Arterial distensibility in Wegener's granulomatosis: a carotid - femoral pulse wave velocity study

Wegener granülomatozu'nda karotis-femoral nabız dalga hızı ile belirlenen arteryel genişleyebilirlik

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ABSTRACT

Objective: The purpose of this study was to test the hypothesis; that chronic inflammation may impair vascular function and lead to an increase of arterial pulse wave velocity (PWV) in patients with Wegener's granulomatosis (WG).

Methods: We recruited 5 patients with WG and 5 healthy age and sex matched controls in this cross-sectional case-controlled study. Aortic PWV was determined by using an automatic device (Complior Colson, France), which allowed on-line pulse wave recording and automatic calculation of PWV.

Results: The carotid-femoral (aortic) PWV was increased in patients with WG as compared with control group (p=0.04). Although we found positive correlation between PWV and heart rate (r=0.75, p=0.01), we did not find any significant correlation between PWV and anthropometric and other hemodynamic parameters (p>0.05). In addition, we found positive correlation between PWV and erythrocyte sedimentation rate in patients with WG (r=0.90, p=0.03).

Conclusion: Pulse wave velocity is increased and arterial distensibility decreased in patients with WG. Measurements of carotid-femoral (aortic) PWV may provide an easy and noninvasive technique to identify patients at increased risk of arterial disease. *(Anadolu Kardiyol Derg 2007; 7: 281-5)*

Key words: Pulse wave velocity, arterial distensibility, Wegener's granulomatosis, inflammation

ÖZET

Amaç: Çalışmanın amacı, kronik enflamasyon Wegener granülomatoz (WG)'lu hastalarda vasküler fonksiyonları bozup arteryel nabız dalga hızı (NDH)'nı artırabilir, hipotezini araştırmaktır.

Yöntemler: Yaş ve cinsiyet olarak uyumlu 5 WG'lu hasta ve 5 sağlıklı kontrol grubu çalışmaya dahil edildi. Aortik NDH, on-line nabız dalga kaydına izin veren ve otomatik ölçüm yapan Complior Colson (Fransa) cihazı ile belirlendi.

Bulgular: Karotis-femoral (aortik) NDH kontrol grubuna göre WG'lu hastalarda daha yüksek bulundu (p=0.04). Nabız dalga hızı ve kalp hızı arasında pozitif yönde korelasyon saptarken (r=0.75, p=0.01), NDH ile antropometrik ve diğer hemodinamik değişkenler arasında anlamlı korelasyon izlemedik (p>0.05). Ek olarak WG'lu hastalarda, NDH ve sedimantasyon arasında pozitif korelasyon saptadık (r=0.90, p=0.03).

Sonuç: Wegener granülomatoz'lu hastalarda NDH artmış arteryel genişleyebilirlik azalmıştır. Karotis-femoral (aortik) NDH artmış arteryel hastalık riski olan hastaların teşhisinde kolay ve non-invazif bir teknik olabilir. *(Anadolu Kardiyol Derg 2007; 7: 281-5)*

Anahtar kelimeler: Nabız dalga hızı, arteryel distansibilite, Wegener granülomatozu, enflamasyon

Introduction

Wegener's granulomatosis (WG) is a rare disease, affecting only 1 in every 30.000-50.000 people, that often begins with inflammation of the upper airways or lungs and may progress to an inflammation of blood vessels throughout the body (1). There is a strong and specific association of WG with presence of anti-neutrophil cytoplasmic antibodies (ANCA) to a defined target antigen, proteinase 3 (PR3-ANCA), which is present within primary azurophil granules of neutrophils and lysozymes of monocytes (2). Upon cytokine priming of neutrophils, this enzyme translocates to the cell surface, where PR3-ANCAs can interact with their antigens and activate neutrophils (3). The presence of ANCA in the plasma of patients and genetic involvement of the human leukocyte antigen system reflects an autoimmune background of the disease. A strong association of WG with distinct HLA-DPB1 alleles or rather an extended haplotype, respectively, in the major histocompatibility complex class II (MHC II) region has been reported (4). This systemic inflammation in WG is an important factor in the initiation or the progression of atherosclerosis (5). Damage to the arterial wall due to

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inflammation and atherosclerosis causes decreased arterial distensibility, compliance and elasticity (6).

Noninvasive ultrasound techniques are used to evaluate vascular system and cardiovascular condition. One such technique is the pulse wave velocity (PWV), which is defined as arterial pulse's velocity of moving along vessel wall. It is accepted as an indicator of arterial elasticity in young patients with rheumatoid arthritis (7). Pulse wave velocity is inversely correlated with arterial distensibility and relative arterial compliance (8).

The purpose of the present case-controlled study was to test the hypothesis; that chronic inflammation may impair vascular function and lead to an increase of arterial stiffness in patients with WG.

Methods

Study protocol

Patient population

We recruited 5 patients with WG (26-65 years old, 1 women) and 5 healthy age and sex matched controls (25-63 years old, 1 women). Patients had satisfied the criteria of American College of Rheumatology (9). Exclusion criteria were a previous myocardial infarction, constrictive, restrictive or dilated cardiomyopathy, heart failure, valvular heart disease, diabetes mellitus, peripheral arterial disease, cerebrovascular disease, anemia (hematocrit <30%), electrocardiographic conduction and rhythm disorders, systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, body mass index ($\geq$35kg/m^2) and waist / hip ratio $\geq$1 cm. Of 5 patients enrolled in the study 2 patients had chronic renal disease and hypertension under medical treatment (urea 68-98 mg/dl, creatinine 2.8-2 mg/dl, respectively). All patients were receiving anti-inflammatory and cytotoxic drug treatment. Characteristics of patients with WG are shown in Table 1. All subjects gave their consent for inclusion in the study. The investigation conforms with the principles outlined in the Declaration of Helsinki. The design of the study was cross-sectional.

Body mass index and waist - hip ratio measurements

Body mass index (kg/m^2) was calculated by dividing body weight in kilograms by square of body height in meters. The circumference of waist divided by circumference of hip, waist - hip ratio was calculated.

Table 1. Characteristics of patients with WG

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean±SD values or %
Sex, Female/ Male	M	M	M	F	M	1/4
WG duration, years	4	8	2	2	1	3.4±2.7
Smoking, %	-	-	-	-	-	0
Hypertension, %	-	+	-	+	-	40
Calcium channel blocker use.,%	-	+	-	+	-	40
HMG-CoA inhibitors use, %	-	-	-	-	-	0
Diabetes mellitus,%	-	-	-	-	-	0
Family history of CVD, %	-	-	-	-	-	0
Total cholesterol, mg/dl	215	194	252	225	299	237.00±40.45
HDL cholesterol, mg/dl	57	71	66	42	42	55.60±13.39
Triglyceride, mg/dl	220	87	85	165	441	199.60±146.37
Hematocrit, %	35	43	44	35	38	39.00±4.30
Sedimentation rate, mm/hr	67	10	21	40	100	47.60±36.40
CRP, mg/dl	1.26	0.01	1.00	2.00	0.50	0.95±0.75
Leukocytes, /mm^3	8800	8600	6800	10000	13300	9500.00±2412.46
Platelets, /mm^3	207000	200000	286000	255000	133000	216200.00±58409.75
Glucose, mg/dl	91	94	85	90	100	92.00±5.52
Urea, mg/dl	68	30	20	20	98	47.20±34.60
Creatinine, mg/dl	2.80	1.00	1.00	1.00	2.00	1.56±0.81
ANCA positive, %	-	-	+	+	+	60
FANA, %	-	-	-	-	-	0
Lung involvement, %	+	+	+	+	+	100
Paranasal sinuses involvement, %	+	+	+	+	-	80
Renal involvement, %	+	+	-	-	+	60
Eye involvement, %	-	+	-	-	-	20
Biopsy, %	+	+	-	+	+	80
Prednisolone use, %	+	+	+	+	+	100
Cyclophosphamide use, %	+	+	-	+	+	80
Azathioprine use, %	-	-	+	-	-	20

ANCA-- anti-neutrophil cytoplasmic antibodies, CRP - C-reactive protein, CVD - cerebrovascular disease, FANA- fluorescent antinuclear antibody, HDL - high density lipoprotein, HMG-CoA - 3-hydroxy-3-methylglutaryl coenzyme A, WG - Wegener granulomatosis

Blood pressure and pulse wave velocity measurements

Clinic blood pressure was measured, in compliance with World Health Organization guidelines (10), using a mercury sphygmomanometer with a cuff appropriate to the arm circumference, in patients after rest for 20 min (Korotkoff phase I for systolic blood pressure and V for diastolic blood pressure).

Arterial distensibility was assessed by automatic carotid-femoral PWV measurement using the Complior Colson (France) device; the technical characteristics of this device have been described (11). Pulse wave velocity, along the aorta can be measured by using two ultrasound or strain-gauge transducers [non- invasively using a TY-306 Fukuda pressure sensitive transducer (Fukuda, Tokyo, Japan)] fixed transcutaneously over the course of a pair of arteries separated by a known distance: the femoral and right common carotid arteries. During preprocessing analysis the gain of each waveform was adjusted to obtain an equal signal for the two waveforms. During PWV measurements, after pulse waveforms of sufficient quality were recorded, the digitization process was initiated by the operator and automatic calculation of the time delay between two upstrokes was started. Measurement was repeated over 10 different cardiac cycles, and the mean value was used for the final analysis. The PWV is calculated from measurements of pulse transit time and the distance (the distance between two recording sites is measured on the surface of body in meters) travelled by the pulse between two recording sites, according to the following formula:

PWV (m/s) = distance (m) / transit time (s)

Table 2. Clinical and hemodynamic parameters of patients with WG and control subjects

Variables	WG group	Control group	p*
Age, years	45.0±15.1	44.0±14.7	0.67
SBP, mmHg	105.00±10.00	114.00±11.40	0.28
DBP, mmHg	69.00±14.31	72.00±8.36	0.83
Pulse pressure, mmHg	38.00±9.08	44.00±8.94	0.27
MBP, mmHg	80.99±12.22	85.99±8.62	0.60
HR, beat/minute	71.20±6.72	63.80±10.35	0.28
PWV, m/s	9.87±1.40	8.54±0.68	0.04
PWTT, s	60.20±5.26	72.59±9.23	0.05

*- p values significance by Mann-Whitney test

DBP- diastolic blood pressure, HR- heart rate, MBP- mean blood pressure, PWTT- pulse wave propagation time, PWV- pulse wave velocity, SBP- systolic blood pressure, WG- Wegener granulomatosis

Table 3. Correlation between PWV and basic data and hemodynamic values in all subjects

Parameters	r	p
PWV-Sex	-0.17	0.63
PWV-Age, years	-0.23	0.51
PWV-Systolic blood pressure, mmHg	-0.30	0.39
PWV-Diastolic blood pressure, mmHg	-0.14	0.69
PWV-Mean blood pressure, mmHg	-0.15	0.67
PWV-Pulse pressure, mmHg	-0.05	0.87
PWV-Heart rate, beat/min	0.75	0.01
PWV- PWTT, s	0.96	<0.001

PWTT- pulse wave propagation time, PWV- pulse wave velocity

Statistical analysis

Statistical analysis were obtained using the ready-to-use program of SPSS for Windows version 8.0 (Chicago, IL, USA). All the values are expressed as mean±standard deviation. The obtained results were assessed by Mann-Whitney U test. Correlations were calculated with the Spearman test. The P value <0.05 was considered significant.

Results

Results are shown in Tables 2 and 3. The carotid-femoral PWV were increased in patients with WG as compared with control group (p=0.04). Although we found positive correlation between PWV and heart rate (r=0.75, p=0.01,), we did not find any significant correlation between PWV and anthropometric and other hemodynamic parameters (p>0.05). There was an inverse strong correlation between PWV and pulse wave propagation time (it is inversely related to the arterial PWV) (r=-0.96, p<0.001). In addition, we found positive correlation between PWV and erythrocyte sedimentation rate (ESR) in patients with WG (r=0.90, p=0.03) (Table 4).

Discussion

Systemic inflammation may play a role in the initiation or the progression of atherosclerosis (5). Since WG is an inflammatory disease, we were interested whether the

Table 4. Correlation between PWV and basic data and hemodynamic values in patients with WG

Parameters	p	r
PWV-Sex	0.55	-0.35
PWV-Age, years	0.74	-0.20
PWV-WG duration, years	0.21	-0.66
PWV-Systolic blood pressure, mmHg	0.43	-0.46
PWV-Diastolic blood pressure, mmHg	0.28	-0.60
PWV-Mean blood pressure, mmHg	0.28	-0.60
PWV-Pulse pressure, mmHg	0.05	0.87
PWV-Heart rate, beat/min	0.26	0.61
PWV-Total cholesterol, mg/dl	0.18	0.70
PWV-HDL cholesterol, mg/dl	0.32	-0.56
PWV-Triglyceride, mg/dl	0.18	0.70
PWV-Hematocrit, %	0.74	-0.20
PWV-Sedimentation rate, mm/hr	0.03	0.90
PWV-C-reactive protein, mg/dl	0.87	0.10
PWV-Leukocytes, /mm^3	0.39	0.50
PWV-Platelets, /mm^3	0.62	-0.30
PWV-Glucose, mg/dl	0.62	0.30
PWV-Urea, mg/dl	0.21	0.66
PWV-Creatinine, mg/dl	0.11	0.78
PWV-ANCA	0.63	0.28
PWV-PWTT, s	<0.001	-1.00

ANCA- anti-neutrophil cytoplasmic antibodies, HDL- high density lipoprotein, PWTT- pulse wave propagation time, PWV- pulse wave velocity, WG- Wegener granulomatosis

carotid-femoral PWV is increased, arterial distensibility decreased, in WG patients or not. We found that the PWV was higher in anti-inflammatory and cytotoxic drug-treated WG patients than in control subjects. We found significant correlation between PWV and heart rate. Increased resting heart rate increases cardiovascular mortality (12,13). Mangoni et al (14) have shown that arterial distensibility decreased in parallel with increased heart rate in rats. Albaldejo et al (15) recently reported a nonsignificant positive trend between PWV and heart rate during cardiac pacing in 11 subjects. Increased heart rate shortens the time available for recoil, which results in arterial stiffening (15). Increased arterial stiffness, which in turn may lead to increased left ventricular load, is associated with decreased myocardial oxygen supply and further aggravates myocardial ischemia.

In this study, two patients had chronic renal disease and hypertension under medical treatment. In experimental rat models of moderate renal insufficiency changes in arterial structure involving increased wall thickness and accumulation of collagen independently of age, mean blood pressure, and conventional cardiovascular risk factors such as plasma cholesterol have been reported (16, 17). Increased stiffness of central arteries is statistically associated with reduced creatinine clearance in subjects with mild-to-moderate renal insufficiency (18). Although several studies have shown that arterial stiffness depended on variation in blood pressure level (especially pulse pressure) (11, 19), we did not find any correlation between PWV and blood pressure. Stiffness becomes higher at high blood pressure and lower at low blood pressure, through mechanical change in arterial wall stretching and resulting change in contribution of elastin and collagen fibers to the elastic modulus (20).

Antihypertensive drugs (angiotensin receptor blocker, angiotensin converting enzyme inhibitors, L- and N-type calcium channel blockers) reduce the risk of arteriosclerosis by decreasing arterial stiffness in addition to exerting antihypertensive effect (21). Although chronic renal disease and hypertension may increase PWV, antihypertensive drugs may decreased PWV in two hypertensive patients in our study.

We found also significant correlation between PWV and erythrocyte sedimentation rate in WG (1). Berthelot et al (22) showed that the activation of endothelial cells in patients with WG and microscopic polyangiitis could be induced by c-ANCA which is a marker autoantibody for WG. The ANCA specific for proteinase 3 and myeloperoxidase are associated with WG (23). It has been shown that ANCA-activated neutrophils contribute to oxidative and proteolytic damage of blood vessels (24). Recent studies showed that atherosclerosis, a systemic inflammatory disease, as determined by carotid intima-media thickness , was increased in patients with WG (25). Various markers of systemic inflammation (leucocytes, ESR, and C reactive protein) have been reported to predict cardiovascular disease development both in healthy subjects and in at-risk patients (26). Blaj et al (27) found that ESR and fibrinogen values are related to pulse pressure, as a marker of large arterial stiffness, values.

In most cases, standard therapy consists of a combination of corticosteroids that reduce inflammation by inhibiting leukocyte function, and a cytotoxic drug that interferes with the abnormal growth of cells. Cyclophosphamide is the most commonly used cytotoxic drug. It acts principally by destroying the cells that produce antibodies. It diminishes inflammation and prolongs transgene expression following delivery of adenoviral vectors to C57BL/6 mice liver and lung (28). Ratcliffe et al (29) showed that there was no significant change in the blood pressure whether or not treatment included doxorubicin and/or cyclophosphamide containing regimens for lymphoma. Despite its life-saving effects in patients with WG, cyclophosphamide cannot be tolerated by certain patients, such as those that develop severe neutropenia or bladder cancer. In those patients azathioprine regimens should be initiated. This anti-inflammatory effects drugs used in WG may decrease PWV and increase the arterial distensibility.

Limitations of the study

Despite the method measures the stiffness of the aorta indirectly, it is the best described method. The pressure wave forms are easily recorded in both areas, the distance between two areas is long enough, and elasticity of arterial wall could have been reflected on a large scale as in aorta, measurement of carotid-femoral pulse wave velocity was preferred (11). We took great care to exclude subjects with pathologies and therapies that might affect arterial distensibility. A second limitation is that all patients were receiving cytotoxic and anti-inflammatory treatment that may influence endothelial function and carotid-femoral PWV. The other limitations, the healthy control subjects had not all laboratory data and two patients had chronic renal disease and hypertension under medical treatment. Finally, our conclusions may not extend to the whole population with WG, since the number of patients was small. Therefore, the results of this study will need confirmation in larger studies.

Conclusions

The carotid - femoral PWV was higher in patients with WG than in control subjects. Measurements of carotid-femoral aortic PWV may provide an easy and noninvasive technique to identify patients at increased risk of vascular disease.

Acknowledgements

We thank Alparslan Şahin, an undergraduate student of Medical Faculty of Gazi University, Ankara, Turkey, for his help during preparation of this manuscript.

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