The carotid-femoral (aortic) pulse wave velocity as a marker of arterial stiffness in familial Mediterranean fever

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AIM: The purpose of the present study was to test the hypothesis that chronic inflammation impairs vascular function and leads to an arterial pulse wave velocity (PWV) increase in patients with familial Mediterranean fever (FMF).

PATIENTS AND METHODS: Twenty-three patients (17 women) with FMF, and 23 age- and sex-matched controls were recruited. Aortic PWV was determined by using an automatic device (Complior Colson, Createch Industrie, France) that allowed on-line pulse wave recording and automatic calculation of the PWV.

RESULTS: The PWV was slightly higher in patients with FMF than in control subjects ($P=0.05$). A significant correlation between PWV and age ($P<0.001$, $r=0.67$), body mass index ($P<0.001$, $r=0.52$) and leukocytes ($P<0.001$, $r=0.66$) was found in both groups combined and also in patients with FMF ($P<0.001$, $r=0.73$; $P=0.01$, $r=0.52$; $P<0.001$, $r=0.69$, respectively).

CONCLUSION: The PWV was slightly higher in patients with FMF compared with control subjects. Colchicine, an anti-inflammatory drug treatment, may have reduced the expected increased level of PWV in FMF patients. PWV is influenced by age, body mass index and leukocytes.

Key Words: Amyloidosis; Arterial stiffness; Colchicine; Familial Mediterranean fever; Inflammation; Pulse wave velocity

Familial Mediterranean fever (FMF) is an autosomal recessive disorder virtually restricted to certain ethnic groups originating from the Middle East: Sephardic Jews, Armenians, Arabs, Druze and Turks (1). It is characterized by recurrent episodes of serosal inflammation, chest pain and arthritis, usually accompanied by fever (1). The main complication in untreated patients is the development of amyloidosis (1). In most FMF patients, colchicine treatment prevents febrile attacks and development of amyloidosis (2). During the febrile attacks, an acute phase response develops, manifested by a marked increase in erythrocyte sedimentation rate, C-reactive protein (CRP), serum amyloid A, fibrinogen and leukocytes (1). Histopathological examination reveals inflammation with infiltration by neutrophils (1). Systemic inflammation is an important factor in

Vélocité de l'onde de pouls carotido-fémorale (aortique) comme marqueur de la rigidité artérielle dans la fièvre méditerranéenne familiale (FMF)

OBJECTIF : Le but de la présente étude était de vérifier l'hypothèse selon laquelle l'inflammation chronique peut nuire à la fonction vasculaire et entraîner une accélération de la vitesse de l'onde de pouls artérielle chez des patients atteints de fièvre méditerranéenne familiale (FMF).

PATIENTS ET MÉTHODES : Vingt-trois patients (17 femmes) atteints de FMF et 23 témoins assortis selon l'âge et le sexe, ont été recrutés. La vitesse de l'onde de pouls aortique a été déterminée à l'aide d'un instrument automatique (Complior Colson, Createch Industrie, France) qui a permis l'enregistrement de l'onde de pouls en ligne et le calcul automatique de sa vitesse.

RÉSULTATS : La vitesse de l'onde de pouls s'est révélée légèrement plus rapide chez les patients atteints de FMF que chez les témoins ($p = 0,05$). Des corrélations significatives entre la vitesse de l'onde de pouls et l'âge ($p < 0,001$, $r = 0,67$), l'indice de masse corporelle ($p < 0,001$, $r = 0,52$) et les leucocytes ($p < 0,001$, $r = 0,66$) ont été observées dans les deux groupes combinés et également chez les patients atteints de FMF ($p < 0,001$, $r = 0,73$; $p = 0,01$, $r = 0,52$; $p < 0,001$, $r = 0,69$, respectivement).

CONCLUSION : La vitesse de l'onde de pouls s'est révélée légèrement plus rapide chez les patients atteints de FMF comparativement aux témoins. La colchicine, un anti-inflammatoire, peut avoir réduit le taux d'augmentation prévu de la vitesse de l'onde de pouls chez les patients. Ce paramètre subit l'influence de l'âge, de l'indice de masse corporelle et des leucocytes.

the initiation or the progression of atherosclerosis (3). Damage to the arterial wall due to inflammation and atherosclerosis causes decreased arterial distensibility, compliance and elasticity (4). Noninvasive ultrasound techniques are widely used to evaluate the vascular system and assess cardiovascular conditions. One such technique, pulse wave velocity (PWV), defined as the arterial pulse velocity moving along the vessel wall, is an indicator of arterial elasticity and correlates with CRP, an acute phase reactant, in patients with end-stage renal failure (5). PWV is inversely correlated with arterial distensibility and relative arterial compliance (6). Inflammation may impair vascular function and lead to an increase in arterial PWV. The present study investigated arterial stiffness using carotid-femoral (aortic) PWV measurements in patients with FMF.

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Figure 1) Pulse wave velocity (9.22 m/s [mean 9.42 ± 0.19 m/s]) and pulse wave propagation time (67 s) in the 10th patient. dB Decibel

PATIENTS AND METHODS

Study protocol

Patient population: Twenty-three FMF patients (17 women, FMF duration 8.0 ± 8.4 years) with typical features of the disease (7), and 23 age- and sex-matched controls (17 women) were recruited. All patients were receiving colchicine treatment in a continuous dose of 1 mg/day to 2 mg/day. Three patients were smokers. All patients gave their consent for inclusion in the study. The investigation conformed with the principles outlined in the Declaration of Helsinki. Exclusion criteria were previous myocardial infarction, constrictive, restrictive or dilated cardiomyopathy, heart failure, valvular heart disease, diabetes mellitus, peripheral arterial disease, cerebrovascular disease, renal failure, anemia (hematocrit less than 0.30), electrocardiogram conduction and rhythm disorders, systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 90 mmHg, body mass index greater than or equal to 35 kg/m^2 and waist-to-hip ratio greater than or equal to 1 cm. None of the patients were treated at the time of examination with antihypertensives or statins.

Body mass index and waist-to-hip ratio measurements: Body mass index was calculated by dividing body weight in kilograms by the square of body height in metres. Waist-to-hip ratios were calculated by dividing the circumference of the waist by the circumference of the hips.

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

$$\text{Pulse pressure} = \text{systolic blood pressure} - \text{diastolic blood pressure}$$

$$\text{Mean blood pressure} = [\text{systolic blood pressure} + 2 \times \text{diastolic blood pressure}] / 3$$

Arterial stiffness was assessed by automatic carotid-femoral PWV measurement using the Complior Colson device (Cretech Industrie, France); the technical characteristics of this device have been described (8). PWV along the aorta was measured by using two ultrasound or strain-gauge transducers (noninvasively using a TY-306 Fukuda pressure-sensitive transducer [Fukuda Denshi Co,

Figure 2) The carotid-femoral pulse wave velocity (PWV) is slightly increased in patients with familial Mediterranean fever (FMF) compared with the control (CONT) group ($P=0.05$). DBP Diastolic blood pressure; SBP Systolic blood pressure

Japan]) fixed transcutaneously over the course of a pair of arteries separated by a known distance; the femoral and right common carotid arteries were used. 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. PWV was calculated from the measurements of the pulse transit time and the distance travelled by the pulse between the two recording sites (measured on the surface of the body in metres) (Figure 1), according to the following formula:

$$\text{PWV (m/s)} = \text{distance (m)} / \text{transit time (s)}$$

Statistical analysis

Statistics were obtained using the ready-to-use program SPSS version 8.0 (SPSS Inc, USA). All the values were expressed as mean $\pm$ SD. The results obtained were assessed by independent samples tests. Correlations were calculated with the Pearson's test. $P < 0.05$ was considered significant.

RESULTS

The carotid-femoral PWV was slightly increased in patients with FMF compared with the control group ($P=0.05$). There were no significant differences in sex, age, body mass index, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, mean blood pressure, pulse pressure, heart rate and laboratory data between the FMF and control group (Figure 2, Table 1). Significant correlation was found between PWV and age ($P < 0.001$, $r=0.67$), body mass index ($P < 0.001$, $r=0.52$) and leukocytes ($P < 0.001$, $r=0.66$) in both groups combined and in patients with FMF (age, $P < 0.001$, $r=0.73$; body mass index $P=0.01$, $r=0.52$; leukocytes, $P < 0.001$, $r=0.69$) (Tables 2 and 3).

DISCUSSION

Inflammation may play a role in the process of arterial stiffening (9,10). Because FMF is an inflammatory disease, we were interested to determine whether the carotid-femoral PWV is increased in patients with this disorder. We found that the

TABLE 1
Basic data, hemodynamic values and laboratory data in control subjects and patients with familial Mediterranean fever (FMF)

	FMF patients Mean $\pm$ SD	Control subjects Mean $\pm$ SD	P
Basic data			
Age (years)	29.4 $\pm$ 8.7	29.2 $\pm$ 9.0	0.92
Body mass index (kg/m ²)	23.29 $\pm$ 3.53	23.47 $\pm$ 4.10	0.87
Waist-to-hip ratio (cm)	0.82 $\pm$ 0.00	0.80 $\pm$ 0.00	0.43
Hemodynamic values			
Systolic blood pressure (mmHg)	101.95 $\pm$ 13.20	108.69 $\pm$ 10.46	0.06
Diastolic blood pressure (mmHg)	65.65 $\pm$ 8.02	68.47 $\pm$ 8.45	0.25
Mean blood pressure (mmHg)	77.75 $\pm$ 9.26	81.87 $\pm$ 7.98	0.11
Pulse pressure (mmHg)	36.30 $\pm$ 8.28	40.21 $\pm$ 9.59	0.14
Heart rate (beats/min)	76.56 $\pm$ 10.50	71.86 $\pm$ 9.98	0.12
Pulse wave velocity (m/s)	8.53 $\pm$ 1.65	7.75 $\pm$ 0.86	0.05
Laboratory data			
Total cholesterol (mmol/L)	4.33 $\pm$ 0.95	4.23 $\pm$ 0.71	0.79
LDL cholesterol (mmol/L)	2.68 $\pm$ 0.69	2.34 $\pm$ 0.67	0.27
Triglycerides (mmol/L)	1.11 $\pm$ 0.44	1.12 $\pm$ 0.31	0.96
Hemoglobin (g/L)	124.9 $\pm$ 13.1	129.4 $\pm$ 7.8	0.40
Hematocrit	0.37 $\pm$ 0.03	0.36 $\pm$ 0.04	0.50
Leukocytes ($\times 10^9$ /L)	11.598 $\pm$ 25.846	5.985 $\pm$ 1.578	0.57
Sedimentation (mm/h)	16.65 $\pm$ 11.97	10.00 $\pm$ 1.63	0.15
C-reactive protein (mg/L)	13.5 $\pm$ 22.6	2.7 $\pm$ 1.1	0.22
Albumin (g/L)	43.4 $\pm$ 2.7	43.0 $\pm$ 2.7	0.69
Total protein (g/L)	77.3 $\pm$ 4.1	77.2 $\pm$ 4.7	0.97
Uric acid (μ mol/L)	213.0 $\pm$ 65.4	223.2 $\pm$ 58.2	0.70

LDL Low-density lipoprotein

carotid-femoral PWV was slightly higher in colchicine-treated FMF patients than in control subjects ($P=0.05$).

PWV is a technique by which large artery elasticity is assessed from analysis of the peripheral arterial waveform (8). It is calculated from measurements of pulse transit time and the distance travelled by the pulse between two recording sites. It is an index of arterial stiffness and a surrogate marker for coronary atherosclerosis. A close relationship between increased PWV and atherosclerosis development has been reported (11).

We found significant correlation between PWV and age. Arterial stiffness can be affected by both structural and functional changes (12). Structural changes involve the composition of the arterial wall, hypertrophy of smooth muscle cells and a decrease in contents of the extracellular matrix (13). Arteries become wider and less elastic (increased PWV) with advancing age, as a consequence of the age-related reduction in arterial elastin and an increase in collagen content (14). Although several studies have shown that arterial stiffness depends on variation in blood pressure (especially pulse pressure), we did not find any correlation between PWV and blood pressure or CRP. Stiffness becomes greater at high blood pressures and lower at low blood pressures, through mechanical changes in arterial wall stretching, and results in change in contribution of elastin and collagen fibres to the elastic modulus (15,16). Amar et al (17) demonstrated an association between CRP and peripheral pulse pressure, but no association between aortic stiffness and the influence of CRP on central pulse pressure, which was found in our study.

TABLE 2
Correlations between pulse wave velocity (PWV), basic data, hemodynamic values and laboratory data in all groups

Correlated to PWV	P	r
Basic data		
Sex	0.44	0.11
FMF duration (years)	0.13	0.32
Age (years)	<0.001	0.67
Body mass index (kg/m ²)	<0.001	0.52
Waist-to-hip ratio (cm)	0.05	0.28
Hemodynamic values		
Systolic blood pressure (mmHg)	0.35	0.14
Diastolic blood pressure (mmHg)	0.06	0.27
Mean blood pressure (mmHg)	0.11	0.23
Pulse pressure (mmHg)	0.68	-0.06
Heart rate (beats/min)	0.95	-0.008
Laboratory data		
Total cholesterol (mmol/L)	0.11	0.29
LDL cholesterol (mmol/L)	0.17	0.25
Triglycerides (mmol/L)	0.79	0.05
Hemoglobin (g/L)	0.22	0.23
Hematocrit	0.19	0.24
Sedimentation (mm/h)	0.40	0.15
C-reactive protein (mg/L)	0.97	-0.006
Albumin (g/L)	0.65	0.08
Total protein (g/L)	0.30	-0.19
Uric acid (μ mol/L)	0.86	0.03
Leukocytes ($\times 10^9$ /L)	<0.001	0.66

FMF Familial Mediterranean fever; LDL Low-density lipoprotein

TABLE 3
Correlations between pulse wave velocity (PWV), basic data, hemodynamic values and laboratory data in patients with familial Mediterranean fever (FMF)

Correlated to PWV	P	r
Basic data		
Sex	0.57	0.12
FMF duration (years)	0.13	0.32
Age (years)	<0.001	0.73
Body mass index (kg/m ²)	0.01	0.52
Waist-to-hip ratio (cm)	0.30	0.22
Hemodynamic values		
Systolic blood pressure (mmHg)	0.30	0.22
Diastolic blood pressure (mmHg)	0.17	0.29
Mean blood pressure (mmHg)	0.20	0.27
Pulse pressure (mmHg)	0.75	0.07
Heart rate (beats/min)	0.66	-0.09
Laboratory data		
Total cholesterol (mmol/L)	0.09	0.35
LDL cholesterol (mmol/L)	0.29	0.23
Triglycerides (mmol/L)	0.72	0.07
Hemoglobin (g/L)	0.19	0.28
Hematocrit	0.11	0.33
Sedimentation (mm/h)	0.56	0.12
C-reactive protein (mg/L)	0.78	-0.05
Albumin (g/L)	0.67	0.09
Total protein (g/L)	0.14	-0.31
Uric acid (μ mol/L)	0.73	0.07
Leukocytes ($\times 10^9$ /L)	<0.001	0.69

LDL Low-density lipoprotein

We found significant correlation between PWV and leukocyte count. FMF is an autosomal recessive disorder characterized by mutations in the Mediterranean fever gene located on the short arm of chromosome 16 (18). The gene encodes a 781-amino acid protein called pyrin, expressed in cells of the myeloid lineage. Although the role of the Mediterranean fever gene in the development of FMF attacks is not yet clearly understood, its malfunction eventually results in inflammation. It has also been proposed that in FMF, any minor stimulus leads to an uncontrolled inflammatory reaction with complement activation, due to an absence of an inhibitor of C5a and excessive tumour necrosis factor release (19-21). The inflammatory process of FMF is also caused by leukotriene B₄, a potent lipid chemoattractant and mediator of acute inflammation (22,23). This inflammation may act to impair endothelial function, arterial compliance and arterial elasticity, and act as a contributing factor in the initiation or the progression of atherosclerosis (9,10).

Circulating leukocytes play an important role in the pathogenesis of atherosclerosis, which is an inflammatory disease (24,25). Positive associations between total leukocyte count and risk factors of atherosclerosis or coronary artery diseases have been frequently mentioned (26-28). The atherosclerotic process is initiated when cholesterol-containing low-density lipoproteins accumulate in the endothelium. Leukocyte adhesion molecules and chemokines promote recruitment of T cells and monocytes. T cells in lesions recognize local antigens and mount T helper-1 responses with secretion of pro-inflammatory cytokines that contribute to local inflammation.

Obesity may adversely affect cardiovascular health through associations with hyperlipidemia, hypertension and inflammation. Obesity, which is a traditional cardiovascular risk factor, could be a marker of inactivity and could represent insulin resistance, and it may also exert adverse effects on the vascular system by decreasing arterial elasticity (29). In the present study, we found a significant correlation between carotid-femoral PWV and body mass index. We found that that arterial stiffening and decreasing elasticity results with increasing body mass index.

Amyloidosis is the most serious complication of FMF, leading to end-stage renal disease. Amyloidosis could also affect the heart, blood vessels and lungs (30). Heart involvement is expressed by restrictive cardiomyopathy, leading to heart failure and arrhythmias. Because colchicine treatment is readily available, the rate of amyloidosis is much lower than previous reports (31) have stated. However, Rogers et al (32) have shown that FMF is still the leading cause (64%) of secondary amyloidosis in the Turkish population. The recurrent inflammatory attacks are accompanied by extremely high concentrations of serum amyloid protein A in FMF patients (31). In the majority of amyloidosis cases, FMF patients are under the age of 40 (31). The diagnosis of amyloidosis is usually confirmed by rectal, gingival or renal biopsy. These previous findings indicate that amyloidosis may increase the carotid-femoral PWV in patients with FMF. We did not have the chance to observe the effects of amyloidosis on PWV, because none of our patients had this complication.

Colchicine reduces severity of inflammation in FMF. It is an alkaloid that exerts its main effect at the cellular level through its interaction with tubulin at the microtubules, inhibiting the motility and exocytosis of cellular granules. Colchicine has a powerful antimitotic effect and may also decrease the expression

of adhesion molecules on the surface of neutrophils and endothelial cells (33,34). Therefore, the anti-inflammatory effect of colchicine is probably due to its inhibitory effect on leukocyte chemotaxis (35). This anti-inflammatory effect of colchicine may decrease PWV (arterial stiffness) and increase the arterial distensibility in patients with FMF. Langevitz et al (36) showed that despite evidence of recurrent inflammation, colchicine-treated FMF patients are not more predisposed to ischemic heart disease than the normal population. Colchicine therapy may also decrease blood pressure and arterial stiffness, because in one study (37) colchicine injections caused significant decrease in blood pressure in male Wistar rats. In arteriosclerotic hypertensive patients, a three- to four-month treatment with 1 mg of colchicine per day resulted in a significant ($P<0.01$) increase of the dermal elastic fibre density (38). Keeley and Alatawi (39) showed that treatment of Dahl rats with colchicine during development of hypertension affected the increase in blood pressure only marginally but abolished the vascular hypertrophic response.

CONCLUSION

The carotid-femoral PWV was slightly higher in patients with FMF than in control subjects ($P=0.05$). Colchicine, which is an anti-inflammatory drug treatment, probably reduced the expected increased level of PWV in FMF patients. PWV is influenced by age, body mass index and leukocytes.

Limitations

Despite the fact that the method used measures the stiffness of the aorta indirectly, it is the best method available (8). We took great care to exclude subjects with known cardiovascular disease or risk factors. However, it is impossible to be certain that none of our patients had undetected disease. A second limitation is that all patients were receiving colchicine treatment, which may have influenced endothelial function and carotid-femoral PWV. Finally, these conclusions may not extend to the general population; therefore, the results of this study need confirmation in larger studies.

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