HYPERHOMOCYSTEINEMIA AND LIPIDS ON THE ONSET ESSENTIAL ARTERIAL HYPERTENSION AND CORONARY DISEASE

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Abstract

Summary: Cardiovascular diseases(CVD) still remain as main factor of invalidity, morbidity and mortality in developed and developing countries. Despite known factors (genetic predisposition, gender, age, arterial hypertension, smoking, obesity, diabetes, dyslipidemia, C reactive protein) recently in the ethiology of CVD raised total Homocysteine (Hcyt) is considered also. Corelation between raised Hcyt and CVD was dissevered 25 years ago by Carson and Neil, who saw a defect of Hcyt metabolism in a patient with rasied Hcyt. In this cases is verified lack several enzymes which enable normal metabolism of Hcyt. Therefore as result of these metabolic disorders of Hcyt, clinical picture of raised Hcyt and its accumulation in blood-hyperhomocysteinema appears. Several studies have verified taht 15-30% of cases with CVD are result of hyperhomocysteinemia (1). Aim of this paper: Aim of this paper is to examine concentrations of Hcyt and lipid profile in patients with essential arterial hypertension and positive personal history for CVD, comparing them with the control group composed from healthy individuals. Our study aimed to verify the role of Homocysteine as new indipendent risk factor on the onset of early atherosclerosis (artherosclerosis prematura) and atheromateous processes in coronary arteries in patients with CVD and the impact of raised Hcy in evaluating arterial hypertension. This paper aimed to propose medical measures to corect and treat hyperhomocysteineia, which obviously would decrease the consequences of Hcyt on CVD and arterial hypertension.**Matherial and methods**: As working matherial was used blood from 360 patients with positieve personal anamnesis for CVD and essential hypertension, from whom 200 were males with mean age of prej=62.50 8.40 and 160 females with mean age =59.80 15.60. Control group was composed from healthy 260 individuals, 160 males and 100 females with identical mean age of =58.70±15.60. Obtained results represent mean values obtaiened once in every three months in 3 year period. 5ccm serum with some drops of heparin was sent in Clinical Laboratory of University Clinic of Skopje.**Results**: In the table it is shown significant difference for analysed parameters in patients with CVD for TG(2.90 ± 0.30),HDL-ch(0.90 ± 0.26) , LDL-ch (4.20 ± 0.80) , and Hcyt (24.50 ± 5.20 µmol/L) with p<0.0001 exept for ChT where no significance between two groups was found (in patients with CVD ChT= 5.20 ± 1.20 mmol/l while in control group=4.90±1.60 mmol/l with p=0.7400). Concentrations of homocysteine and lipids in patietns with CVD compared to the control group showed satisticaly significant difference with p=0.0001, expected results and verified in many other multicentric studies. Also in table 4 obtained results obtained from the group with essential hypertension (HTA ess) for all examined parameters compared with the control group showed significant difference especially for homocysteine =18.20 ± 6.40 (which was object of our study) with p=0.0001, but levels of Hcyt in this group were lower than Hcyt in patients with CVD=24.50 ± 5.20 µmol/. These facts show that raised Hcyt have more immpact on the onset of CVD and less impact on the onset of arterial hypertension.When Hcy levels are raisd in blood, the activity of cystathionine—synthethasae enzyme is raised. It is believed that this enzyme plays vital role on the metabolism of Hcyt. Recent years a lot of studies have been made on the effect of hyperhomocysteinemia and its impact on the onset of coronary and cerebral atherosclerosis and all have verified that hyperhomocysteinemia is a significant parameter for the onset of early artherosclerosis of coronary and cerebral arteries (5). When hyperhomocysteinemia is corelated with lipid disorder (dyslipidemia, hypertygliceridemia, hypercholesterolemia) effects on cardiovascular system and CVD prevalence is higher. For this reason we decided in our study to include lipid panel also in patients with CVD and HTA ess. Conclusion: In the end we can conlude that also in our study high levels of Hcyt in patients with CVD and HTA ess were found, which are in line with many multicentric studies on the role of Hcyt as new indipendent risk factor for early coronary arteriosclerosis and its moderate effect on the onset of HTA ess.In above mentioned cases it is recommended substituive therapy with folic acid, pyridoxine, cyanocobalamine, tocoferol and other antioxidants which is found that have effect on prevention of premature artherosclerosis in patients with CVD and raised Hcyt: PTCA, CARB, acute myocardial infarction, angina pectoris, Stenting and prevention of stroke.

Term Index: Total Homocysteine (Hcyt), lipid profile, Cardiovascular diseases (CVD), essential arterial hypertension (HTAess).

1 Introduction

CVD and their high mortality still remain as big problem and with high prevalence in general population. High concentrations of Hcyt in serum are considered as risk factor for CVD and can be associated with hypertension. Although between hyperhomocysteinemia and CVD is found a significant corelation, still the role of homocysteine on cardiovascular manifestations remanis unclear. It is verified that concentrations of homocysteine increases with somoking, aging and some diets with low folates, cyanocobalamin and pyridoxine. Many studies have verified a signifficant relationship between raised Hcyt and arterial hypertension and lipid distorders, compared with normotensive individuals. Lowering Hcyt concentrations can have some benefits in decreasing the risk of CVD in old ageCorelation between high levels of homocysteine and coronary artery diseases is discovered 25 years ago, when for first time was verified that patients with hyperhomocysteinuria are potential candidates for developing early artherosclerosis in puberty and before 20 years of age. In these cases is verified the lack of some enzymes responsible for metabolisation of Hcyt, as result hyperhomocysteinemia occurs. Increased C reactive proteine, positive history for any CVD disease, hypercreatinemia, hyperuricemia, hyperuremia, von Willebrand factor, old age, smoking, genetical predisposition and adiposity are immportant factors for developing CVD and HTAess.

Homocysteine was discovered in 1932, and chemical analysis showed similarity with cysteine. For this discovery Vincent du Vigneaud in 1955 was awarded Nobel Price in Chemistry for his work on sulfur components , especially for synthesis of polypeptide hormone(3).

Homocysteine is sulfudric amynocide as intermediary product of normal biosynthesis of methionine and cysteine (4).

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Hcy in serum is found in three forms: 1% is in free form, 70-80% as residual disulfides and 20-30% in combined form with other thilos. (5).Homocysteine is synthesized from essential aminoacid methionine. Cystathionine-β-syntheta-sae is an enzyme, while pyridoxine (B6) is essential cofactor which converts homocysteine in cysteine. Hyperhomocysteinemia is a condition with raised homocysteine levels in blood above 15 µmol / L (6,7,8). High levels of homocysteine are recorded in patients after stroke as result of neuronal damage and overstimulation of NMDA receptors (N-methyl-D-aspartate receptor). Because hypothalamus controlls cardiac function by sympathetic system, in patients with stroke cardiac function is impaired also. Homocysteine is knows as risk factor for CVD for its negative effects on cardiovascular endothelium. CVD have high prevalence and still remain as main reason for high mortality and morbidity in world. Ethilology of CVD is multifactorial and mos often they are result of narrowed or occluded coronary arteries (9,10). Homocysteine as risk factor for CVD, stroke, thrombotic processes, vascular hypercoagulability and atherosclerotic processes is known sinci early 1990. Several studies have verified a high positive corelation between coronary diseases, chronic renal injury and hyperhomocysteinemia (11). Scientists thought on homocysteine as risk factor on developing CVD still are controversial. Some scientists believe high concentrations of Hcyt are not a risk factor for CVD (12), while lot of research results show high positive corelation between raised Hcyt and CVD diseases. Genetic mutations of C and S homozygote can cause severe hyperhomocysteinemia where Hcy concentrations are 40 times higher than normal. This disease have incidence of 1:100.000. Another rare genetic cause of hyperhomocysteinemia is because od homozygote mutations of MTHFR-methylene tetra hydrofolate reductasae. These individuals with MTHFR defects are exposed to early CVD. Homocysteine is indipendent risk factor for early arthrosclerosis. Atherosclerosis is progressive inflamatory injury or arterial intimal layer, with increased permeability, lipidic deposition and calcification of intima. Corelation between hyperhomocysteinemia and atherosclerosis for first time was identified by McCully in 1969. Atherosclerosis is common pathological process which leads to CVD (myocardial infarction, atheromatous processes pf carotid arteries, heart failure, stroke) (13).

Some of mechanisms of these effects are: endothelial disfunction, oxidative injury, increased collagen production, damage of arterial wall and increased C reactive proteine in vitro and in vivo (14).

One study has shown that in patients with CVD Hcy levels during fasting are lower, compared with the same patients after fasting, with a statistical significance of $p<0.00001$ (15).Many in vitro studies have verified that homocysteine

causes dilataion of blood vessels and injury of smooth muscles and plays role in increased avcitivity of HMGCoA reductase which in turn causes increased collagen production and early manifestation of atheromatous processes on coronary and cerebral arteries. In patients with hyperhomocysteinem changes in intima and media of carotid arteries are confirmed (16). Role of homocysteine on endothelial malfunction is believed to be intermediated by mechanisms: oxidative stres, lipid peroxidation and NF-kb factor, inflamation and and inhibition ENOSI-endothelial nitrous oxide synthet-asae. Possible mechanism of hyperhomo-cysteinemia on stiffnes of aorta still remain unknown. But there are verified facts that hyperhomocysteinemia plays potential role on arterial wall remodeling which causes injury of blood vessels, venous thormbosis and atherosclerotic processes. Hyperhomocysteinemia plays vital role on adhesion of platelets on endothelial cells and it has role on icreasing levels of prothrombic factors such b-thromboglobuline, plasminogen activation and VII factor of coagulation which causes thrombous formation. It is verified that hyperho-mocysteinemia favors LDLox effects and onset of atherosclerotic processes. Many studies have concluded that 15-30% of cases with CVD are result of high concentrations of homocysteine in blood (11). In these processes many mecha-nisms are believed to be involved: genetic predisposition, folate deficiency, pyridoxine and cyanocobalamin. Corelation between Hcyt metabolism and atherosclerotic changes of coronary arterirs for first time were described by Carson and Neill which in the blood of one patient found deffect on the metabolism of Hcy and high concentration in blood. Hcy metabolism proceeds in three pathways: a) by converting Hcyt in Cysthation and cystine with the help pf pyridoxine as cofactor b) by betaine which is limited and c) by converting Hcyt in methionine by tethrafolic acid and cyanocobalamin (17). When high concentrations of Hcyt in blood appear, activity of Cystathioine-Beta-synthetassae enzyme is increased and plays vital role in regulating the metabolism of Hcyt and its concentration in blood and urine. Recent years studies have been made on the role of raisd Hcyt and onset of artherosclerosis in patients with CVD and hypertension, and all have confirmed that hyper-homocysteinemia is important indicator for the onset of early artherosclerosis in coronary and cerebral arteries (18). Many authors propose that medical tretment of homocysteinemia should begin even when homocysteine levels in blood are >9 µmol/L. In vitro experiments in animals have verified that raised Hcyt damages the vascular endothelium and as result atheromatous processes in coronary arteries occur (19) with early manifestation of CVD. Many studies have verified that by lowering high concentrtions of Hcyt results in decrease of atherosclerotic manife-stations of coronary arteries.

Atherosclerotic effect of hyperhomocysteinemia is developed in three mechanisms: a) Hcyt with its toxic effect directly damages intima and media of artery wall; b) by oxidating low density lipoproteins (LDL) and c)by interfering with factors of coagualtion. It is verified that every increase of Hcyt for 10% increases the risk for atherosclerosis 10% also (20). Supplementing organism with 1-2mg folic acid, 10mg pyridoxine and 400 µg cyanocobalamine can normalise high levels of homocysteine (21,22,23). In literature three forms of homocysteine disorders are known:

a) mild form: 16-30 µmol/L;
b) moderate form: 31-100 µmol/L
c) severe form: >100 µmol/L

2 Matherial and Method

As working matherial was used blood taken from patients veins and control group at 8am in room temperature of 19-24 C, in lying position (to avoid all anomalies and possible variations of 9-12% if the blood qould be taken in sitting or standing position) after 12 hour hunger. Homocyesteine and lipid profile were analysed in 360 patients with anamnesis for CVD and HTA ess, from whom 200 where males with mean age of =62.50 8.40 while 160 were females with mean age of =59.80 15.60. Control group was composed from 260 individuals, from whom 160 were males and 100 females with identical mean age of =58.70±15.20 . Obtained results represent mean values obtaiened once in every three months in 3 year period. 5ccm serum with some drops of heparin was sent in Clinical Laboratory of University Clinic of Skopje.

Table 1: Number of patients and control group by mean age and gender

Total pts N^{O}=360	The average age ± SD	Control group N^{O}=260 pts, ± SD
M=N^{U}-200	62.50 ± 8.40	59.80 ± 15.60

Table 1: Number of patients and control group by mean age and gender

F=N^{O}-160	59.80 ± 19.60	59.80 ± 15.60

Table 2: Tabelary presentation of patients by CVD and HTAess

With a family history for CVD	**160 (42.8 %)**
Arterial hypertension (HTA)	**120 (38.60 %)**
APNS	**40 (9.50 %)**
St. Post Infarctum Myocardi	**40 (9.50 %)**
Smoker	**290(62.50 %)**
Control group N^{O}== 2 6 0 (1 0 0 %)	**The average age ± SD 58.70±15.20**

Concentrations of Hcyt were determined according to Miller's method of American Immuno-fluorescence with Immulite DPC machine, and normal ranges are =5-13 µmol/L, while lipid profile was determined by standard routinely methods

Statistical analysis of the examined material

Statistical basic methods that were used are the arithmetic mean value and standard devijacioni X ± SD. Comparative statistics and LPL lipid parameters betwe-en the two groups was analyzed by test called STUDENTOV and for examples of dependent or independent and non-para-metric tests were used the tests: Mann-Whitney and Wilcoxon's test. Statistically significant The differences between the Group of patients and control group obta-ined the values of lipid parameters and test LPL analyzed the so-called ,, Anonova Two-Factor "with the amounts of domestic statistics for p <5%, Namely p <statistical averages and proportional / x, p /) were tested with accuracy higher than 95%, or rather, for Mr. > SEM 1.78.

0.0005.Dependence between parameters that are examined is calculated with linear regression formula (y = Bx + A) it is also calculated the coefficient of correlation ,, r "with statistical accuracy for ,, p 'of less than 1% Namely p <0.0001. And the frequency distribution was tested with test c ^{2} The amount of change (z) between the mean values of parameters analyzed / arithmetic averages and proportional / x, p /) were tested with accuracy higher than 95%, or rather, for Mr.> SEM 1.78.The results of the lipid profile and Hcys presented in the form of graphicones,

The results of the lipid profile and Hcy are presented in the form of graph-cones, table and in the form of

processed diagrams made with standard statistical program.

3 Results

Table 3: Obtained results from patients with CVD and control group for Hcyt and lipid profile

	N°	ChT mmol/l	TG mmol/l	HDL-ch mmol/l	LDL-ch mmol/l	tHcy µmol/L
Patients with CVD, St.post MI, APNS	240	5.20 ± 1.20	2.90 ± 0.30	0.90 ± 0.26	4.20 ± 0.80	24.50 ± 5.20 ↑↑
Control group	260	4.90 ± 1.60	1.14 ± 0.50	1.80 ± 0.50	2.80 ± 0.40	7.40 ± 3.0
p		0.7400	0.0001	0.0001	0.0001	0.0001

Table 4: Obtained results from patients with HTA ess and control group for Hcyt and lipid profile

	N°	ChT mmol/l	TG mmol/l	HDL-ch mmol/l	LDL-ch mmol/l	tHcy µmol/L
Patients with HTA ess	160	5.40 ± 1.50	2.80 ± 0.30	1.02 ± 040	3.5 ± 1.08	18.20 ± 6.40 ↑
Control group	260	4.90 ± 1.60	1.14 ± 0.50	1.60 ± 0.70	2.80 ± 0.60	7.40 ± 3.00
p		0.7400	0.0001	0.0001	0.0001	0.0001

Table 3 shows significant difference for following analysed parameters in patients with CVD for TG= 2. 90 ± 0.30, HDL-ch=0.90 ± 0.26 , LDL-ch = 4.20 ± 0.80 and Hcyt=(24.50 ± 5.20 µmol/L) with p<0.0001 exept for ChT where no significant difference between two groups was found (in patients with coronary disease ChT= 5.20 ± 1.20 mmol/l while in control group=4.90±1.60 mmol/l with p=0.7400). Concentrations of homocysteine and lipids in patients with CVD compared with control group showed significant statistical difference with p=0.0001, exept for total cholesterole where no significance was recorded (p=0.7400), expected results and verified by many other multicentric studies. Table 4 results from group with HTA ess for all examined parameters showed significance compared with the control group especially for homocysteine =18.20 ± 6.40 which was object of our study, with p=0.0001. Hcyt levels in patients with HTAess were lower than the group with CVD (24.50 ± 5.20) which virifies that high concentrations of Hcyt have bigger impact on the onset of CVD than arterial hypertension. Therefore all facts point that hyperhomocysteinemia have impact on CVD manifestations but the effect on the onset of arterial hypertension needs more studies with longer period of time and with more patients in order to verify or dismiss its impact on arterial hypertension because nowaday thoughts are contradictory (24,25,26,27,28).

4 Discusion

Hyperhomocysteinemia can be caused by deficiency of folate, vitamine B6 and B12 in food. An individual with deficiency of these abovementioned vitamines can develop raised leveles of Hcyt and have risk from hyperho-mocysteinemia. Disorders of homocy-steine metabolism and other sulfuric aminoacids in patients with renal injury are described in 1980 by Willen et al. for first time, who saw that uremic patients treated with HD had raised cysteine and Hcyt (29,48). High levels of homocysteine were found in patients with chronic renal injury also, with increased urea, hypothyroidism, cancer, psoriasis, diabetes, exess alcohol, smoking, cafee, old age and menopause. Homocysteine is eliminated from the organism with kidneys therefore during renal injury when GFR is decreased the excretion of Hcy from organism is decreased, which causes moderate hyperho-mocysteinemia. Concentrations of homocysteine in serum can be increased different diseases which cause disturbance in the metabolism of folates, B6, B12, lipides, lipoproteins, inflamation etc. Prevalence of hyperhomocysteinema can vary between different populations and is tightly dependet on age, diet, genetic predisposition while in turn physical activity, moderate consumption of alcohol, folates and B12 are associated with lower levels of Hcyt.Many studies have found that vegetarians can have higher risk for hyperhomo-cysteinemia compared with non vegetarians because of lower B12 levels in their diet (30).There are studies which have verified that in uremic patients increased Hcyt for 1 µmol/L increases the risk for CVD 1% (31). Still unknown remains the impact and atherosclerotic effect of raised Hcyt, but it is believed it interferes with endothelial function, coagulation and paltelets (32). In normal individuals, homocysteine concentrations can be decreased slightly by using folic acid. This B vitamin is converted in 5-methyltetrahydrofolate which gives one methyl group to homocysteine and remodels methionine from which homocysteine is derived. In patients with CVD, folic acid of 400-600mg can decrease Hvyt for 20-30% while in patients with chronic terminal kidney injury even very high doses of folic acid doesnt show decrease of Hcyt concentrations in blood (33). Corelation between hyperhomocysteinemia and CVD in uremic patients for first time was investigated 25 years ago when scientists discovered that patients with rare disease-homocysteinuria- because of their high levels of homocysteine in blood and urine are potential candidates for atheromatous disease of coronary arteris in young age. In these cases it is verified the lack of an enzyme which mediates the metabolism of Hcyt and as result hyperhomo-cysteinemia occurs (34). Homocysteine is an aminoacid, product of Demthyltion-Methionin and precursor of Cystein-Byosinthases (19). Originally was thought that homocysteine isnt present in human blood. It was supposed that Hcy in humans blood exist like an substrate with unknown origin, but latter it was discovered that 70% of homo-cysteine together with serum proteins form a complex also known as homocysteine-proteine complex, consisting from albumines. Nowaday studies have found that 15-30% of coronary diseases are related with reaised Hcyt levels, where important role plays: genetic predisposition, folate, pyridoxine, cyanocobalamin and vitamin E deficiency. (35,36,37,48). High concentrations of Hcy can be normalized by substituting 1 or 2 from above mentioned deficient vitamines. Homocysteinuria is geneticaly transmited disease. If a patients inherits 2 defective aleles the risk is much higher that in patients who inehret 1 alele. It is verified that in 100 individuals 1 person inherets 1 defective alele. Nair et al. in a study in indian population verified genetic mutations of Methylen-tetra-hydrofolate-reductasae, which is main cause of hyperhomocysteinemia in this population (25,26). Many studies have documented that high levels of Hcyt are risk factor for the onset of atheromatous changes in coronary, cerebral and periferical arteries. It is found that during hyperhomocysteinuria the activity of cystathionine-Beta-synthetasae is enormously increased, an anzyme responsible for Hcyt metabolism. Another study has found that every increase of homocysteine for 55 µmol/L is associated with CVD consequences for 20-25%. A new multicentric study which included 80.000 female individuals, for 14 years, found that onset of CVD was lower in the group which during that time consumed subsitutive therapy with vitamines or consumed with food higher concentrations of abovementioned vitamines compared with the group who havent consumed enough of them (38). Authors Victor and Hebert in their studies concluded that low levels of folic acid are as result od decreased absorbtion of vitamin B12 which is tightly related with old age (42). It is verified that by lowering Hcyt in serum the risk for atherosclerosis, CVD and stroke in patients with homocysteinuria decreases also. Even after many studies regarding to hyperhomocysteinemia exeprts still canot conclude and verify that by lowering high levels of homocystein decreases the risk for CVD (18,39). Regarding to this , an 4 year study in 101 patients with CVD who every day consumed folic acid, pyridoxine and cyanocobalamin found a decrease in the size of their atheromatous plaques, even better results were obtained in those patients who before the study had higher levels of Hcyt. The cause of hyperhomo-cysteinemia in patients with chronic renal failure still is unknown, and an appropriate therapy for normalizing Hcy in these patients doesnt exist.Experts suggest that patients with CVD should analyse their Hcyt levels, and those with levels from 9-10 µmol/L should be treated at least one month with substituive therapy, this has shown positive effects. An recent study on positive effects of folic acide and vitamine B12 (combined or separately) on hyperhomocysteinemia has verified that by substituting B6 and B12, organism can easily correct Hcyt levels. In USA, Canada and Europe an study with 60.000 individuals, still ongoing, are studying the effect of raised Hcyt and onset of myocardial infarction, cerebrovascular embolia and possible ways of decreasing it (27). Some studies have concluded that hyperhomocysteinemia is result of convertion of hydrogen peroxide in free oxygen radicals and convertion of oxidated Hcy in Homocysteine disulfide. Efect of oxidated Hcy which is increased by hydrogen peroxide explains the LDL raise. Hydrogen peroxyde causes endothelial desquamation, with inhibitory effect on prostacyclines and prostaglandines who are antagonists of platelet adhesion (28,29,30,31).

Many studies have verified that patients after undergoing stenting or angioplasty with normalised Hcy levels have lower incidence of re-occuring of atheromatous processes compared with those who have high Hcy. A recent study, which has lastet 6

months, a time which in patients vitamine B6 and B12 was given found that cardiac events and need for revasularisation was 1/3 time lower compared with patients who havent consumed abovementioned therapy (32,44). High levels of Hcyt can be as result of cyanocobalamine deficiency which occurs because of vitamine B12 malabsorbtion as result of gastric atrophy, which is more often seen after age of 50. B12 deficiency causes anemia. If this deficiency is let untreated it causes damage to nervous system and early atherosclerosis. Individuals above 50 years of age are advised to consume folic acid and vitamine B12 because in this age most of them have gastric atrophy. An multicentric study concluded that females during menopause have raised homocysteine and an increase of coronary diseases, compared to females before menopause (33). From all what was mentioned above, question rises: which are definitive mechanisms who can normalise Hcyt levels in organism? how can we prevent hyperhomocysteinemia? The answer for the first question isL by substituting vit. B6, B12, tocoferol and folic acide. Regarding to the second question the answer is hard, because on the onset of early atherosclerosis many unknow factors are included, which are hard to control and corect, therefore more studies need to be made, larger and with longer timespan, with more patients.Negative effects of hyperhomocysteinemia on coronary arteries are increased even more if it is associated with hypertriglyceridemia, hypercholesterolemia (LDL-ch, LDL-ox). It is fact that hyperhomocysteinemia is in corelation with folate, pyridoxine and cyanocobalamin deficiency (33,36). Consultet literature and many studies have concluded that in the ethiology of coronary artheriosclerosis many factors are included: genetic predisposition, environment, life style, sedentary life, obesity etc. There are facts that by suplementing vitamine B12 has decreased Hcyt concentrations with 17-30%. For decreasing Hcy and correcting dyslipidemia intravenous application of acetylcysteine is required. Many studies have shown that by apllicating folic acid, vitamine B12 and B6 can reduce Hcy levels for 35% (36-42). In a larger study , it was documented that patients with coronary disease who were treated with folic acid, after 2 year follow up homocysteine decrease for 18% occured, but mortality didnt show significant reduction (34,35,43). Documented facts exist that folic acid, cyanocobalamin and acetilcysteine have positive effects on decreasing homocysteine in one side and improving blood vessel function in other side. Nevertheless to verifu or to dismiss abovementioned facts more studies need to be made, with more patients and more countries, so the final conclusion can be taken on the effect of folic acid, cyanocobalamine and acetylcysteine on improving endothelial funciton of blood vessels (42-48).

5 Conclusion

We can conclude that in our paper also high levels of Hcyt were recorded in patiets with CVD and HTA ess. These results are in line with many other multicentric studies, on the role of Hcyt as new indipendent risk factor for early atherosclerosis and moderate effect on the onset of HTA ess.
In abovementioned cases it is prefered substitutive therapy with folic acid, pyridoxine, cyanocobalamin, tocoferol, acetylsalicilates and other antioxidantive agents, which clearly can prevent ealry atherosclerosis in CVD with: PTCA, CARB, AMI, APNS, Stening and prevention of stroke.

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