McCredie R.M. Distribution in healthy and coronary populations of the methylenetetrahydrofolate reductase (MTHFR) C677T mutation. Arterioscler. Thromb. Vasc. Biol. 1996; 16: 878–882.