Original article

Increased levels of inflammatory markers in hypertensives with target organ damage

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Abstract

Introduction: Inflammatory markers have been reported to be elevated in hypertension.

Aim: We compared levels of inflammatory markers between hypertensives (HT) with target organ damage (TOD) but without associated clinical conditions (ACC), n=55, HT with ACC, n=42, HT without TOD/ACC, n=22 and normotensive controls, n=41.

Methods: Serum levels of CRP, fibrinogen, TNF-α and anti-HSP60 antibodies were measured. Hypertensive complications were assessed on the basis of clinical history and the following investigations: M-mode echocardiography (left ventricular hypertrophy), Doppler: mitral and pulmonary vein flow and isovolumetric relaxation time (diastolic dysfunction), vascular ultrasound (common carotid artery intima-media thickness - IMT), pulse wave velocity (carotid-femoral arterial stiffness) and creatinine concentration (renal function).

Results: HT with TOD had higher concentrations of CRP than controls (1.71 *vs* 0.76 mg/l, p <0.0001); higher fibrinogen and TNF-α *vs* controls and also *vs* HT without TOD/ACC (2.80 *vs* 2.53 *vs* 2.49 g/l, p <0.0001) and (2.49 *vs* 2.00 *vs* 1.83 pg/ml, p=0.04), respectively. HT without TOD/ACC did not differ from the control group in inflammatory marker concentrations. HT with ACC did not differ from HT with TOD in inflammatory marker concentrations. There were no differences in anti-HSP60 antibody concentrations between all groups. In multiple regression analysis only IMT was influenced by inflammatory markers: fibrinogen (β=0.2, p=0.02) and TNF-α, (β=0.17, p=0.05).

Conclusions: We conclude that inflammatory markers are elevated in HT with TOD and are not elevated in uncomplicated HT without TOD.

Key words: hypertension; target organ damage; inflammation; fibrinogen; C-reactive protein; tumour necrosis factor

Introduction

Essential arterial hypertension (HT) coexists with a number of risk factors that promote the development of complications and add greatly to the global risk associated with this disease [1]. Inflammatory markers, similar to traditional risk factors, may coexist with HT. In cross-sectional studies levels of various inflammatory markers, such as C-reactive protein (CRP), fibrinogen, tumour necrosis factor α (TNF-α) and heat-shock protein 60 (HSP60) have been shown to be higher in hypertensives than in normotensives [2-6]. There is evidence from a prospective study showing a relationship between inflammation and HT [7]. Prospective studies have also proved that inflammatory markers such as CRP, fibrinogen, TNF-α and antibodies to HSP60 can predict increased risk of atherosclerotic complications [8-11]. Some studies suggest that inflammatory markers are associated with arterial or cardiac remodelling. C-reactive protein, fibrinogen and anti-HSP60 were found to correlate with intima-media thickness (IMT) [1-15], although an independent correlation between CRP and IMT was not confirmed by other investigators [16]. C-reactive protein and fibrinogen have also been shown to be associated with arterial stiffness [12,17]. In one study, hypertensives with elevated fibrinogen level had greater chance of having at least one preclinical cardiovascular abnormality such as left ventricular

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hypertrophy (LVH) or increased arterial stiffness [12]. In the same study, LV mass (LVM) correlated, in multiple regression analysis, with fibrinogen level.

Since concentrations of inflammatory markers tend to correlate with cardiovascular remodelling and atherosclerotic complications it could be possible that target organ damage (TOD) and/or atherosclerotic complications are responsible for increased levels of inflammatory markers that are seen in hypertensives. We hypothesised that levels of inflammatory markers would be higher in hypertensives with TOD or atherosclerotic complications and that there would be a link between these markers and indices of subclinical HT-induced cardiovascular remodelling. To verify this hypothesis, a cross-sectional study was designed to measure various atherosclerosis-associated inflammatory markers (CRP, fibrinogen, TNF-α, anti--HSP60 antibodies) in hypertensives with associated clinical conditions (ACC), hypertensives with TOD but without ACC, hypertensives without TOD/ACC and healthy normotensives. We also assessed the relationship between these markers and intima-media thickness (IMT), pulse wave velocity, LVH and parameters of LV diastolic function.

Methods

Characteristics of patients and controls

Patients of a specialised HT outpatient unit at a university teaching hospital with diagnosed essential HT entered the study. Those with acute inflammatory condition within the previous 6 weeks, chronic inflammation or infection, autoimmune disease, cancer, severe heart or renal failure, myocardial infarction, unstable angina or stroke within the previous 3 months, diabetes or other endocrine disorder were excluded.

There were 119 hypertensives, mean age 55.9±11 years, 63 men and 56 women, including 100 patients with severe and 19 patients with moderate HT. All patients received combined antihypertensive treatment; median duration of HT was 11 years. The following data were obtained from all patients: age, weight, height, atherosclerotic complications (coronary heart disease, stroke, intermittent claudication), smoking and current pharmacotherapy.

Forty-one healthy volunteers without a history of HT (24 women and 17 men, mean age 52.0±9 years) served as controls. To exclude subjects with undetected HT, all controls had their blood pressure measured conventionally with a mercury sphygmomanometer and 24-hour ambulatory blood pressure monitoring (ABPM) (Space-Labs 90207). Arterial hypertension was diagnosed when mean conventional blood pressure obtained on two separate occasions exceeded normal limits (≥140 mmHg for systolic and ≥90 mmHg for diastolic blood pressure),

when the subject was receiving an antihypertensive drug or when mean systolic or diastolic blood pressure for the entire 24 hrs (ABPM) exceeded 125 and 80 mmHg, respectively [1]. In the control group, the ABPM mean systolic blood pressure was 118±6 mmHg and diastolic – 75±4 mmHg. The conventional mean systolic and diastolic blood pressure were 122±9 mmHg and 80±6 mmHg, respectively. None of the controls received medical therapy.

Laboratory tests

Blood samples were obtained at least 12 hours after the last meal. Concentrations of fibrinogen and lipids were measured directly after blood sampling. Plasma and serum samples for measurements of CRP, TNF-α, creatinine and anti-HSP60 antibodies were frozen at –30°C and assayed after collection of all the material. Concentrations of serum CRP were determined using a high sensitivity nephelometric assay – the Dade Behring N Latex CRP mono kit with the sensitivity range 0.175-11 mg/l and Behring Nephelometer Analyzer II. Fibrinogen was measured using the modified Klauss method with the Dade Behring Multifibren U kit (sensitivity range: 0.8-2 g/l) and an automatic analyser, the Behring Coagulation System. Concentrations of serum TNF-α were measured using a quantitative sandwich immunoassay technique with the Quantikine HS Human TNF-α, R&D Systems kit with a limit of detection of 0.12 pg/ml. Concentrations of plasma IgG, IgA and IgM antibodies to human HSP60 were determined using ELISA with the Anti-Human Hsp60 (total), Stressgen Biotechnologies kit with a limit of detection of 2.88 ng/ml.

Echocardiographic measurements

All echocardiographic studies were performed with a Hewlett-Packard Sonos 2000 and 2.5 MHz transducer by a single, experienced cardiosonographer, who was unaware of the biochemical and clinical data. M-mode echocardiograms were obtained from parasternal view under 2D control and all LV and Doppler parameters were calculated as the mean of at least three consecutive measurements. Left ventricular mass was calculated with the Devereux formula: LVM=0.8 {1.04 (IVS + LVEDD + PWT)^3 – (LVEDD)^3} + 0.6 g. Left ventricular hypertrophy was defined according to the ESC guidelines, i. e. when LVM index was >125g/m^2 in men and >110g/m^2 in women [1]. Pulse wave (PW) Doppler recordings were performed in the apical four-chamber projection with a 2.0 MHz transducer. Pulse wave Doppler sample volume was placed in LV at the tips of the mitral leaflets to obtain the mitral flow profile. To detect diastolic dysfunction in patients with pseudonormalisation of mitral

inflow, we also evaluated pulmonary venous flow velocities with pulsed Doppler sample volume placed in the left atrium, with the help of colour Doppler, at the orifice of the pulmonary veins that offered the optimal signal for analysis. Left ventricular diastolic function was measured from the following parameters: the ratio of early (E) to late (A) peak velocities of transmitral flow (E/A), E wave deceleration time (EDT), isovolumetric relaxation time (IVRT), peak forward pulmonary venous flow velocity at systole and diastole and peak retrograde pulmonary venous flow at atrial contraction. Diastolic dysfunction was diagnosed according to the guidelines of the European Study Group on Diastolic Heart Failure using the above-mentioned parameters [18].

Pulse wave velocity (PWV) and IMT measurements

All measurements of IMT and PWV were performed by the same physician, who was unaware of the biochemical and clinical data. The intima-media thickness was measured in the left and right common carotid artery on the near and far wall, two cm distal from the carotid bifurcation using a HP Sonos 2000 and 7.5 MHz sector transducer in the B-mode. The intima-media thickness was not measured in areas of obvious localised thickening (over 100% increase in thickness compared with normal adjacent wall). In each patient IMT was determined as the average of 12 consecutive measurements. The IMT value ≥0.9 mm was considered abnormal [1]. Carotid-femoral PWV was measured using an automatic device recording transcutaneously the pulse pressure wave simultaneously at two distant sites (Complior, Colson, Garges les Genose, France and the TY 306 pressure transducer, Fukuda Denshi, Tokyo, Japan). Transducers were placed at the base of the neck for the right common carotid artery and over the right femoral artery. The distance travelled by PW was measured over the body surface as the distance between the two transducers. Carotid-femoral PWV was automatically calculated by dividing the distance between the two points by transit time determined by the Complior device. At least 15 technically correct single measurements were obtained in each subject to calculate the average velocity. The PW value >13 m/s was considered abnormal [19].

Statistical analysis

Variables with skewed distribution (CRP, fibrinogen, TNF-α, anti-HSP60 antibodies) were transformed logarithmically for further analysis with parametric tests. The ANOVA test was used to compare mean values between groups with Scheffe's test for post-hoc analysis; Kruskall-Wallis ANOVA was used in the case of not normally distributed variables. ANCOVA was used to adjust for confounding factors (age, BMI, smoking). Multiple regression analysis was used to assess relationships between inflammatory variables and cardiovascular remodelling indices. The Pearson Chi-square test was used to compare frequency of hypercholesterolaemia, smoking and gender distribution among groups. Statistical analysis was performed with Statistica for Windows 6.0 PL software (StatSoft Inc., Tulusa, Oklahoma, USA). A p value <0.05 was considered significant.

Results

Among hypertensives there were 42 patients with ACC which included: coronary heart disease – 33 patients, previous stroke – 11 patients, and intermittent claudication – 2 patients. Among patients without ACC, 55 were identified as having preclinical TOD, including LVH in 40 patients, LV diastolic dysfunction in 34 patients (most of these also had other TOD, only 4 patients had isolated diastolic dysfunction), increased IMT in 14 patients, increased PWV in 40 patients and mild renal failure (creatinine >115 µmol/l for men, >107 µmol/l for women) in 6 patients. There were no differences in age between controls versus hypertensives without TOD/ACC and also versus hypertensives with TOD. As compared with hypertensives without TOD/ACC, patients with TOD were older and, as compared with controls, had higher body mass index (BMI) (Table I). There were no differences in smoking, mean lipid levels or frequency of hypercholesterolaemia (defined as total cholesterol >5.0 mmol/l or LDL >3.0 mmol/l or treatment with statins) between the groups.

Results of the laboratory tests are summarised in Table II (raw data) and Table III (adjusted data). Hypertensives with TOD as well as hypertensives with ACC were found to have higher CRP, fibrinogen and TNF-α levels as compared with healthy normotensives and with hypertensives without TOD/ACC. After adjustment for age, BMI and smoking, the differences remained significant for CRP and fibrinogen, whereas the differences for TNFα were of borderline significance (p=0.07). Hypertensives without TOD/ACC did not differ from the controls in inflammatory marker levels. There were no differences in inflammatory marker levels between hypertensives with TOD and hypertensives with ACC. No differences were observed in anti-HSP60 antibody values between the subgroups.

Of the cardiovascular remodelling indices (IMT, LVH, PWV, and LV diastolic function), only IMT was associated with inflammatory markers in multiple regression analysis. When taking into account age, BMI, total cholesterol, pack-years, anti-HSP60, TNF-α, CRP, fibrinogen, creatinine and systolic blood pressure, there were

Table I. Characteristics of the study population

Parameter		HT without TOD/ACC	HT with TOD	HT with ACC	Controls	p
Number [n]		22	55	42	41	—
Age [years ± SD]		46.6±12	57.3±10#	58.9±11* #	52.0±9	0.001
Gender	Males	12	27	24	17	0.52
	Females	10	28	18	24	
BMI [kg/m²]		26.2±3	28.3±3*	27.3±4	25.8±3	0.004
Total cholesterol [mmol/l]		5.6±0.8	5.5±1.0	5.5±1.0	5.7±0.9	0.91
LDL cholesterol [mmol/l]		3.4±0.7	3.4±0.8	3.2±1.0	3.5±0.8	0.70
HDL cholesterol [mmol/l]		1.4±0.3	1.3±0.5	1.4±0.8	1.4±0.4	0.84
Triglycerides [mmol/l]		2.0±2.2	1.8±0.8	2.2±1.1	1.6±0.8	0.10
Hypercholesterolaemia [%]		82	87	81	76	0.60
Smoking [pack-years]		5.9±10	8.7±12	12.1±14	4.7±10	0.14
Smoking (current) [%]		23	15	14	20	0.76
Smoking (past and current) [%]		41	49	59	37	0.18

Abbreviations: HT – hypertension; TOD – target organ damage; ACC – associated clinical conditions
* vs controls
 # vs HT without TOD/ACC

Table II. Markers of inflammation in hypertensives according to the presence of TOD and complications

Parameter [unit]	HT without TOD/ACC n=22	HT with TOD n=55	HT with ACC n=42	Controls n=41	p
CRP [mg/l]	1.02(0.56-1.86)	1.71(0.92-2.53)*	1.96(1.1-3.65)* #	0.76(0.45-1.24)	0.0001
Fibrinogen [g/l]	2.49 (2.30-2.70)	2.80(2.50-3.40)* #	3.05(2.50-3.45)* #	2.53(2.30-2.80)	0.0001
TNF-α [pg/ml]	1.83(1.35-2.45)	2.49(1.90-3.29)* #	2.54(1.79-3.28)	2.00(1.59-2.75)	0.04
anti-HSP60 [ng/ml]	11.19 (7.20-13.20)	11.60(9.00-18.90)	11.45(7.50-20.40)	14.23(8.80-18.10)	0.28

Data presented as geometric means plus interquartile range (25 -75th percentile). Abbreviations: as in Table I
* vs controls
 # vs HT without TOD/ACC

Table III. Markers of inflammation in hypertensives according to the presence of TOD complications. Data adjusted for age and BMI.

Parameter [unit]	HT withoutTOD/ACC n=22	HT with TOD n=55	HT withACC n=42	Controls n=41	p
CRP [mg/l]	1.05	1.56	1.91	0.78	0.001
Fibrinogen [g/l]	2.52	2.85	2.96	2.53	0.001
TNF-α [pg/ml]	1.83	2.51	2.40	2.01	0.07

Values expressed as geometric means. Abbreviations: as in Table I

significant relationships between IMT and age, fibrinogen and TNF-α (Table IV).

Discussion

C-reactive protein and fibrinogen

In the present study, higher CRP and fibrinogen levels were found in hypertensives with TOD and also in hypertensives with ACC than in hypertensives without TOD/ACC and controls. The CRP and fibrinogen levels in patients with uncomplicated HT without preclinical TOD (i. e. without LVH, with normal LV diastolic function, normal IMT, normal PWV and normal renal function) were similar to those in controls. Hypertensives with TOD did not differ in CRP or fibrinogen levels from

Table IV. Correlations between intima-media thickness and other parameters in multiple regression analysis

parameter	β	p
Age	0.59	0.0001
Fibrinogen	0.20	0.02
TNFα	0.17	0.05
BMI	0.11	0.17
Systolic blood pressure	0.11	0.17
Anti-HSP60	-0.05	0.53
CRP	- 0.02	0.83
Pack-years	0.10	0.24
Total cholesterol	0.03	0.68
Creatinine	-0.12	0.19

Multiple R=0.74, r²=0.55, p <0.0001

hypertensives with ACC. Adjustment for potential confounding factors (age, BMI) did not affect the results significantly. In the present study, fibrinogen but not CRP was found to influence slightly the IMT values in multiple regression analysis. There was a weak correlation between CRP and IMT in univariate analysis (results of univariate analyses not shown) but in multiple regression, after adding fibrinogen, age and BMI as covariates, this association became insignificant. This is similar to the results of a large cross-sectional study that assessed the relationship between CRP and indicators of subclinical atherosclerosis [16].

Studies in large groups revealed elevated CRP and fibrinogen levels in hypertensive patients and a correlation of these markers with blood pressure (Table V) [3, 4, 8, 20-22]. In these studies, CRP and fibrinogen levels were evaluated in patients who were not divided into those with complicated or uncomplicated HT. For this reason it is not clear whether increased CRP and fibrinogen levels were found only in patients with complicated HT similar to our study. However, other studies demonstrating a correlation between CRP and/or fibrinogen with increased IMT [23], impaired renal function [24], retinopathy, LVH [25], arterial compliance (PWV) [17], and a risk of stroke or myocardial infarction [26, 27], imply that it is possible. What is more, in three studies increased fibrinogen level was found in patients with complicated HT [12, 22, 28].

Tumour necrosis factor

In the present study higher levels of TNF-α were found in hypertensives with TOD as compared with controls and hypertensives without TOD/ACC. There was a weak positive correlation in multifactorial analysis between increased TNF-α and increased IMT. Evidence on the relationship between HT and TNF-α is limited. Some investigators have demonstrated higher levels of TNF-α in patients with HT [6, 29], while others have failed to detect such a relationship [30, 31]. None of these studies considered the effects of TOD/ACC, which may be a reason for the disparity. Only Ridker et al. in their prospective study have shown that TNF-α, similar to other inflammatory markers, may be a predictor of cardiovascular complications [10]. This may be a reason for the higher levels of TNF-α in patients with complicated HT in the present study.

Heat-shock proteins

Elevated blood pressure is a mechanical stress to the endothelium – theoretically it may be a factor inducing enhanced expression of heat-shock proteins on the endothelial cell surface. Animal models have revealed a relationship between elevated blood pressure and increased expression of HSP [32]. In the present study there were no differences in levels of anti-HSP60 antibodies between hypertensives and normotensives. Pockley et al. obtained similar results assessing levels of HSP60 and anti-HSP60 antibodies in hypertensives [5]. These investigators found that levels of HSP60, but

Table V. Studies demonstrating the relationship between inflammatory markers and arterial hypertension

Higher levels of CRP, fibrinogen, TNF-α and HSP60 in hypertensives showed in cross-sectional studies (without assessment of the presence of target organ damage).	Kannel et al. 1987 [21], Dotevall et al. 1994 [20], Lip et al. 1995 [33], Folsom et al. 1998 [4], Koenig et al. 1999 [8], Rohde et al. 1999 [34], Bautista et al. 2001 [35], Yamada et al. 2001 [36], Pockley et al. 2002 [5], Furumoto et al. 2002 [29], Bermundez et al. 2002 [37], Sung et al. 2003 [38], Blake et al. 2003 [3], Bautista et al 2004 [6].
Increased risk of hypertension in patients with higher CRP levels in a prospective study.	Sesso et al. 2003 [7].
Increased levels of fibrinogen in hypertensives with target organ damage in cross-sectional studies.	Sechi et al. 2000 [22]. Lechi et al. 2003 [38].
Increased risk of target organ damage in hypertensives with higher fibrinogen levels in a prospective study.	Palmieri et al. 2001 [12].

not anti-HSP60 antibodies, were increased, and that HSP60 but not anti-HSP60 antibodies correlated with the IMT values. The results of these studies and our findings suggest increased expression of HSP60 in HT without enhanced autoimmune reaction mediated by anti-HSP60 antibodies.

Limitations of the study

All four subgroups were not well matched with respect to age. Yet there were no differences in age between controls and hypertensives without TOD/ACC and also between controls and hypertensives with TOD. Age difference was only significant between hypertensives with ACC and those without TOD/ACC as well as controls, and also between hypertensives with TOD versus those without TOD/ACC. This was taken into consideration by using age-adjusted comparison (ANCOVA) and using age as a correlate in multi-regression analysis. A rather small number of patients and a large panel of studies to exclude TOD, including PWV, IMT and LV diastolic function assessment, which are rarely performed in clinical practice, resulted in an unexpectedly low number of hypertensives without TOD/ACC and disparate group numbers. This leads to increased risk of type one and type two errors. However, to the best of our knowledge, there are no studies evaluating inflammatory markers in a larger group of patients with uncomplicated HT without TOD. Diabetic patients were excluded from the present study, and therefore our study group could not be representative of the general hypertensive population. However, in diabetics levels of inflammatory markers are higher and complications are more frequent, which could affect the results [27]. In the present study, we did not analyse separately the effects of statins on the level of CRP; however, of 31 patients receiving statins, almost all had complicated HT. This could have slightly reduced CRP levels in this group. However, the major outcome of the study was generally unchanged because, despite statin therapy, levels of CRP were much higher in patients with complicated HT as compared with the other groups.

Conclusions

The present findings are concordant with other cross-sectional studies showing increased levels of various inflammatory markers in essential HT. However, in none of the studies assessing CRP level in HT was the presence of TOD and atherosclerotic complications taken into consideration. In the present study, in which TOD was studied thoroughly, we found that levels of inflammatory markers were not elevated in hypertensives without TOD and atherosclerotic complications. In contrast, patients with only preclinical TOD had higher levels of CRP, fibrinogen and TNF-α than controls and no different than the group with clinical atherosclerotic complications. A question arises whether inflammatory markers and TOD are parallel indicators of high global risk in these hypertensives or if they are pathophysiologically related. In this study, in multiple regression analysis, TNF-α and fibrinogen levels did correlate with IMT, yet prospective data on the effect of inflammatory markers on the development of TOD are scarce; therefore it is still difficult to answer this question.

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Podwyższone stężenia markerów zapalenia u chorych na samoistne nadciśnienie tętnicze z powikłaniami narządowymi

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Streszczenie

Wstęp: W licznych badaniach stwierdzono podwyższone stężenia markerów zapalenia u chorych na samoistne nadciśnienie tętnicze (HT).

Cel: Porównanie stężenia markerów zapalenia pomiędzy: chorymi z HT z uszkodzeniami narządowymi (TOD), ale bez chorób powiązanych (ACC), n=55, chorymi z HT z ACC, n=42, chorymi z HT bez TOD/ACC, n=22 oraz osobami zdrowymi, n=41.

Metodyka: Oznaczono stężenie białka c-reaktywnego (CRP), fibrynogenu, czynnika martwicy nowotworu (TNF-α) oraz przeciwciał przeciw białkom szoku cieplnego 60 (anty-HSP60). Obecność TOD oraz ACC oceniono na podstawie wywiadu oraz badań: echokardiografii M-mode (przerost mięśnia lewej komory), echokardiografii dopplerowskiej: profil napływu mitralnego i z żył płucnych (funkcja rozkurczowa), ultrasonografii: tętnica szyjna wspólna (grubość kompleksu intima-media, IMT), pomiaru szyjno-udowej prędkości fali tętna aparatem Complior, oraz stężenia kreatyniny (uszkodzenie nerek).

Wyniki: HT z TOD mieli wyższe stężenie CRP niż grupa kontrolna (1,71 *vs* 0,76 mg/l, p <0,0001); oraz wyższe stężenie fibrynogenu (2,80 *vs* 2,53 i *vs* 2,49 g/l, p <0,0001) i TNF-α (2,49 *vs* 2,00 i *vs* 1,83 pg/ml, p=0,04) w stosunku do grupy kontrolnej a także w stosunku do grupy HT bez TOD/ACC. Grupa HT bez TOD/ACC nie różniła się od grupy kontrolnej, a grupa HT z ACC nie różniła się od grupy HT z TOD w zakresie markerów zapalenia. W analizie regresji wieloczynnikowej na IMT niezależnie wpływały następujące markery zapalenia: fibrynogen (β=0,2, p=0,02) i TNF-α, (β=0,17, p=0,05).

Wnioski: Stężenie markerów zapalenia jest podwyższone u chorych na nadciśnienie tętnicze powikłane uszkodzeniami narządowymi lub chorobami powiązanymi. U chorych z nadciśnieniem niepowikłanym nie stwierdzono podwyższonego stężenia markerów zapalenia.

Słowa kluczowe: nadciśnienie tętnicze, powikłania narządowe, zapalenie, białko c-reaktywne, fibrynogen, czynnik martwicy nowotworu

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