Normal arterial stiffness in familial Mediterranean fever. Evidence for a possible cardiovascular protective role of colchicine

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ABSTRACT

Objective. *Familial Mediterranean fever (FMF) is an autoinflammatory disorder with episodic and persistent inflammation, which is only partially suppressed by continuous colchicine treatment. While chronic inflammation is considered an important cardiovascular risk factor in many inflammatory disorders, its impact in FMF is still disputed. We measured arterial stiffness, a marker of atherosclerotic cardiovascular disease, in a group of FMF patients, in order to evaluate the cardiovascular consequences of inflammation in FMF and the role of colchicine in their development.*

Methods. *Eighty colchicine treated FMF patients, without known traditional cardiovascular risk factors, were randomly enrolled in the study. Demographic, genetic, clinical and laboratory data were retrieved from patient files and examinations. Arterial stiffness was measured using pulse wave velocity (PWV). The recorded values of PWV were compared with those of an age and blood pressure adjusted normal population, using internationally endorsed values.*

Results. *FMF patients displayed normal PWV values, with an even smaller than expected proportion of patients deviating from the 90th percentile of the reference population (5% vs. 10%, p=0.02). The lowest PWV values were recorded in patients receiving the highest dose of colchicine (≥2 mg vs. 0-1 mg, p=0.038), and in patients of North African Jewish origin, whose disease was typically more severe than that of patients of other ethnicities; both observations supporting an ameliorating colchicine effect (p=0.043).*

Conclusion. *Though subjected to chronic inflammation, colchicine treated FMF patients have normal PWV. Our findings provide direct evidence for a cardiovascular protective role of colchicine in FMF.*

Introduction

Systemic inflammatory disorders are considered risk factors for ischaemic cardiovascular disease (ICVD) (1-4). Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder, manifested with short attacks of serositis, accompanied by a vigorous inflammatory response (5). Despite colchicine prophylaxis, aimed at preventing FMF attacks and suppressing the associated inflammation, a substantial number of patients (>30%) continue to suffer from recurrent attacks and persistent inflammation (6). This is demonstrated by elevated levels of C-reactive protein (CRP) and serum amyloid A (SAA), anaemia, splenomegaly and progression to amyloidosis, the most serious complication of FMF (6). In contrast to other inflammatory disorders, the possible link of FMF with ICVD is still debated. This is due to the conflicting results demonstrated by studies assessing vascular function and structure, as well as the actual incidence of ICVD in FMF (7-9).

Increased arterial stiffness is recogniaed both as a cause of early endothelial damage and as an independent marker of ICVD (10-13). Systemic inflammation undoubtedly has an important role in its development (14). Arterial stiffness can be estimated by measuring pulse wave velocity (PWV), since in stiff vessels the passage of blood gains speed by transforming vertical to horizontal motion. PWV has repeatedly been shown to be abnormally increased in systemic inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis, Crohn's disease, systemic lu-

pus erythematosus (SLE) and others (15-19). Arterial stiffness has also been assessed in FMF, but only scarcely and with inconclusive results (19, 20).

We sought to further substantiate our clinical and research experience that in FMF, as compared to other inflammatory diseases, patients are relatively protected from increased occurrence of ICVD despite the inflammatory burden they face (7); and to investigate the role of colchicine in this seeming paradox. Therefore, we set out to assess PWV, which is considered the gold standard for evaluation of arterial stiffness (21, 22), in a sample of our FMF population.

Materials and methods

Study design

The purpose of the study was to determine whether arterial stiffness in FMF is greater than in a normal population and to define the role of colchicine in the development of arterial stiffness. To this end, we compared PWV in FMF patients and in a normal population, and investigated parameters that may affect PWV in FMF.

Enrolment

Consecutive, unselected patients, attending the FMF outpatient clinic for a scheduled follow up visit, between April 2012 and December 2014, who met the inclusion criteria and did not meet any of the exclusion criteria and who consented to participate, were enrolled in the study. All participants provided signed informed consent. The study was approved by Sheba Medical Center Institutional Review Board.

Inclusion criteria

a) FMF patients, men or women, fulfilling the diagnostic criteria for FMF (5); b) Age 18 to 60 year old; c) Treated with colchicine, in any dose between 0.5-3 mg/day, based on their physicians' discernment (23); d) Willing and able to provide signed informed consent.

Exclusion criteria

a) Traditional risk factors for atherosclerotic cardiovascular disease, known to the patient, either treated or untreated, such as diabetes mellitus, hypertension and hyperlipidaemia; b) Other inflammatory or autoimmune conditions, such as rheumatoid arthritis, Behçet's disease, ankylosing spondylitis, etc.; c) Already existing ICVD, such as cerebro-coronary- or peripheral vascular diseases; d) Other diseases, including chronic kidney disease, amyloidosis or proteinuria above normal limits, active infection, current malignant diseases, chronic obstructive pulmonary disease (COPD); e) pregnancy.

Of note, colchicine by itself, as an obligatory drug in participants, does not affect lipid or glucose levels (24, 25).

Evaluation

Patients were interviewed, completed a questionnaire and underwent a complete physical examination. Blood pressure was measured at rest in a seated position, using an automated oscillometer and the average of three consecutive measurements was recorded.

FMF characteristics

Based on the interview, medical records and the questionnaire, patients were classified with active or inactive FMF. Inactive disease was defined by less than one FMF attack in 3 months and the absence of inflammatory markers as determined by elevated CRP and/or SAA levels between the attacks. This definition was adopted from a definition of colchicine responsiveness (26). Severity of the disease was evaluated by the Mor scale (27), and was graded as mild, moderate or severe.

The questionnaires accessed information on the age of disease onset, disease duration, the number of sites involved during the course of the disease, mutations, additional medical conditions and their treatment, history of smoking and the history of colchicine consumption. In light of changes in colchicine doses over time, we examined three treatment-related parameters: mean daily colchicine dose, years of exposure to colchicine and colchicine-years; the latter was computed by multiplying each dose by the duration of exposure to it and summing all colchicine-year values for each patient.

Laboratory data

Laboratory data were obtained from the records of the most recent patient visits and included haemoglobin, fasting serum glucose levels and lipid profile. The tests were performed in the clinical laboratories of the patients' health insurance organisations.

Examination of arterial stiffness in the study group and a reference group

Carotid-femoral PWV was measured with a Sphygmocor system algorithm (AtCor Medical, Sydney, Australia), according to the manufacturer's instructions and published recommendations (28). Each examinee had duplicate examinations and the average PWV value (in m/sec) was reported.

PWV was compared to age-adjusted and blood pressure-adjusted norms, based on PWV values of 11,000 healthy subjects from various countries (22), endorsed by the European Heart Association and the European Society of Hypertension (EHA/ESH) as the reference gold standard PWV values for healthy adults (29). Similar to the reference population, we excluded patients with treated hypertension, hyperlipidaemia, and diabetes mellitus or ICVD. Abnormally elevated PWV among FMF patients was defined as a value above the 90th percentile of the age- and blood pressure-adjusted reference population. Reference PWV values for different age and blood pressure groups is shown in Table SI in the supplementary material.

Statistical analysis and determination of the role of colchicine

Statistical analysis was performed using descriptive statistics, with standard central tendency and dispersion determinations. The recorded PWV values were standardised for age and blood pressure, based on the reference groups presented in Table SI, and marked with PWV_Z. PWV_Z was defined as the number of standard deviations of a patient's PWV, from the mean value for his/her age- and blood pressure-adjusted reference group. PWV_Z enabled comparing and analysing PWV measurements in the study population, with a wide range of age and blood pressure. The effects of several variables (mutation type, patient country of origin, number of affected sites and disease

activity) on PWV were tested using one way ANOVA to compare between mean values of PWV_Z of subgroups. To determine the effect of colchicine treatment, non-parametric values of colchicine dose and treatment duration were correlated, using Spearman's Rho. Finally, a linear regression model was constructed to test for the effect of various parameters on the prediction of PWV_Z values. All analyses were performed using SPSS v. 22.

Results

We studied 80 patients (40 men). Clinical and demographic characteristics of the study participants are shown in Table I. The mean age was 35±10 years. The mean blood pressure (average of 3 measurements per patient) was 111±12/70±10, which is in the optimal blood pressure range, as defined by the reference study (Table SI) (22). Mean BMI, lipid profile, fasting glucose and cholesterol levels were also in the normal range, attesting to the absence of traditional cardiovascular risk factors in our studied subjects. As expected for an Israeli FMF patient population, the majority of patients were of North African or Iraqi Jewish extraction (56.3%). The results of PWV measurement are shown in Table II. Both, the mean and median PWV were 6.75 m/sec, implying that the wave of pressure travels at a normal or lower than normal speed (Table SI). While per definition, 10% of healthy individuals are above the 90th percentile, we found only 4 of the 80 (5%) FMF patients to be above the 90th percentile of the age- and blood pressure-adjusted reference population (one-sided 95% CI [1%, 5%], p=0.02; Table II, Fig. 1). This finding firmly defines the PWV in the studied FMF population as normal.

Subgroup analyses to detect possible effects of various parameters on the PWV were performed by stratifying the population according to the type of mutation (694/694, 694/other, 694/0, none, others), origin (North Africa/ Iraqi/Ashkenazi/Arabs/ others), number of sites involved and disease activity. The ANOVA test, revealed no statistically significant differences between the PWV_Z values within each subgroup (p=0.631, p=0.230, p=0.086, p=0.669, respectively). We expected that subgroups that expressed more severe disease would display higher values of PWV. However, we found clear inverse relationships with trends for gradual increase in PWV_Z values, of patient populations coded according to disease severity, from North African Jewish (high severity) patients to Arab patients (low severity) (Fig. 2A); and from those experiencing attacks in three sites, compared to only one site (Fig. 2B).

The inverse association between ethnicity and PWV was confirmed by regression analysis, using another statistical model, the backward elimination method, considering 4 parameters: type of mutation, patient origin, number of involved sites and mean colchicine dose. Only the coded ethnic origin was significantly inversely correlated with the PWV_Z values, with the highest PWV_Z values in Arabs (a population with milder disease), and the lowest PWV_Z values in North African Jews (one-sided t-test p=0.043). Although this analysis did not directly define a link between colchicine and PWV, the patients of North African origin, with the lowest PWV_Z, had significantly more colchicine-years compared to their Arab counterparts (40.65±29.5, vs. 12.14±8.8, p=0.043).

To further address the role of colchicine, the association between colchicine exposure and PWV_Z was studied, by examining the mean colchicine dose, duration of colchicine treatment and the product of colchicine dose and years of treatment (colchicine-years).

Table I. Demographic, clinical and genetic characteristics.

Demographic data	Male sex (%)	50
	Age (y)	35 ±10
	Origin: North Africans/ Iraqi/ Ashkenazi/ Arabs/ Other (%)	43.8/12.5/2.5/8.8/32.5
Cardiovascular risk factors	Systolic pressure (mm Hg)	111 ±12
	Diastolic pressure (mm Hg)	70 ±10
	BMI (kg/m^2)	23.30 ±3.5
	Glucose (mg/dcl)	87 ±10
	Cholesterol (mg/dcl)	161 ±36
	LDL (mg/dcl)	96.9 ± 25.75
	HDL (mg/dcl)	46 ±16
	Triglycerides (mg/dcl)	113 ±54
	Ever smoked (%)	32.5%
FMF clinical data	Severity: mild/moderate/severe (%)	45.6/17.7/36.7
	Activity: Yes/No (%)	56 /44
	Number of sites involved 1/2/3/4 (%)	27.3/24.7/29.9/18.2
	Duration of FMF (from onset of symptoms) (y)	23 ±12
	Anaemia (%)	16.3%
	Haemoglobin (g/dcl)	14 ±1
	Inflammation by APRs [1] (%)	25.3%
FMF genotype	Genotypes: 694/694, 694/other, 694/0, none, other (%)	38.7/25.3/16/6.7/13.3
Colchicine treatment	Duration of colchicine use (y)	16 ±12
	Mean dose of colchicine (mg)	1 ±1
	Good Compliance[2] (%)	51.25

Data are expressed as mean ±SD unless otherwise specified.
[1]As indicated by CRP or ESR. [2]Patient self-report.
BMI: body mass index, LDL: low density lipoprotein, HDL: high density lipoprotein, FMF: Familial Mediterranean fever, APR: acute phase reactants, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

Table II. Pulse wave velocity analysis.

Parameter	Number of patients (%)	Median	Mean ±SD (distribution)
PWV (m/sec)	80	6.75	6.75 ± 1.06 (4.1–10.9)
Abnormal PWV (Above 90th percentile)	4 (5)		
PWV_Z	80	0.0	0.00 ± 0.83 (-2.27–2.22)

PWV_Z: Adjusted PWV - Number of standard deviations from the mean pulse wave velocity of adjusted normal population.

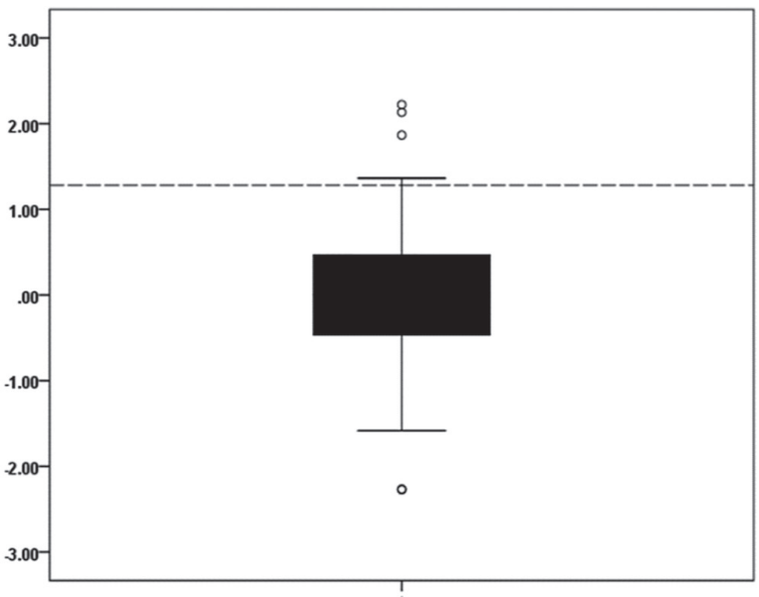

Fig. 1. The distribution of PWV_Z values in FMF is normal.
Carotid-femoral pulse wave velocity (PWV) was measured using the Sphygmocor system algorithm. PWV_Z values (number of standard deviations from the mean value of adjusted normal population) were computed. The figure demonstrates that only 4 of 80 (5%) randomly enrolled FMF patients had PWV_Z values above the 90th percentile (indicated by empty circles + the solid line above the dashed line), instead of the expected 10% (one-sided 95% CI [1%, 5%] p=0.02). The distribution of the remaining measurements is confined to the shaded area.

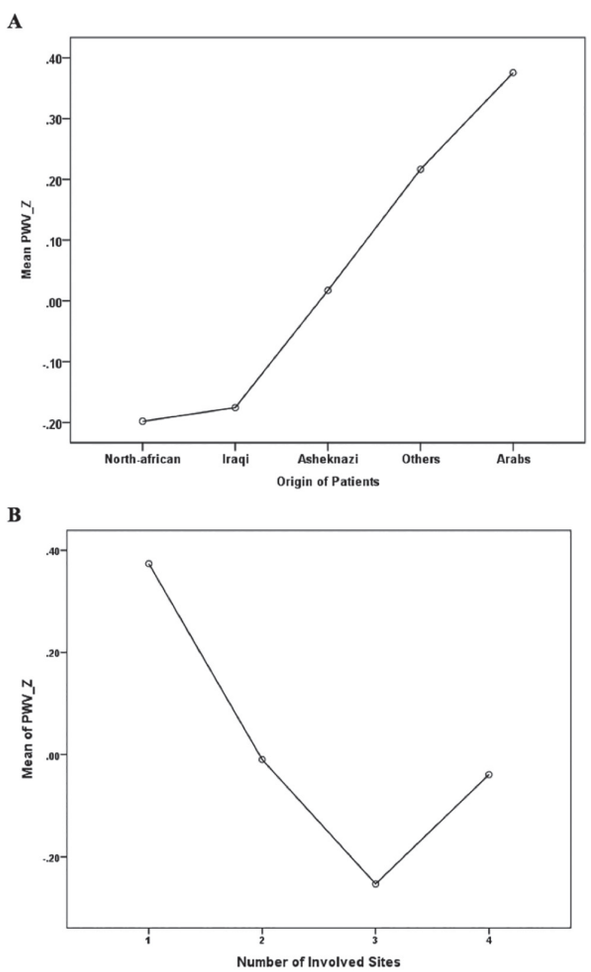

Fig. 2. Correlates of increased disease severity are inversely associated with PWV_Z.
A. Mean PWV_Z (determined as in Fig. 1) in FMF patients pooled according to ethnic origin. The ANOVA test yielded a non-significant trend for the difference in mean PWV_Z values between ethnicities (p=0.23). However, as seen in the figure, there is a clear trend (increasing slope) for the gradual increase in mean PWV_Z values of patient subgroups arranged according to disease severity, from North African Jewish patients to Arabic patients.
B. Mean PWV_Z (determined as in Fig. 1) in FMF patients, as related to the number of sites involved in FMF attacks during the course of the disease (a measure of severity). The ANOVA test yielded a non-significant trend for the difference in mean PWV_Z values between characteristics (p=0.086). However, as displayed, there is a clear trend (increasing slope), for the progressive increase in mean PWV_Z values of patients analysed according to the number of sites involved, from 3 to only one.

Spearman's rho analysis yielded a borderline significant correlation between mean colchicine dose and PWV_Z (Spearman's rho =-0.185; p=0.05, Table III). However, when the lowest mean dose of colchicine (1 mg/d or less) was compared to the highest mean dose of colchicine (2 mg/day or more), a significant difference between the PWV_Z values of the groups was observed (PWV_Z difference -0.44, p= 0.038), with the lowest PWV_Z measured in patients receiving the highest colchicine dose.
Regression analysis to determine the effect of traditional risk factors (within the normal range), such as sex, BMI, smoking history, glucose and lipid profile did not find a significant correlation between PWV_Z and any of these parameters in the tested FMF population.

Discussion

Arterial stiffness, as measured by PWV, is elevated in patients with traditional risk factors, and thereby constitutes a predictor of atherosclerotic cardiovascular disease. Increased PWV is also induced by inflammation and heralds ICVD in patients with rheumatoid arthritis, psoriatic arthritis, Crohn's disease and SLE (15-18). Inflammation-associated increased arterial stiffness is thought to be mediated by inflammatory cytokines (such as IL-1, TNF- alpha), proteins (CRP), matrix metalloproteinases, tissue degradation products and impairment of nitric oxide function and production, which together lead to elastin breakdown, collagen over production, and proliferation of endothelial and smooth muscle cells (30-32). These mediators are also involved in the inflammatory process of FMF (6). Nonetheless, our results show that large artery stiffness in individuals with FMF is not higher than that of healthy controls. Thus, the paradigm of inflammation-associated increased PWV does not seem to apply to colchicine treated FMF. This finding of normal PWV in FMF was obtained despite the large proportion of patients with severe (36%) and active (56%) disease (Table I).
A finding of normal PWV in FMF was also reported by Sari *et al*. (33), but not by two other authors (20, 34). Howev-

Table III. Association of colchicine parameters with adjusted pulse wave velocity (PWV_Z).

	Colchicine years *vs*. PWV_Z (n=80)	Colchicine dose *vs*. PWV_Z (n=78)	Colchicine dose-years [1] *vs*. PWV_Z (n=78)
Correlation Coefficient	- 0.124	- 0.185	- 0.174
P value [2] (one-tail, left-sided)	0.14	0.05	0.06

[1]Summation of the products of multiplications of the dose by years the specific dose was consumed.
[2]Using Spearman's rho coefficient ($p \leq 0.05$ is considered significant).
PWV-Z: adjusted PWV (see Table II).

er, normal PWV concurs with our experience of low prevalence of clinically overt ICVD in FMF. Indeed, the only paper that examined the prevalence of ICVD in FMF found it to be comparable to that of the general population and of a control group, which comprised spouses of the studied FMF patients; and lower than in patients with other inflammatory or autoimmune diseases (7). Of 24 FMF patients, younger than 50 years, who were admitted over the last 15 years to our tertiary medical centre with an ICVD disease, at least one of the traditional risk factors to explain their disease presented in all except one. This suggests that FMF related CVD is indeed rare (Livneh A, unpublished data). The rate of ICVD related death in the FMF population appears also to be normal (35).

In our search for underlying factors that may be associated with our main finding, we found that the dose of colchicine inversely correlated with the grade of PWV, with lowest PWV_Z values measured among those receiving the highest dose of colchicine (p=0.038). Thus, while Langevitz *et al*. (7) only speculated on the cardioprotective effect of colchicine, the present study provides, for the first time in FMF, direct evidence that supports such a role. It is unclear how colchicine protects from the occurrence of ICVD in FMF. The current study suggests that the cardiovascular protection by colchicine is not due to its anti-inflammatory effect. The dissociation between cardioprotection and suppression of inflammation is inferred from the finding that FMF patients of North African origin, who express the most severe FMF phenotype, had the lowest PWV values (Fig. 2A). This surprising finding, however, is consistent with a cardiovascular protective role of colchicine, as suggested by higher values of colchicine-years in North African Jewish patients, compared to Arab patients (p=0.043). Previously, we reported a dissociation between cardioprotection and suppression of inflammation, based on our finding that the rate of ICVD in colchicine resistant and colchicine responsive FMF patients is comparable, despite ongoing attacks and continuous inflammation in the former (36).

The awareness that colchicine may protect against ICVD, independent of systemic inflammation, may lead to a broader application of its use. Indeed, several studies have addressed the cardioprotective effect of colchicine in non-FMF populations. One such study tested the role of colchicine in secondary prevention of restenosis in patients who underwent percutaneous coronary intervention. A second study investigated the effect of colchicine prophylaxis on the progression of coronary disease in patients with stable angina pectoris, and a third evaluated the development of ICVD in patients with gout who received colchicine. All confirmed the cardioprotective role of colchicine (37-39).

The current study has a number of limitations. We did not measure PWV in a normal local control group, but rather used normal reference values, endorsed by the EHA/ESH. Our methodology may allegedly have caused errors related to ethnicity and country of residence. However, we preferred to refer to the existing knowledge on thousands of individuals, rather than to build a local reference based on a small sample of one hundred or so individuals. Moreover, the population in the large reference group was obtained from various ethnicities, which may further attenuate this low probability risk for error. Another limitation is that the study was carried out on a relatively small number of patients. However, the patients were recruited consecutively, and reflected the typical FMF population attending a large FMF clinic in a tertiary medical centre. This minimises any possible bias due to the small population. Moreover, although small, this is the largest study to date on PWV in FMF.

In conclusion, this study suggests that the inflammatory burden of FMF in colchicine-treated patients does not create a risk factor for the development of increased arterial stiffness, which is both a marker and a cause of ICVD. The analysis employed in this paper provides, for the first time, direct evidence for a cardioprotective role of colchicine in FMF.

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